UFBA
Universidade Federal da Bahia
Instituto de Ciências da Saúde

Dimitri Gusmão Flôres

PROCESSOS INTERATIVOS DOS ÓRGÃOS E SISTEMAS
PROGRAMA DE PÓS GRADUAÇÃO • ICS • UFBA

Propriedades psicométricas de instrumentos diagnósticos para *delirium* no paciente grave em unidade de terapia intensiva

Salvador
2013

UNIVERSIDADE FEDERAL DA BAHIA
INSTITUTO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO
PROCESSOS INTERATIVOS
DOS ORGÃOS E SISTEMAS

DIMITRI GUSMÃO FLÔRES

PROPRIEDADES PSICOMÉTRICAS DE INSTRUMENTOS DIAGNÓSTICOS PARA *DELIRIUM* NO PACIENTE GRAVE EM UNIDADE DE TERAPIA INTENSIVA

SALVADOR
2013

DIMITRI GUSMÃO FLÔRES

PROPRIEDADES PSICOMÉTRICAS DE INSTRUMENTOS DIAGNÓSTICOS PARA *DELIRIUM* NO PACIENTE GRAVE EM UNIDADE DE TERAPIA INTENSIVA

Tese apresentada ao Programa de Pós Graduação em Processos Interativos dos Órgãos e Sistemas, Instituto de Ciências da Saúde, Universidade Federal da Bahia, como requisito para obtenção do grau de doutor em Processos interativos dos órgãos e sistemas.

Orientador: Prof. Dr. Lucas de Castro Quarantini

SALVADOR
2013

AGRADECIMENTOS

A conclusão do Doutorado só foi possível pois tive apoio e incentivo de muitos.

Agradeço à minha esposa, Susana Carolina, que acreditou em tudo o que está ocorrendo antes mesmo de eu pensar em trilhar este caminho. Com seu apoio foi possível seguir em frente com um peso menor sobre os ombros.

Agradeço aos meus pais e irmãos por estarem sempre torcendo, acreditando e vibrando com as minhas conquistas, mesmo que distantes.

Agradecimento especial ao meu orientador, Dr. Lucas de Castro Quarantini, que soube me conduzir de forma impecável durante toda esta trajetória. Sempre presente e estimulando que a conclusão da tese não fosse o fim, mas o fruto de uma linha de pesquisa sólida e promissora.

Agradeço ao meu amigo e grande incentivador, Dr. Antônio Raimundo, com que eu tenho o privilégio de conviver e trabalhar na enfermaria 4A do Complexo HUPES. Acho que nada estaria ocorrendo na minha vida acadêmica sem apoio dele.

Agradeço a todos os estudantes e participantes do grupo de estudo de *delirium* que muito contribuíram para manter a motivação e continuarmos avançado nesta linha de pesquisa.

Agradeço a todos os colegas de turma do programa de Pós graduação em Processo Interativo dos Orgãos e Sistemas do primeiro semestre de 2011. A nossa turma foi espetacular e a convivência com todos vocês foi enriquecedora.

Por fim, a todos os colegas e amigos que de alguma forma apoiaram e acreditaram.

Salvador, 26 de outubro de 2013.

Dimitri Gusmão Flôres

GUSMAO-FLORES, Dimitri. Propriedades psicométricas de instrumentos diagnósticos para *delirium* no paciente grave em unidade de terapia intensiva. Tese (Doutorado) - Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, 2013.

RESUMO

Delirium é uma das formas comuns de apresentação de disfunção neurológica aguda em pacientes graves. É definido segundo os critérios do DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*) como um transtorno agudo e flutuante da consciência e cognição, tem alta prevalência em unidades de terapia intensiva (UTI) e está associado a alta mortalidade e maior tempo de internamento hospitalar. A despeito da sua importância, por muito tempo os estudos clínicos a respeito deste tema foram comprometidos pela ausência de uma terminologia uniforme e de critérios específicos para o diagnóstico. O objetivo desta tese é estudar as propriedades psicométricas de ferramentas diagnósticas para *delirium*, com ênfase: 1) na validação para o idioma português brasileiro de três instrumentos para o diagnóstico de *delirium* no paciente grave: o *Confusion Assessment Method for the Intensive Care Unit* (CAM-ICU), o CAM-ICU *Flowsheet* e o *Intensive Care Delirium Screening Checklist* (ICDSC), 2) na realização da síntese por meta-análise da acurácia de duas destas ferramentas (CAM-ICU e ICDSC), 3) na identificação de limitações para o uso do CAM-ICU. No estudo de validação, 119 pacientes foram avaliados e 38,6% foram diagnosticados com *delirium* pelos critérios do DSM-IV. O CAM-ICU e CAM-ICU *Flowsheet* apresentaram a mesma acurácia com uma sensibilidade de 72,5% e uma especificidade de 96,2 e o ICDSC teve uma sensibilidade de 96,0% e uma especificidade de 72,4%. No subgrupo de pacientes em uso de ventilação não-invasiva a concordância entre o CAM-ICU e o DSM-IV foi de 100%. Na meta-análise, foram incluídos na análise final 09 estudos que avaliaram o CAM-ICU (totalizando 969 pacientes) e quatro estudos que avaliaram o ICDSC (n= 361 pacientes). A sensibilidade combinada do CAM-ICU foi de 80,0% (95% intervalo de confiança (IC): 77,1-82,6%), e a especificidade combinada foi de 95,9% (95 % IC: 94,8-96,8 %). A sensibilidade combinada do ICDSC foi de 74 % (IC de 95%: 65,3-81,5%), e a especificidade combinada foi de 81,9% (IC 95%: 76,7-86,4%). Foi também observado que o CAM-ICU tem menor sensibilidade para diagnosticar *delirium* em pacientes com níveis menores de sedação. Em conclusão, o diagnóstico de *delirium* no paciente grave pode ser realizado, com boa acurácia, utilizando o CAM-ICU e o ICDSC no idioma português brasileiro. A versão modificada, o CAM-ICU *Flowsheet,* também pode ser utilizada com a vantagem de permitir que a avaliação ocorra de forma mais rápida. Nos pacientes em uso de suporte ventilatório não invasivo o diagnóstico de *delirium* pode ser feito utilizando o CAM-ICU. Por fim, em pacientes com menores níveis de sedação o CAM-ICU parece perder acurácia.

Palavra-chave: *delirium*, CAM-ICU, ICDSC, CAM-ICU *Flowsheet.*

GUSMAO-FLORES, Dimitri. Psychometric properties of instruments for diagnosing delirium in critically ill patients in the intensive care unit. Thesis (Doctor's degree) - Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, 2013.

ABSTRACT

Delirium is a common form of presentation of acute neurologic dysfunction in critically ill patients. It is defined, according to DSM- IV (Diagnostic and Statistical Manual of Mental Disorders), as an acute and fluctuating disturbance of consciousness and cognition, has a high prevalence in intensive care units (ICU) and is associated with high mortality and longer hospital stay. In spite of its importance, for long time clinical studies on this topic have been compromised by the lack of a uniform terminology and specific criteria for delirium diagnosis. The thesis's objective is to study the psychometric properties of diagnostic tools for delirium, with emphasis in: 1) validation of the Portuguese versions of the three tools to diagnose delirium in critically ill patients: the Confusion Assessment Method for the Intensive Care Unit (CAM -ICU) the CAM-ICU Flowsheet and the Intensive Care Delirium Screening Checklist (ICDSC), 2) summarize by meta-analysis the accuracy of two of these tools (CAM -ICU and ICDSC), 3) to identify limitations to the use of CAM-ICU. In the validation study, 119 patients were evaluated and 38.6% were diagnosed with delirium by DSM-IV. The CAM-ICU and the CAM-ICU Flowsheet had the same accuracy, a sensitivity of 72.5% and a specificity of 96.2%, and the ICDSC had a sensitivity of 96,0% and a specificity of 72.4%. In the subgroup of patients using non-invasive ventilation the agreement between the CAM-ICU and the DSM-IV was 100%. In the meta-analysis, 09 studies evaluating the CAM-ICU (including 969 patients) and four studies evaluated the ICDSC (n = 361 patients) were included in the final analysis. The pooled sensitivity of the CAM-ICU was 80.0% (95% confidence interval (CI): 77.1 to 82.6%), and the pooled specificity was 95.9% (95% CI: 94.8-96.8%). The pooled sensitivity of ICDSC was 74 % (95% CI: 65.3 to 81.5 %), and the pooled specificity was 81.9% (95% CI: 76.7 to 86.4%). The diagnosis of delirium using the CAM-ICU is less frequent when patients with lower levels of sedation are evaluated. In conclusion, the diagnosis of delirium in critically ill patients can be performed with good accuracy using the CAM-ICU and ICDSC in Brazilian Portuguese language. A modified version of the CAM-ICU Flowsheet can also be used. In patients using noninvasive ventilatory support the diagnosis of delirium can be done using the CAM-ICU. Finally, in patients with lower levels of sedation the CAM-ICU seems to lose accuracy.

Key Word: *delirium*, CAM-ICU, ICDSC, CAM-ICU *Flowsheet*

LISTA DE ABREVIATURAS, NOTAÇÕES E SIGLAS

ACCP	*American College of Chest Physician*
APACHE II	*Acute Physiology And Chronic Health Evaluation*
AUC	*Area Under the Curve*
CAM-ICU	*Confusion Assessment Method for the Intensive Care Unit*
CID	Classificação Internacional de Doenças
CIWA-Ar	*Alcohol Withdrawal Assessment Scoring*
COPD	*Chronic Obstructive Pulmonary Disease*
CSF	*Cerebrospinal Fluid*
CT	*Computed Tomography*
CTD	*Cognitive Test for Delirium*
DDS	*Delirium Detection Score*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DSR-98-R	*Delirium Rating Scale-98-Revised*
EEG	Eletroencefalograma
GCS	*Glasgow Coma Score*
ICDSC	*Intensive Care Delirium Screening Checklist*
ISPOR	*International Society for Pharmacoeconomics and Outcome Research*
LPS	Lipopolissacarídeo
MEEM	Mini Exame do Estado Mental
MRI	*Magnetic Resonance Imaging*
NIV	*Non Invasive Ventilation*
NSE	*Neuronal Specific Enolase*
QUADAS	*Quality Assessment of Diagnostic Accuracy Studies*
SCCM	*Society of Critical Care Medicine*
SE	*Septic Encephalopathy*
ROC	*Receiver Operating Characteristic*
RASS	*Richmond Agitation Sedation Scale*
SAS	*Sedation-Agitation Scale*
SOFA	*Sequential Organ Failure Assessment*
UTI	Unidade de Terapia Intensiva

SUMÁRIO

1 APRESENTAÇÃO

A presente tese foi desenvolvida tendo o *delirium* como temática central.

O eixo da tese é formado pelos estudos publicados abordando a avaliação de instrumentos diagnósticos para o *delirium* particularmente nos pacientes internados em Unidade de Terapia Intensiva (UTI). Adicionalmente, outras publicações são apresentadas envolvendo *delirium*, mas que não estão restritas a questão da psicometria desta condição sindrômica.

A decisão de estudar, inicialmente, a validação e avaliação de acurácia das ferramentas diagnósticas de *delirium* é por considerar esta uma etapa precedente e essencial para realização de qualquer outro estudo com esta população. Com a identificação da melhor ferramenta e das suas limitações, entendemos ser possível avançar nesta linha de pesquisa.

A realização de parte do estudo requereu trabalho colaborativo e envolveu a parceria de pesquisadores de outros centros de diferentes estados do Brasil, e suas respectivas UTIs. Esta colaboração foi relevante por dois aspectos: primeiro, permitiu maior validação externa no trabalho que avaliou acurácia em língua portuguesa de ferramentas diagnóstica para o *delirium*; segundo, possibilitou nossa aproximação de outros grupos mais experientes nesta área.

Todo o processo de desenvolvimento desta Tese ocorreu em parceria com o serviço de Psiquiatria do Complexo Universitário Professor Edgar Santos, visto o tema *delirium* ser assunto de interesse tanto de psiquiatras quanto de intensivistas.

Esta linha de pesquisa gerou até o momento 10 artigos publicados (4 estudos originais e 6 cartas para o editor) sendo duas destas cartas com dados originais.

O primeiro artigo a ser apresentado foi um estudo original multicêntrico de validação, em português brasileiro, de três ferramentas diagnósticas para *delirium* no paciente grave. Em seguida, será apresentada uma revisão sistemática e meta análise destas ferramentas diagnósticas, além de uma revisão sistemática sobre métodos para estratificar *delirium*. Posteriormente, são apresentadas Cartas ao Editor que acrescentam dados originais sobre estratégias diagnóstica para *delirium* e que abordam aspectos referentes a prognóstico e tratamento do *delirium*. Por fim, é apresentada uma revisão sistemática sobre "Encefalopatia Séptica" cuja forma de apresentação pode ser um quadro clínico compatível com *delirium*.

Esta tese é apresentada na forma de artigo, portanto, após a fundamentação teórica, os manuscritos são apresentados em sua íntegra.

2 FUNDAMENTAÇÃO TEÓRICA

1. INTRODUÇÃO

O *delirium* pode ser definido como um estado confusional agudo caracterizado por flutuação dos sintomas, desatenção proeminente e alteração do nível de consciência que geralmente resulta de uma disfunção orgânica subjacente (APA, 2013).

Apesar de um dos primeiros transtornos mentais descritos, já com citações nos textos de Hipócrates, particularmente no livro *Epidemics* (LINDESAY, 1999), o *delirium* continua sendo um distúrbio pouco reconhecido, principalmente nos pacientes graves (SPRONK et al., 2009), de fisiopatologia incerta (CEREJEIRA et al., 2010) e tratamento não bem definido (BARR; PANDHARIPANDE, 2013).

Um dos pontos que possivelmente contribuíram para esta situação, além da falta de um substrato anatomopatológico, foi a mudança conceitual que ocorreu com o tempo, levando a uma inconsistência na caracterização dos pacientes (LIPTZIN, 1999). Após o reconhecimento do delirium como entidade diagnóstica, feito em 1980 com a publicação da terceira versão do *Diagnostic and Statistical Manual of the American Psychiatric Association* (DSM III) (TUCKER, 1999), diversos ajustes com o objetivo de refinar os critérios foram realizados até a publicação da versão mais recente, o DSM 5 (APA, 2013).

Esta inconsistência mencionada acima fica evidente observando os achados de um estudo que teve como objetivo comparar o diagnóstico de *delirium* segundo as diferentes versões do DSM (DSM III e DSM III-R) e com a classificação internacional de doenças (CID 10) (LIPTZIN et al., 1991). Dos 125 pacientes incluídos e com diagnóstico de *delirium* utilizando a DSM III, 26 não preenchiam critério pela DSM III-R e apenas 30 pacientes apresentaram *delirium* com os critérios da CID 10. Sugerindo que o DSM III era mais inclusivo e o CID 10 bastante restritivo.

Do ponto de vista de pesquisa clínica, falhas na identificação de algum transtorno, principalmente com a utilização de ferramentas que determinem altas taxas de falso positivo, alteram significativamente a população estudada comprometendo as análises sobre epidemiologia, fisiopatologia e tratamento (LIPTZIN, 1999).

Estes aspecto tem impacto ainda mais negativo quando não se utilizam avaliações estruturadas para identificação de pacientes com *delirium*. Nos pacientes graves, internados em Unidade de Terapia Intensiva (UTI), a avaliação clínica não sistematizada subdiagnostica *delirium* em cerca de 75% dos pacientes (SPRONK et

al., 2009).

No entanto, à despeito das imperfeições das ferramentas diagnósticos existentes e constante evolução dos que são considerados "padrão-ouro" (DSM 5), além da fragilidade de avalições clínicas não sistematizadas para o diagnóstico de *delirium*, a presença desta manifestação de disfunção cerebral está, repetidamente e de forma independente, associada com diversos desfechos negativos: aumento de mortalidade (PISANI et al., 2009), do tempo de internamento hospitalar (ELY; GAUTAM; et al., 2001), do custo (MILBRANDT et al., 2004) além de déficit cognitivo a longo prazo (PANDHARIPANDE et al., 2013).

2. DIAGNÓSTICO DE *DELIRIUM* NO PACIENTE GRAVE

A utilização do considerado "padrão-ouro", ou seja, os critérios do DSM 5, para diagnóstico de *delirium* em Unidade de Terapia Intensiva exige conhecimento de aspectos específicos de neurociência, além de um maior tempo para avaliação, o que inviabiliza o seu uso rotineiro. Em 2001, duas das mais utilizadas e validadas ferramentas para o diagnóstico de *delirium* em pacientes graves foram descritas: o *Intensive Care Delirium Screening Checklist* e o *Confusion Assessment method for the Intensive Care Unit* (BERGERON et al., 2001; ELY; MARGOLIN; et al., 2001).

2.1 *CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT* (CAM-ICU)

Diante da necessidade de uma ferramenta de avaliação de *delirium* acurada e que permitisse avaliação com rapidez por profissionais não psiquiatras treinados, Inouye e col. desenvolveram e validaram o *Confusion Assessment Method* (CAM) (INOUYE et al., 1990). Os principais objetivos no desenho do CAM foram atingir alta sensibilidade e alto valor preditivo negativo – uma vez que seria, primariamente, uma ferramenta de detecção de *delirium*, e não de confirmação diagnóstica. Alta especificidade também foi considerada, mas como objetivo secundário.

Com base em revisão de literatura e em consenso entre especialistas, foram adotados do DSM-III (versão corrente em 1990, ano de publicação do CAM) nove características clínicas entendidas como importantes no diagnóstico de *delirium*: 1. instalação aguda/curso flutuante, 2. desatenção, 3. pensamento desorganizado, 4.

alteração de nível de consciência, 5. desorientação, 6. déficit de memória, 7. perturbação perceptual, 8. alteração da atividade psicomotora e 9. distúrbio do ciclo sono-vigília. Destas, os características 1 e 2 foram definidas como condições necessárias para o diagnóstico de *delirium*. A necessidade da presença do característica 3 ou 4 foi baseada na opinião de especialistas e na prática clínica (ANEXO A). As cinco outras características não foram incluídas no algoritmo, pois não aumentaram a sensibilidade ou especificidade do CAM. Importante destacar que a resposta verbal oferecida pelo paciente era necessária para a avaliação dos itens atenção e organização do pensamento.

A validação do CAM foi feita através da comparação da avaliação por meio deste instrumento por geriatras com a avaliação do psiquiatra baseada nos critérios do DSM-III (INOUYE et al., 1990). As avaliações tiveram um intervalo máximo de 6 h entre elas. O estudo foi feito em dois hospitais, ambos com pacientes com idade superior ou igual a 65 anos. Em um dos locais, pacientes com suspeita de demência ou depressão foram incluídos no estudo para promover maior desafio no diagnóstico. Os pacientes que apresentaram diagnósticos discrepantes (1 falso negativo e 2 falsos positivos) possuíam demência subjacente severa, com desatenção e pensamento desorganizado em seu estado basal. As discrepâncias também podem ter ocorrido devido o fato do psiquiatra e do geriatra terem feito as avaliações em momentos diferentes; usarem diferentes fontes de informação; e o psiquiatra utilizar instrumentos mais detalhados para avaliação da cognição. O CAM mostrou-se, portanto, com alta sensibilidade (94 a 100%), alta especificidade (90 a 95%) e alta concordância inter observador. Devido ao seu alto valor preditivo negativo (90 a 100%), o CAM pode ser um teste útil na detecção de *delirium*, particularmente em grupos de pessoas que estão sob risco de desenvolvimento de *delirium* como pacientes idosos hospitalizados e pacientes cirúrgicos.

Especificamente nos pacientes graves internados em UTI, a utilização do CAM precisaria de ajustes pois uma parcela destes indivíduos não podem verbalizar por estarem utilizando tubo orotraqueal para auxílio à ventilação mecânica.

Este ponto ficou evidente ao avaliar um dos primeiros estudos que utilizaram a versão original do CAM em pacientes graves, no pós-operatório de cirurgia não cardíaca (MARCANTONIO et al., 1994). Por conta da necessidade de resposta verbal dos pacientes, aqueles que estavam em ventilação mecânica tiveram de ser excluídos.

Com a finalidade de resolver esta limitação do CAM, Ely et al. idealizaram uma

ferramenta que permitia utilizar métodos não verbais para a avaliação da atenção e do pensamento (ELY; MARGOLIN; et al., 2001). Esta ferramenta foi o *Confusion Assessment Method for the Intensive Care Unit* – CAM-ICU, e o métodos não verbal foi o Teste Cognitivo para *delirium* para pacientes em uso de ventilação mecânica (HART et al., 1997; HART et al., 1996).

No CAM-ICU (ANEXO B), além de utilizar o teste das figuras para avaliar a atenção dos pacientes, também fez-se uso das perguntas dicotômicas padronizadas utilizadas no Teste Cognitivo para *Delirium* como forma de avaliar a organização do pensamento. Dessa forma, não mais se necessitava de instrumentos como o Mini Exame do Estado Mental (MEEM) do paciente (FOLSTEIN; FOLSTEIN; MCHUGH, 1975).

Atualmente escalas de sedação, como a *Richmond Agitation-Sedation Scale* (RASS) e a *Riker Sedation-Agitation Scale* (SAS) (ANEXO C), têm se mostrado efetivas para avaliar de forma objetiva o nível de consciência do paciente. Estudo recente mostrou boa correlação de concordância entre elas (k = 0,93) e concluiu que ambas podem ser usadas conjuntamente com o CAM-ICU para o diagnóstico de *delirium* (KHAN et al., 2012).

No estudo original de validação do CAM-ICU, foram admitidos na UTI de junho a agosto de 1999, 86 pacientes (ELY; MARGOLIN; et al., 2001). Foram excluídos pacientes com história de demência severa, psicose ou doenças neurológicas. Houve também uma perda de oito pacientes que se recusaram a participar do estudo. Não foram incluídos na análise 18 pacientes que não puderam ser avaliados por falta de investigadores disponíveis. Dos 48 pacientes que foram computados para o estudo, cinco permaneceram comatosos e cinco não foram avaliados por especialista. A amostra final foi de 38 pacientes que foram submetidos ao CAM-ICU. O instrumento primário usado para avaliar a atenção foi o teste das figuras descrito por Hart e col. (1996 e 1997). O teste consiste em mostrar cinco figuras por três segundos ao paciente e pedir que ele se recorde. Imediatamente após esta fase, mostram-se dez figuras, das quais cinco são novas, e se pede para que ele identifique quais dessas já foram vistas.

Encontrou-se que o ponto de corte de oito ou mais respostas certas, a sensibilidade de 86% (IC 95%, 64 a 97%), especificidade de 77% (IC 95%, 50 a 93%) e uma razão de verossimilhança de 3,5 (IC 95%, 1,8 a 7,1). Os pacientes com déficit visual foram submetidos ao teste das letras descrito no Anexo D.

Dos 38 pacientes do estudo, 87% desenvolveram delirium em algum momento da sua estadia na UTI, com início médio no segundo dia (+/− 1,7 dia) e com uma duração média de 4,2 dias (+/− 1,7 dia). Houve três discordâncias entre enfermeiros e intensivistas (2 falsos positivos e 1 falso negativo), que podem ser explicadas por: a) a dose do sedativo ou analgésico foi administrada entre a avaliação do CAM-ICU e DSM-IV; b) foram decorridas três horas entre as avaliações.

Nos três subgrupos nos quais se pensava que haveria maior desafio (pacientes com mais de 65 anos, intubados ou com suspeita de demência), o CAM-ICU teve alta especificidade, sensibilidade e concordância interobservador. Assim, por essas razões e pelo fato de ser um teste de fácil aplicação e durar 2 a 3 minutos, o CAM-ICU se mostrou uma ferramenta útil à prática da UTI.

A escala CAM-ICU já foi traduzida para língua portuguesa (utilizando as recomendações da ISPOR (*International Society of Pharmacoeconomics and Outcome Research*) (WILD et al., 2005), por Salluh e Dal-Pizzol, porém a tradução literal deste instrumento é insuficiente para a utilização, pois é necessário um processo formal de validação utilizando o método padrão de referência (DSM).

2.2 CAM-ICU *FLOWSHEET*

O CAM-ICU *Flowsheet* surge a partir do CAM-ICU, com o propósito de reduzir o tempo de aplicação da ferramenta de detecção de delirium. A redução do tempo de aplicação se faz a partir da inversão da ordem das característica 3 (pensamento desorganizado) e 4 (alteração do nível de consciência) do CAM-ICU (Anexo E). A reorganização dessa sequência lógica se faz devido a evidências de que há maior prevalência de alteração de nível de consciência – apresentando maior taxa de especificidade – do que de pensamento desorganizado em pacientes com *delirium*. Dessa forma, a maioria dos pacientes pode ser diagnosticada com *delirium* ainda na característica 3 (se estiver alterada), sendo necessária a avaliação da característica 4 em apenas uma minoria dos pacientes.

Seu primeiro estudo de validação foi realizado em alemão envolvendo 54 pacientes de uma UTI cirúrgica, sendo aplicado por dois avaliadores e comparado ao padrão-ouro DSM-IV (GUENTHER et al., 2010). Nesse estudo, o CAM-ICU *Flowsheet* apresentou sensibilidade de 88 a 92% e especificidade de 100% para ambos os avaliadores. Demonstrou, também, que a característica 4 raramente era necessária

para o diagnóstico de *delirium* (em 25 pacientes), e em apenas 7 deles fez-se necessária a avaliação da característica 4 do CAM-ICU *Flowsheet* para o estabelecimento do diagnóstico.

2.3 *INTENSIVE CARE DELIRIUM SCREENING CHECKLIST (ICDSC)*

Em 2001, um grupo canadense utilizando o DSM IV como referência validou um *uma* lista de verificação para diagnóstico de *delirium* composto por oito itens: consciência, atenção, desorientação, presença de alucinações ou psicose, retardo ou agitação psicomotora, humor ou discurso inapropriados, distúrbios do sono e a flutuação dos sintomas (BERGERON et al., 2001).

Estes itens são classificados em "sim" ou "não", sendo "sim" correspondente a um ponto e "não" correspondente a zero. Caso um determinado item não pudesse ser avaliado, era pontuado como zero. Sendo uma escala que varia de 0 a 8, um paciente é considerado com *delirium* se obtiver uma pontuação maior ou igual a 4.

No estudo original, Bergeron et al. validaram o ICDSC em uma unidade de terapia intensiva mista, incluindo 93 pacientes (BERGERON et al., 2001). A prevalência de delirium encontrada foi de 16%, que é relativamente baixa em relação à literatura, mas cabe ressaltar que os doentes já admitidos em *delirium* não foram considerados na análise estatística. A sensibilidade foi alta (99%) para o diagnóstico de *delirium* com o ICDSC, no entanto a especificidade foi apenas razoável (64%), provavelmente por inclusão de pacientes com outras doenças neurológicas prévias, tais como demência ou diagnósticos psiquiátricos. A concordância entre os avaliadores foi alta (94%). Houve um número significativo de pacientes classificados como portadores de *delirium* pelo ICDSC e não confirmados pela avaliação psiquiátrica (19% da amostra).

3 OBJETIVOS

3.1 OBJETIVO GERAL

Validar instrumentos diagnósticos para *delirium* no paciente grave em unidade de terapia intensiva.

3.2 OBJETIVO ESPECÍFICO

- Validar para o idioma português brasileiro três instrumentos para o diagnóstico de *delirium* no paciente grave: CAM-ICU, CAM-ICU *Flowsheet* e o ICDSC
- Revisar a literatura, de forma sistemática, sobre os estudos de validação do CAM-ICU e do ICDSC.
- Realizar a síntese por meta-análise da acurácia de duas ferramentas diagnóstica de *delirium* no paciente grave (CAM-ICU e o ICDSC)
- Descrever a acurácia do CAM-ICU para o diagnóstico de *delirium* nos pacientes em uso de ventilação mecânica não invasiva.
- Revisar de forma sistemática as ferramentas utilizadas para estratificar *delirium* nos pacientes internados em UTI.

4 ARTIGOS PUBLICADOS

ARTIGO 1

Título: “Validade e confiabilidade das versões em português de três ferramentas para diagnóstico de *delirium* nos pacientes graves".

Autores: **Dimitri Gusmao-Flores**, Jorge IF Salluh, Felipe Dal-Pizzol, Cristiane Ritter, Cristiane D Tomasi, Marco ASD Lima, Lauro Reis Santana, Rita MP Lins, Patrícia P Lemos, Gisele V Serpa, Jenisson Oliveira, Ricardo A Chalhub, Melissa T Pitrowsky, Acioly L.T. Lacerda, Karestan C. Koenen, **Lucas C. Quarantini**

Jornal: *Clinics*

Ano de publicação: 2011 Fator de Impacto (no ano da publicação): 2,058

Número de citações: 12 (fonte: *web of knowledge*)

Objetivo: Os objetivos deste estudo foram comparar a sensibilidade e especificidade de três ferramentas de diagnóstico para *delirium* (o ICDSC, o CAM-ICU e o CAM-ICU *Flowsheet*), em uma população mista de pacientes graves e para validar o CAM-ICU em Português.

Métodos: O estudo foi realizado em quatro unidades de terapia intensiva no Brasil. Os pacientes foram avaliados para a presença de *delirium* por um psiquiatra ou neurologista utilizando os critério do DSM-IV. Os doentes foram posteriormente avaliados por um médico intensivista usando traduções em português destas três ferramentas.

Resultados: Cento e dezenove pacientes foram avaliados e 38,6% foram diagnosticadas com delirium pelos critérios do DSM-IV. O CAM-ICU teve uma sensibilidade de 72,5% e uma especificidade de 96,2 %, o CAM-ICU *Flowsheet* teve uma sensibilidade de 72,5% e uma especificidade de 96,2 %, e o ICDSC teve uma sensibilidade de 96,0% e uma especificidade de 72,4 %. Houve uma forte concordância entre o CAM-ICU e o CAM-ICU *Flowsheet* (coeficiente kappa = 0,96).

Conclusão: Todos os três instrumentos são ferramentas de diagnóstico eficazes em pacientes graves internados em UTI. Além disso, a versão em português brasileiro do CAM-ICU é válida e o instrumento confiável para a avaliação de *delirium* entre os pacientes graves.

CLINICS 2011;66(11):1917-1922

CLINICAL SCIENCE

The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients

Dimitri Gusmao-Flores,[I,VII] Jorge Ibrain Figueira Salluh,[II,III] Felipe Dal-Pizzol,[IV] Cristiane Ritter,[IV] Cristiane Damiani Tomasi,[IV] Marco Antônio Sales Dantas de Lima,[V] Lauro Reis Santana,[VI] Rita Márcia Pacheco Lins,[VI] Patrícia Pimenta Lemos,[VI] Gisele Vasconcelos Serpa,[VI] Jenisson Oliveira,[VI] Ricardo Ávila Chalhub,[VII] Melissa Tassano Pitrowsky,[II] Acioly L.T. Lacerda,[VIII] Karestan C. Koenen,[IX] Lucas C. Quarantini[VI,VII]

[I] Universidade Federal da Bahia, University Hospital Prof. Edgar Santos, Intensive Care Unit, Salvador, BA/Brazil. [II] D'Or Institute of Research and Education, Rio de Janeiro, RJ/Brazil. [III] Instituto Nacional do Câncer (INCA), Intensive Care Unit, Rio de Janeiro, RJ/Brazil. [IV] Universidade do Extremo Sul Catarinense, Laboratório de Fisiopatologia Experimental and Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Criciúma/SC, Brazil. [V] Instituto Nacional do Câncer (INCA), Neurosurgery Section, Rio de Janeiro, RJ/Brazil. [VI] University Hospital Prof. Edgar Santos, Universidade Federal da Bahia, Department of Psychiatry, Salvador, Bahia/Brazil. [VII] Universidade Federal da Bahia, Programa de Pós-graduação em Processos Interativos dos Órgãos e Sistemas, Instituto de Ciências da Saúde (ICS), Salvador, BA/Brazil. [VIII] Universidade Federal de São Paulo, Laboratório Interdisciplinar de Neurosciências Clínicas – LiNC, Department of Psychiatry, São Paulo/SP, Brazil. [IX] Harvard School of Public Health, Departments of Society, Human Development, and Health & Epidemiology.

OBJECTIVES: The objectives of this study are to compare the sensitivity and specificity of three diagnostic tools for delirium (the Intensive Care Delirium Screening Checklist, the Confusion Assessment Method for Intensive Care Units and the Confusion Assessment Method for Intensive Care Units Flowsheet) in a mixed population of critically ill patients, and to validate the Brazilian Portuguese Confusion Assessment Method for Intensive Care Units.

METHODS: The study was conducted in four intensive care units in Brazil. Patients were screened for delirium by a psychiatrist or neurologist using the Diagnostic and Statistical Manual of Mental Disorders. Patients were subsequently screened by an intensivist using Portuguese translations of the three tools.

RESULTS: One hundred and nineteen patients were evaluated and 38.6% were diagnosed with delirium by the reference rater. The Confusion Assessment Method for Intensive Care Units had a sensitivity of 72.5% and a specificity of 96.2%; the Confusion Assessment Method for Intensive Care Units Flowsheet had a sensitivity of 72.5% and a specificity of 96.2%; the Intensive Care Delirium Screening Checklist had a sensitivity of 96.0% and a specificity of 72.4%. There was strong agreement between the Confusion Assessment Method for Intensive Care Units and the Confusion Assessment Method for Intensive Care Units Flowsheet (kappa coefficient = 0.96).

CONCLUSION: All three instruments are effective diagnostic tools in critically ill intensive care unit patients. In addition, the Brazilian Portuguese version of the Confusion Assessment Method for Intensive Care Units is a valid and reliable instrument for the assessment of delirium among critically ill patients.

KEYWORDS: CAM-ICU; ICDSC; CAM-ICU Flowsheet; Critical care; Delirium.

Gusmao-Flores D, Salluh JIF, Dal-Pizzol F, Ritter C, Tomasi CD, Lima MASD, et al. The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients. Clinics. 2011;66(11):1917-1922.

Received for publication on May 19, 2011; **First review completed on** June 14, 2011; **Accepted for publication on** July 18, 2011

E-mail: dimitrigusmao@gmail.com

Tel.: 00 55 71 3245-2515

INTRODUCTION

Delirium is an acute and fluctuating disturbance of the consciousness that occurs in up to 80% of patients in intensive care units (ICU) and is associated with increased mortality, longer hospital stays, and long-term cognitive impairment.[1-4]

Despite its high prevalence and its negative impact on outcomes, the epidemiology and clinical management of delirium have long been compromised by the lack of uniform terminology and validated instruments for detecting and monitoring at-risk patients. Recently, an international effort culminated in a uniform definition and terminology for delirium.[5] The need for a specialized professional to evaluate patients according to the Diagnostic and Statistical Manual of

No potential conflict of interest was reported.

Mental Disorders (DSM-IV) and the dependence on clinical evaluations rather than validated diagnostic tools frequently leads to the underdiagnosis of delirium.[6,7] In 2001, an adapted Confusion Assessment Method (CAM) was validated in a cohort of critically ill patients.[8,9] Since then, the CAM-ICU and other tools, such as the Intensive Care Delirium Screening Checklist (ICDSC), have been tested in various ICU populations.[10] Compared to the delirium checklist (ICDSC), the CAM-ICU demonstrated good agreement with delirium detection for critical care surgical subjects.[11] In a large prospective evaluation, Pun et al. showed that the CAM-ICU demonstrated good compliance and excellent interrater reliability when implemented on a large scale by nursing staff.[12] Recently, the CAM-ICU Flowsheet derived from the CAM-ICU was developed to reduce the time required for patient assessment.[13]

Although a Brazilian national survey of ICU physicians showed that the Brazilian Portuguese version of the CAM-ICU is the most widely used diagnostic tool for delirium diagnosis in critically ill patients, no validation of this tool had been performed prior to the present study.[7]

The main objectives of the present study were to compare the sensitivity and specificity of three diagnostic tools for delirium (the ICDSC, the CAM-ICU and the CAM-ICU Flowsheet) in critically ill patients and to validate the CAM-ICU in Brazilian Portuguese.

MATERIALS AND METHODS

The study was conducted in four medical-surgical intensive care units (two general ICUs in university hospitals, one medical-surgical ICU in a tertiary hospital and one medical-surgical ICU in a comprehensive cancer center) in three cities in diverse regions of Brazil (Salvador/Bahia in the Northeast, Rio de Janeiro/RJ in the Southeast, and Criciúma/Santa Catarina in the South). Each institution recruited a different number of patients. Two units in Salvador (one general ICU in a university hospital and one in a tertiary hospital) enrolled a total of 30 patients, one center in Rio de Janeiro (medical-surgical ICU) recruited 25 patients, and one center in Criciúma (general ICU) recruited 64 patients.

Data collection was conducted between July and November 2010. The local ethics committees approved the study.

Non-consecutive patients over 18 years of age and hospitalized in the ICU for more than 48 hours were included. This convenience sample was obtained with two evaluations every week according to the availability of participating neurologists and psychiatrists to perform evaluations using DSM-IV criteria. All patients had to be arousable (with a score of greater than or equal to -3 according to the Richmond Agitation Sedation Scale) for the evaluation. To prevent the effects of withdrawal, patients were excluded if they had a history of alcohol or narcotic abuse. Those who were unable to communicate (i.e., because of hearing and/or visual impairment) or who did not understand Portuguese were also excluded.

Only one intensivist in each unit was responsible for the application of delirium scales. All intensivists who applied the CAM-ICU and CAM-ICU Flowsheet were trained and had expertise in the use of the tools. With the exception of one center that used two psychiatrists to simultaneously rate the patients, the DSM-IV evaluation was conducted by only one neurologist or psychiatrist.

The ICDSC and the CAM-ICU were previously translated into Portuguese using the recommendations of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR)[14] by Salluh and Dal-Pizzol (www.icudelirium.com). Thirty minutes after the intensivist's initial evaluation based on the CAM-ICU, a psychiatrist or neurologist applied the DSM-IV criteria as a reference standard. Subsequently, the patient was evaluated by the same intensivist using the CAM-ICU Flowsheet[15] and the ICDSC. The items evaluated by the ICDSC included the following: changes in the level of consciousness, inattention, disorientation, hallucinations, delusions, psychosis, psychomotor agitation or retardation, speech or inappropriate mood, sleep/wake cycle disturbance, and symptom fluctuations.[16] Patients were considered to have delirium if the ICDSC was equal to or greater than 4. Scores between 1 and 3 indicated subsyndromal delirium. The CAM-ICU Flowsheet was developed from the CAM-ICU and involves switching the original numbering of features 3 and 4, as most ICU patients with delirium are given positive scores in the order of the Flowsheet; switching the numbering allows the CAM-ICU Flowsheet to be completed with only three features and the fourth feature is only necessary in a minority of patients.

The intensivists who performed the CAM-ICU and ICDSC were kept unaware of the clinical diagnoses made by the psychiatrist or neurologist.

Patients diagnosed with delirium on any scale were classified into one of three groups: hypoactive, hyperactive, or mixed.[17] Delirium subtypes were classified into motoric subtype groupings according to the Richmond Agitation Sedation Scale (RASS). Patients were considered to have hypoactive delirium if their RASS ratings were between −3 and 0, and were considered to have hyperactive delirium if their RASS ratings were between 1 and 4; mixed-type delirium was defined as alternating between these two ranges.

Demographic and clinical characteristics were collected in addition to the APACHE II score. Patients were followed for up to 28 days, and the following outcomes were recorded: the ICU length of stay, the duration of mechanical ventilation, and 28-day mortality.

Statistical Analysis

Standard descriptive statistics were applied. Using 2x2 tables, the diagnostic values of the CAM-ICU, the CAM-ICU Flowsheet and the ICDSC were described with regard to sensitivity (true positive/[true-positive + false-negative]), specificity (true-negative/[false-positive + true-negative]), positive predictive value (true-positive/[true-positive + false-positive]), and negative predictive value (true-negative/[false-negative + true-negative]). The kappa test was used to verify the reproducibility between instruments, and the chi-square test was used to detect differences in the diagnoses based on the instruments. A receiver operating characteristic (ROC) curve was used to evaluate the performance of the ICDSC in classifying delirium.

Statistical analyses were performed with the statistical software package STATA (version 10.0) using a significance level of 5%.

RESULTS

The characteristics of the 119 patients who met the inclusion criteria are presented in Table 1.

Table 1 - The primary patient characteristics.

Gender	
Male	70 (58.3%)
Female	49 (42.7%)
Age (mean ± SD)	57±16
Apache II (mean ± SD)	15±6
Ventilation	
Spontaneous	50 (41.6%)
Mechanical	58 (49.1%)
Non-invasive	11 (9.3%)
Type of patient	
Medical	66 (55.4%)
Surgical	53 (44.6%)
Main reason for ICU admission	
Cardiovascular	27 (22.8%)
Sepsis	11 (9.3%)
Respiratory failure	17 (14%)
Neurologic	08 (6.7%)
Trauma	03 (2.5%)
Abdominal surgery	20 (16.9%)
Renal failure*	03 (2.5%)
Other	29 (24.5%)
Delirium diagnosed according to DSM-IV	46 (38.6%)
28-day mortality	20 (17%)

*chronic renal failure (requiring dialysis). DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

As demonstrated by their severity-of-illness scores (APACHE II scores of 15±6), the sample of patients was determined to be critically ill. The patients represented a mixed ICU population.

Using standard evaluation technique (DSM-IV), delirium was observed in 38.6% (46/119) of the patients. The types of delirium observed in these patients included hypoactive (69.5%), hyperactive (19.5%), and mixed (11%) delirium. Most patients (76.4%) were easily arousable at the time of their evaluation (RASS-0 or RASS-1).

The CAM-ICU identified 26.8% of the delirious patients and showed an overall sensitivity of 72.5% and specificity of 96.2%. The CAM-ICU Flowsheet showed similar accuracy. The ICDSC identified 25.2% of the patients as delirious and had a sensitivity of 96% and a specificity of 72.4% (Table 2).

The kappa coefficient was used to detect the correlation between the diagnostic tools. We observed a concordance of 98.32% with a kappa of 0.96 between the CAM-ICU Flowsheet and the CAM-ICU (Table 3). The McNemar test ($p = 1.00$) suggested that there were no significant differences between the two instruments.

To assess the correlation between the ICDSC and the CAM-ICU, it was necessary to exclude patients with a diagnosis of subsyndromal delirium that was diagnosed based only on the ICDSC (27 patients). We found a kappa of 0.59 (Table 4). As expected, similar findings were observed when comparing the CAM-ICU Flowsheet and the ICDSC.

The ICDSC classified delirium adequately when compared with the DSM-IV (area under the ROC curve = 0.91). The ROC curve is displayed in Figure 1. A diagnostic cutoff value of 5 or more for the ICDSC total score provided 67.5% sensitivity and 96.2% specificity for diagnosing delirium. With this cutoff, delirium was correctly classified in 86.5% of cases.

DISCUSSION

The aim of this study was to validate the Brazilian Portuguese version of the CAM-ICU according to DSM-IV criteria. The scale showed an overall sensitivity of 72.5% (95% CI: 55.9% – 84.9%) and specificity of 96.2% (95% CI: 88.5% – 99%). Moreover, the scale demonstrated high positive (90.6%; 95% CI: 73.8% – 97.5%) and negative (87.4%; 95% CI: 78.1% – 93.2%) predictive values, which suggests that very few cases of delirium remain unidentified when the scale is used systematically. Thus, our data demonstrate that the CAM-ICU is valid in Brazilian Portuguese. In addition, there is high accuracy for delirium diagnosis among the three tools (CAM-ICU, CAM-ICU Flowsheet, and ICDSC), and the CAM-ICU and CAM-ICU Flowsheet can be used interchangeably.

The development and validation of diagnostic tools is important to a thorough understanding of clinical disorders. Unfortunately, studies have demonstrated that a clinical impression is insufficient for delirium diagnosis.[18] Recently, a Dutch group observed a low sensitivity for delirium diagnosis with only clinical observation (45%),[19] making it necessary to develop and validate diagnostic tools. In 1990, using DSM-III-R criteria, Inouye[20] created and validated the Confusion Assessment Method (CAM), an algorithmic technique that uses only four of the DSM-III-R criteria for delirium. In the intensive care environment, the CAM has been adapted as the CAM-ICU because many patients are unable to speak after being intubated and ventilated.

The first validation study of the CAM-ICU included only 38 patients.[21] Two nurses and two intensivists compared the CAM-ICU method with the standard DSM-IV. In addition to a high specificity and sensitivity, an excellent interrater correlation was observed. The same investigators published a second study that included 111 patients who were on mechanical ventilation; in addition to confirming a high interrater correlation (kappa coefficient: 0.99, 95% CI: 0.92 – 0.99), they reported a sensitivity and specificity of approximately 100%.[22]

Our study differs in some respects from the studies by Ely et al. described above.[21,22] First, we did not observe as high a sensitivity for the CAM-ICU, which varied in Ely et al. from 93% to 100%. In our study, the sensitivity of the CAM-ICU was 72.5%. Although there is not a clear explanation, the difference is not likely related to the implementation of the CAM-ICU in Portuguese, as similar

Table 2 - The sensitivity and specificity of the CAM-ICU, CAM-ICU Flowsheet and ICDSC in 119 critically ill patients.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CAM-ICU	72.5 (55.9 – 84.9)	96.2 (88.5 – 99.0)	90.6 (73.8–97.5)	87.4 (78.1–93.2)
CAM-ICU Flowsheet	72.5 (55.9 – 84.9)	96.2 (88.5 – 99.0)	90.6 (73.8–97.5)	87.4 (78.1–93.2)
ICDSC	96.0 (81.5 – 99.8)	72.4 (58.6 – 83.0)	65.0 (49.7–78.2)	97.7 (86.2–99.9)

PPV: positive predictive value; NPV: negative predictive value.

Table 3 - A comparison of the CAM-ICU and the CAM-ICU Flowsheet.

		CAM-ICU		
		Positive	Negative	Total
CAM-ICU Flowsheet	Positive	31	1	32
	Negative	1	86	87
	Total	32	87	119

Kappa coefficient: 0.96.

results have been observed in other languages, including Spanish.[23] One possible explanation is a change in the sensitivity of the CAM-ICU when it is used in a cohort of mechanically ventilated and sedated patients. We observed that most patients had a RASS score of zero (60.5%), which may not only represent the lower degree of severity in our cohort but may also represent a current trend toward less sedation in ICU patients.[24] When comparing diagnostic instruments for delirium, Luetz et al. demonstrated that the sensitivity of the CAM-ICU is higher in patients with a RASS score of higher than 0.[25] However, a common feature of every published study is the high specificity of the CAM-ICU.

The CAM-ICU has been translated and validated in many languages [26,27] and has become the most frequently employed tool for diagnosing delirium in ICU patients.[7,28] A distinct advantage of this tool is that it does not require the patient to speak, which can be useful in patients who are on mechanical ventilation. In our study, we observed no difference in the accuracy of the CAM-ICU between the patients who were ventilated and those who were not. We also observed different scales in patients undergoing noninvasive ventilation (NIV). Eleven patients were observed with NIV (three of whom presented with delirium), and there was a 100% correlation among the CAM-ICU Flowsheet, the CAM-ICU and the ICDSC.

The CAM-ICU Flowsheet was developed to decrease the time required for the evaluation of patients with suspected delirium. However, to the best of our knowledge, only a single study has evaluated its performance.[29] In our study, we observed an excellent correlation between the CAM-ICU and the CAM-ICU Flowsheet, with a kappa of 0.96. Guenther et al. evaluated the CAM-ICU Flowsheet in German (with a duration of application that did not exceed 2 minutes) and noted a sensitivity of 88% to 92% and a specificity of 100% with close interobserver correlation.[30] In our study, the sensitivity was 72.5%, and the specificity was 96.2%. In some cases, less than one minute was necessary for completion of the instrument.

Table 4 - A Comparison of the CAM-ICU/CAM-ICU Flowsheet and the ICDSC.

		ICDSC		
		Positive	Negative	Total
CAM-ICU Flowsheet	Positive	30	0	30
CAM-ICU	Negative	19	43	62
	Total	49	43	92

Kappa coefficient: 0.59.

The ICDSC checklist is an eight-item screening tool (one point for each item) that is based on DSM criteria and applied to data that can be collected through medical records or on information obtained from a multidisciplinary team. Bergeron et al. observed a high sensitivity (99%) when a cutoff of 4 was used, but a moderate specificity was observed (64%).[16] Similarly, our study found a high sensitivity (96%) and a moderate specificity (72.4%). Other studies have reported a low sensitivity for the ICDSC (43%) compared with the standard method of diagnosis (DSM-IV).[31] In the mixed population of patients in this earlier study, the CAM-ICU showed a higher sensitivity (64%) but a lower specificity. More recently, the German version of the ICDSC was compared with the CAM-ICU in a population of surgical patients with a close correlation (kappa coefficient: 0.8; 95% CI: 0.78 – 0.84; $p<0.001$).[13] In our study, we observed a low correlation between the CAM-ICU and the ICDSC (kappa coefficient: 0.59). A change in the cutoff would likely change the correlation between these diagnostic tools. A cutoff of 5 correctly identified 86.5% of cases, whereas a cutoff of 4 correctly identified 80.6% of cases. For this analysis, it was necessary to exclude cases that were considered to be subsyndromal delirium (a cutoff of 3). Evaluating all 119 cases, we observed a high degree of accuracy with this tool and the DSM-IV, with an area under the ROC curve of 0.91. Because the CAM-ICU and CAM-ICU Flowsheet responses are dichotomous (yes or no), it was not possible to draw an ROC curve.

We found the CAM-ICU and the CAM-ICU Flowsheet to be similar and to be highly accurate for delirium diagnosis, which suggests that these are appropriate tools for developing a diagnostic profile. However, because of its high specificity and only moderate sensitivity, the ICDSC may be more useful in stratifying patients with delirium. Recently, Tomasi et al. suggested that the CAM-ICU is a better predictor of outcomes than the ICDSC, which is probably because of the high rate of false positives with the ICDSC.[32]

Our study has some notable limitations. First, as the study was performed in different regions, the tools evaluated (CAM-ICU, CAM-ICU Flowsheet, and ICDSC) were applied by different intensivists in different ICUs. Thus, we could not perform an interrater correlation with the tools that were applied. However, we believe that the evidence is strong enough to demonstrate a close correlation between the raters because the tool is simple and easily applied. We measured the performance of the scales against the DSM-IV, which is considered to be the standard technique for clinical assessment. Therefore, the application of the CAM-ICU and the CAM-ICU Flowsheet by the same investigator does not imply an evaluation bias.

Our study also has several strengths. Not only was our study the first to validate the CAM-ICU and the CAM-ICU Flowsheet for Brazilian Portuguese, but it was performed as a multicenter evaluation in three different and representative regions of Brazil. The study evaluated a mixed population of critically ill patients, including ventilated and non-ventilated patients. These methodological characteristics increase the external validity of the results.

The present data demonstrate that the CAM-ICU and the ICDSC are valid tools that can be used in Brazilian Portuguese with a high degree of accuracy. The CAM-ICU Flowsheet has an excellent agreement with the CAM-ICU (kappa coefficient = 0.96) and can be employed as a fast,

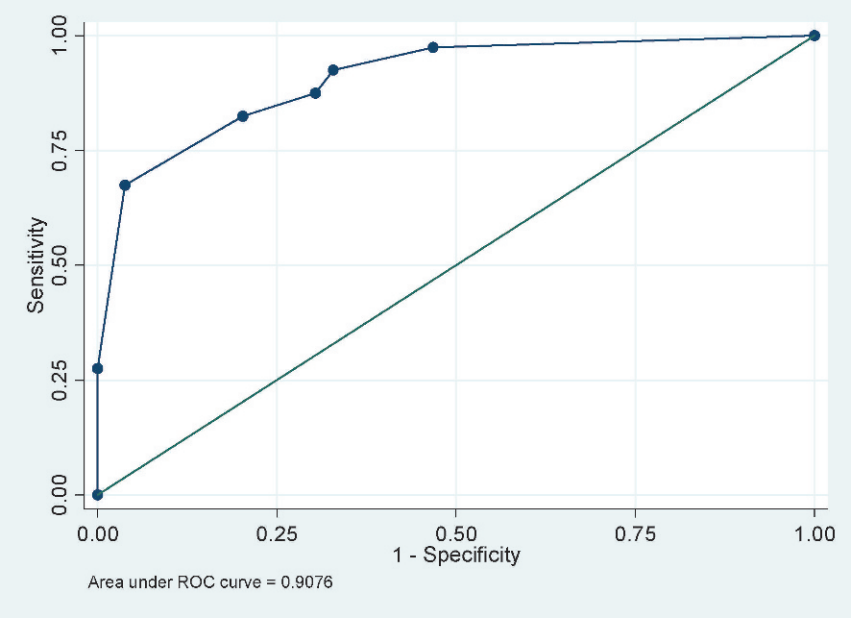


Figure 1 - Receiver operating characteristic curve based on the total score (0-8) obtained on the ICDSC.

practical and reliable tool. Finally, the ICDSC has a high sensitivity for diagnosing delirium but a moderate specificity and a poor correlation with the CAM-ICU and CAM-ICU Flowsheet.

ACKNOWLEDGMENTS

This project was partially supported by the National Council of Technological and Scientific Development (CNPq): [474869/2010-5] - Edital Universal MCT/CNPq 14/2010.

AUTHOR CONTRIBUTIONS

Gusmão-Flores D and Salluh JIF designed the study and wrote the protocol, applied the scales and performed the data collection, undertook the statistical analysis, and contributed to the writing of the first draft of the manuscript. Pitrowsky MT applied the scales, performed the data collection, and contributed to the writing of the first draft of the manuscript. dal-Pizzol F, Ritter C, Tomasi CD designed the study and wrote the protocol, applied the scales and performed the data collection. Lima MASD, Santana LR, Lins RMP, Lemos PP, Serpa G and Oliveira J applied the scales, performed the data collection and contributed to the writing of the first draft of the manuscript. Quarantini LC designed the study and wrote the protocol, contributed to writing the first draft of the manuscript, applied the scales and performed the data collection. Chalhub RA applied the scales and performed the data collection. Lacerda ALT and Koenen KC contributed to the writing of the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

REFERENCES

1. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med. 2004;32:2254-59, doi: 10.1097/01.CCM.0000110878.49476.42.
2. Lima DP, Ochiai ME, Lima AB, Curiati JA, Farfel JM, Filho WJ. Delirium in hospitalized elderly patients and post-discharge mortality. Clinics. 2010;65:251-5, doi: 10.1590/S1807-59322010000300003.
3. Salluh JI, Soares M, Teles JM, Ceraso D, Raimondi N, Nava VS, et al. The DECCA (Delirium Epidemiology in Critical Care) Study Group. Delirium epidemiology in critical care (DECCA): an international study. Crit Care. 2010;14:R210.
4. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38:1513-20, doi: 10.1097/CCM.0b013e3181e47be1.
5. Morandi A, Pandharipande P, Trabucchi M, Rozzini R, Mistraletti G, Trompeo AC, et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. Intensive Care Med. 2008;34:1907-15, doi: 10.1007/s00134-008-1177-6.
6. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc. 2003;51:591-8, doi: 10.1034/j.1600-0579.2003.00201.x.
7. Salluh JI, Dal-Pizzol F, Mello PV, Friedman G, Silva E, Teles JM, et al. Brazilian Research in Intensive Care Network. Delirium recognition and sedation practices in critically ill patients: a survey on the attitudes of 1015 Brazilian critical care physicians. J Crit Care. 2009;24:556-62, doi: 10.1016/j.jcrc.2009.04.004.
8. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). Crit Care Med. 2001;29:1370-9, doi: 10.1097/00003246-200107000-00012.
9. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion method assessment for the intensive care unit (CAM-ICU). JAMA. 2001;286:2703-10, doi: 10.1001/jama.286.21.2703.
10. van Eijk MM, van Marum RJ, Klijn IA, de Wit N, Kesecioglu J, Slooter AJ. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med. 2009;37:1881-5, doi: 10.1097/CCM.0b013e3181a00118.
11. Plaschke K, von Haken R, Scholz M, Engelhardt R, Brobeil A, Martin E, et al. Comparison of the confusion assessment method for the intensive care unit (CAM-ICU) with the Intensive Care Delirium Screening Checklist (ICDSC) for delirium in critical care patients gives high agreement rate(s). Intensive Care Med. 2008;34:431-6, doi: 10.1007/s00134-007-0920-8.
12. Pun BT, Gordon SM, Peterson JF, Shintani AK, Jackson JC, Foss J, et al. Large-scale implementation of sedation and delirium monitoring in the intensive care unit: a report from two medical centers. Crit Care Med. 2005;33:199-205, doi: 10.1097/01.CCM.0000166867.78320.AC.
13. Guenther U, Popp J, Koecher L, Muders T, Wrigge H, Ely EW, et al. Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients. J Crit Care. 2010;25:144-51, doi: 10.1016/j.jcrc.2009.08.005.
14. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for patient reported outcomes (PRO) measures: report of the ISPOR taskforce for translation and cultural adaptation. Value Health. 2005;8:94–104, doi: 10.1111/j.1524-4733.2005.04054.x.
15. Amirfarzan H, Pun BT, Ely EW. CAM-ICU Flowchart CAM-ICU. www.icudelirium.org.
16. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27:859–64, doi: 10.1007/s001340100909.

17. Peterson JF, Pun BT, Dittus RS, Thomason JW, Jackson JC, Shintani AK, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. J Am Geriatr Soc. 2006;54:479-84, doi: 10.1111/j.1532-5415.2005.00621.x.
18. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35:1276-80, doi: 10.1007/s00134-009-1466-8.
19. van Eck van der Sluijs JF, Oldenbeuving AW, Roks G, Tilanus JJ. Delirium on intensive care frequently missed: clinical impression alone is not enough. Ned Tijdschr Geneeskd. 2010;154:A1290.
20. Inouye S, van Dyck C, Alessi CA, Balkin S, Siegal A, Horwitz R. Clarifying confusion: Th Confussion Assesment Method. Ann Inter Medicine. 1990;113:941-8.
21. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29:1370-9, doi: 10.1097/00003246-200107000-00012.
22. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286:2703-10, doi: 10.1001/jama.286.21.2703.
23. Tobar E, Romero C, Galleguillos T, Fuentes P, Cornejo R, Lira MT, et al. Confusion Assessment Method for diagnosing delirium in ICU patients (CAM-ICU): cultural adaptation and validation of the Spanish version. Med Intensiva. 2010;34:4-13, doi: 10.1016/j.medin.2009.04.003.
24. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375:475-80, doi: 10.1016/S0140-6736(09)62072-9.
25. Luetz A, Heymann A, Radtke FM, Chenitir C, Neuhaus U, Nachtigall I, et al. Different assessment tools for intensive care unit delirium: which score to use? Crit Care Med. 2010;38:409-18, doi: 10.1097/CCM.0b013e3181cabb42.
26. Toro AC, Escobar LM, Franco JG, Díaz-Gómez JL, Muñoz JF, Molina F, et al. Spanish version of the CAM-ICU (Confusion Assessment Method for the Intensive Care Unit). Pilot study of validation. Med Intensiva. 2010;34:14-21.
27. Chuang WL, Lin CH, Hsu WC, Ting YJ, Lin KC, Ma SC. Evaluation of the reliability and validity of the Chinese version of the confusion assessment method for the intensive care unit. Hu Li Za Zhi. 2007;54:45-52.
28. Patel RP, Gambrell M, Speroff T, Scott TA, Pun BT, Okahashi J, et al. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. Crit Care Med. 2009;37:825-32, doi: 10.1097/CCM.0b013e31819b8608.
29. Vreeswijk R, Toornvliet A, Honing MLH, Bakker K, de Man T, Daas G, et al. Validation of the Dutch version of the Confusion Assessment Method (CAM-ICU) for delirium screening in the Intensive Care Unit. Neth J Crit Care. 2009;13:73-8.
30. Guenther U, Popp J, Koecher L, Muders T, Wrigge H, Ely EW, et al. Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients. J Crit Care. 2010;25:144-51, doi: 10.1016/j.jcrc.2009.08.005.
31. van Eijk MM, van Marum RJ, Klijn IA, de Wit N, Kesecioglu J, Slooter AJ. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med. 2009;37:1881-5, doi: 10.1097/CCM.0b013e3181a00118.
32. Tomasi CD, Grandi C, Salluh J, Soares M, Giombelli VR, Cascaes S, et al. Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes. J Crit Care. 2011;Jul 5. [Epub ahead of print].

ARTIGO 2

Título: “O CAM-ICU e o ICDSC para o diagnóstico de delirium: revisão sistemática e meta análise dos estudos clínicos".

Autores: **Dimitri Gusmao-Flores**, Jorge I Salluh, Ricardo A Chalhub, **Lucas C Quarantini**

Jornal: *Critical Care* Fator de Impacto: 4,72

Ano de publicação: 2012

Número de citações: 7 (fonte: *web of knowledge*)

Estudo premiado pela BioMed Central. Primeiro colocado: ***Clinical Medicine Category Research Award 2012***

Introdução: O objetivo deste estudo é avaliar a evidência atual sobre a precisão CAM-ICU e do ICDSC para o diagnóstico de delirium em pacientes criticamente enfermos.

Métodos: A revisão sistemática foi realizada para identificar artigos sobre a avaliação do CAM-ICU e do ICDSC em pacientes de UTI. Foi realizada busca de dados no MEDLINE, SciELO, CINAHL e EMBASE para artigos publicados no idioma Inglês, envolvendo populações adultas e que compararam essas ferramentas de diagnóstico com o padrão-ouro, os critérios do DSM-IV. Os resultados foram resumidos por meta-análise. A escala QUADAS foi usado para avaliar a qualidade dos estudos.

Resultados: Nove estudos avaliando o CAM-ICU (incluindo 969 pacientes) e quatro que avaliaram o ICDSC (n= 361 pacientes) foram incluídos na análise final. A sensibilidade combinada do CAM-ICU foi de 80,0% (95% intervalo de confiança (IC): 77,1-82,6%), e a especificidade combinada foi de 95,9% (95 % IC: 94,8-96,8 %). A razão de chances de diagnóstico foi 103,2 (95% IC: 39,6 - 268,8). A área sob a curva ROC (AUC) foi de 0,97. A sensibilidade combinada do ICDSC foi de 74 % (IC de 95%: 65,3-81,5%), e a especificidade combinada foi de 81,9% (IC 95%: 76,7-86,4%). A razão de chances de diagnóstico foi de 21,5 (IC 95%: 8,51-54,4). A AUC foi de 0,89.

Conclusões: O CAM-ICU é uma excelente ferramenta de diagnóstico em pacientes graves em UTI, enquanto que o ICDSC tem moderada sensibilidade e boa especificidade. Os dados disponíveis sugerem que tanto o CAM-ICU e o ICDSC podem ser usado como uma ferramenta de triagem para o diagnóstico de *delirium* em pacientes criticamente enfermos.

Gusmao-Flores et al. Critical Care 2012, 16:R115
http://ccforum.com/content/16/4/R115

CRITICAL CARE

RESEARCH Open Access

The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies

Dimitri Gusmao-Flores[1,2*], Jorge Ibrain Figueira Salluh[3,4], Ricardo Ávila Chalhub[2] and Lucas C Quarantini[2,5,6]

Abstract

Introduction: Delirium is a frequent form of acute brain dysfunction in critically ill patients, and several detection tools for it have been developed for use in the Intensive Care Unit (ICU). The objective of this study is to evaluate the current evidence on the accuracy of the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) for the diagnosis of delirium in critically ill patients.

Methods: A systematic review was conducted to identify articles on the evaluation of the CAM-ICU and the ICDSC in ICU patients. A MEDLINE, SciELO, CINAHL and EMBASE databases search was performed for articles published in the English language, involving adult populations and comparing these diagnostic tools with the gold standard, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Results were summarized by meta-analysis. The QUADAS scale was used to assess the quality of the studies.

Results: Nine studies evaluating the CAM-ICU (including 969 patients) and four evaluating the ICDSC (n = 361 patients) were included in the final analysis. The pooled sensitivity of the CAM-ICU was 80.0% (95% confidence interval (CI): 77.1 to 82.6%), and the pooled specificity was 95.9% (95% CI: 94.8 to 96.8%). The diagnostic odds ratio was 103.2 (95% CI: 39.6 to 268.8). The pooled area under the summary receiver operating characteristic curve (AUC) was 0.97. The pooled sensitivity of the ICDSC was 74% (95% CI: 65.3 to 81.5%), and the pooled specificity was 81.9% (95% CI: 76.7 to 86.4%). The diagnostic odds ratio was 21.5 (95% CI: 8.51 to 54.4). The AUC was 0.89.

Conclusions: The CAM-ICU is an excellent diagnostic tool in critically ill ICU patients, whereas the ICDSC has moderate sensitivity and good specificity. The available data suggest that both CAM-ICU and the ICDSC can be used as a screening tool for the diagnosis of delirium in critically ill patients.

Introduction

Delirium is a prevalent form of acute brain dysfunction that occurs in critically ill patients [1]. Despite its elevated frequency and association with increased morbidity and mortality [2], delirium remains an underdiagnosed condition in the intensive care unit (ICU), and a standard clinical evaluation does not have an adequate accuracy for the diagnosis [3]. Several methods have been developed and validated to diagnose delirium in ICU patients [4], but the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most frequently employed tools for this purpose [5].

Since the validation of the CAM-ICU and the ICDSC, these tools have been translated into and validated in many languages [6-12] and have been widely employed in clinical practice [5,13]. However, studies show different results regarding their accuracy for the diagnosis of

* Correspondence: dimitrigusmao@gmail.com
[1]Intensive Care Unit, University Hospital Prof. Edgar Santos, Universidade Federal da Bahia, Rua Augusto Viana, Salvador, 40110-910, Brazil
Full list of author information is available at the end of the article

delirium, possibly affecting the reported incidence of this clinical condition and the implementation of prompt preventive and therapeutic measures [14].

The aim of this study was to perform a systematic review and use a meta-analytic approach to pool previously published studies presenting data on the CAM-ICU and the ICDSC for the diagnosis of delirium in the critically ill.

Materials and methods

A two-stage systematic review process was performed. First, we performed a systematic MEDLINE, SciELO, CINAHL and EMBASE databases search using the keywords "CAM-ICU" or "Confusion Assessment Methods for the Intensive Care Unit" (Figure 1) and "ICDSC" or "Intensive Care Delirium Screening Checklist" (Figure 2) from January 2001 through 18 November 2011. However,

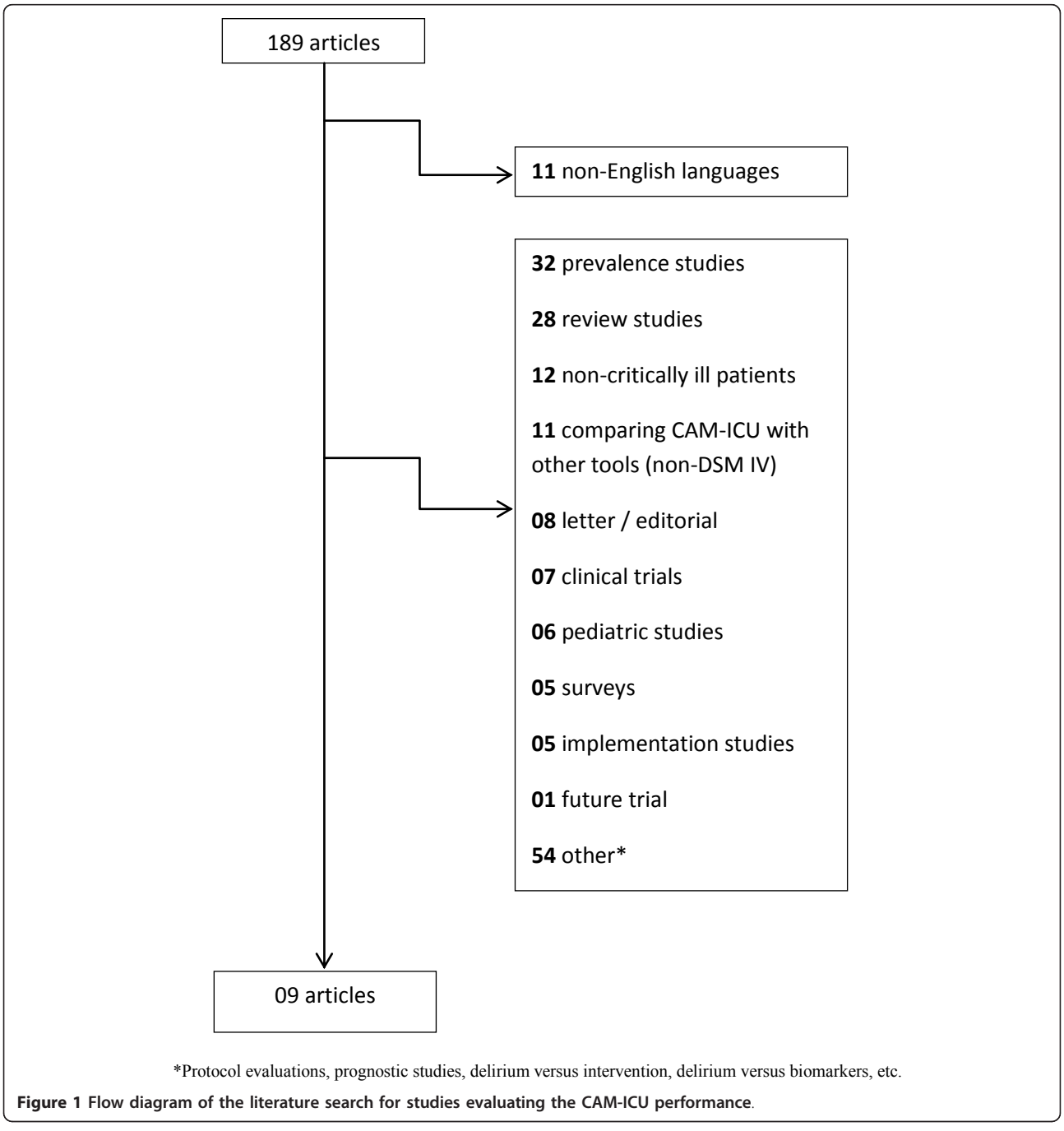


Figure 1 Flow diagram of the literature search for studies evaluating the CAM-ICU performance.

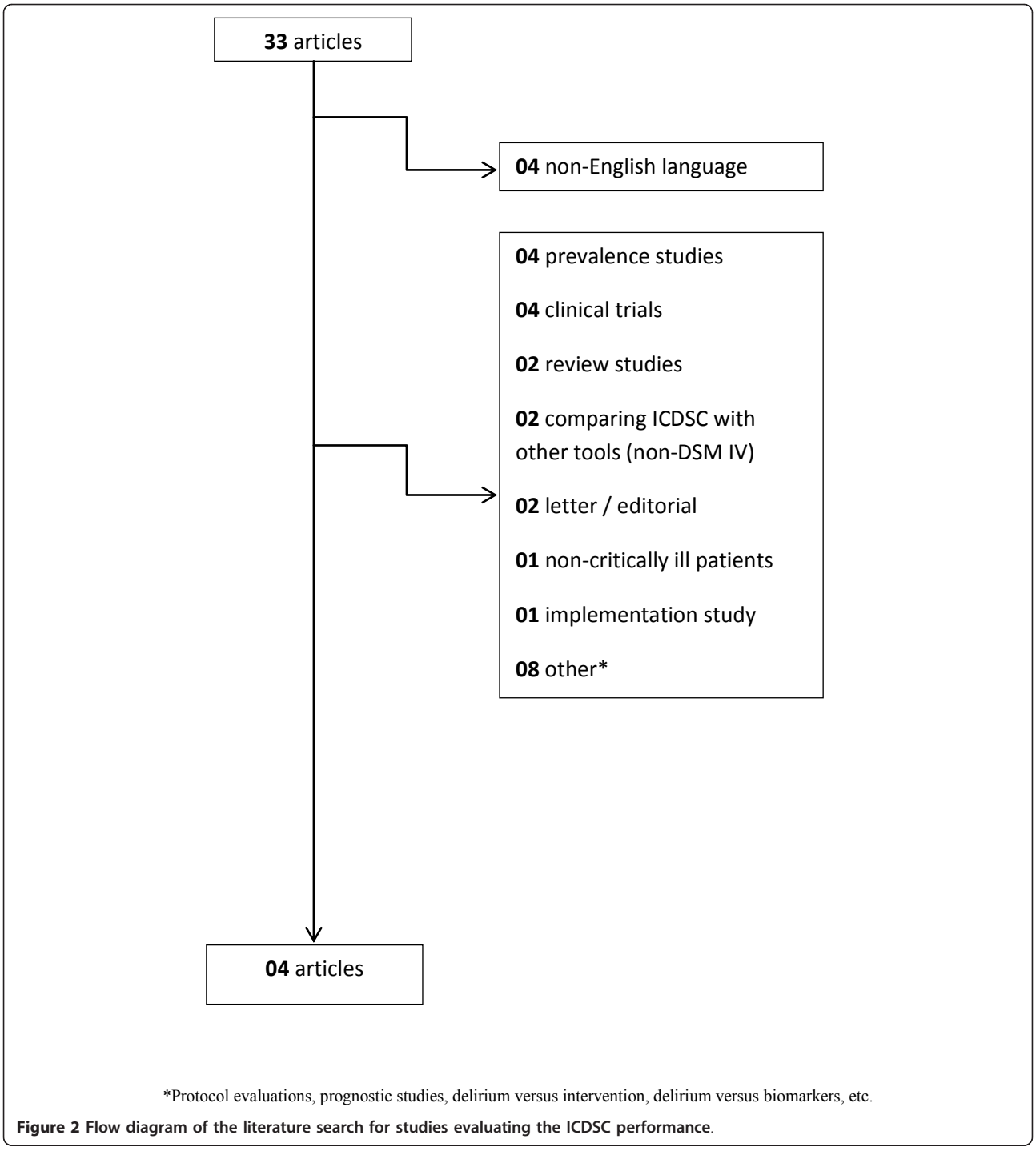


Figure 2 Flow diagram of the literature search for studies evaluating the ICDSC performance.

the automatic alert system of MEDLINE was used to identify studies published during the process of the analysis of the results.

The aim of the review was to identify full-text, English-language publications that evaluated the performance of the CAM-ICU and the ICDSC in critically ill patients. Only articles comparing these diagnostic tools with the gold standard, the DSM-IV criteria, were included.

Original peer-reviewed studies involving the adult population were selected and analyzed. We excluded case reports, review articles, studies that have used these tools to evaluate the correlation between delirium and morbidity or mortality, or compare it with other tools

(those not based on DSM-IV criteria). All letters and comments were analyzed for information on validation or implementation of these tools. Studies that assessed children were initially excluded, but further analysis was performed and data including this distinct population were attached in the Additional file 1, Figures S1 and S2. In stage two, eligibility assessment (articles comparing the CAM-ICU or the ICDSC with DSM-IV criteria) and data abstraction were performed independently in an unblinded, standardized manner by two reviewers (DGF and RAC). Discrepancies in the search were resolved by consensus among the authors.

Subsequently, the identified articles were screened electronically. For each eligible article, using a predefined categorization system, information was extracted on the authors, journal, year of publication, study design, inclusion period, number of patients, number of observations, patient population, total number of patients diagnosed with delirium, APACHE II score and sensitivity and specificity of the CAM-ICU and the ICDSC. Moreover, when available, we extracted information about accuracy of these tools in different subgroups of patients analyzed in each paper.

In studies that involved more than one assessor (nurses and/or physicians) in the process of the validation of the tools, we selected the highest sensitivity and included it in the meta-analysis (data from all evaluators are attached in Additional file 2, Table S1). In addition, several studies evaluated the same patient at multiple time-points with different diagnostic tools. In this case, the accuracy of the tool was calculated based on the total number of assessments and not on the number of patients.

The QUADAS scale (first version) was employed to assess the quality of the studies [15]. This tool was developed specifically to assess the quality of studies of diagnostic accuracy included in systematic reviews. Fourteen items were evaluated and, accordingly, each included study was scored from 0 to 14, with a high value indicating a better quality of study. Finally, results were summarized by meta-analysis.

Statistical analysis

All of the tests were performed using the package STATA v. 9.0 and MetaDiSC® (Unit of Clinical Biostatistics Team of the Ramón y Cajal Hospital, Madrid, Spain) [16] adopting a significance level of 0.05.

The MetaDiSC® software was used to calculate the pooled values of sensitivity, specificity and diagnostic odds ratios of each of the tools. The heterogeneity of the studies was checked by the chi-square test ($P \leq 0.05$). The summary receiver operating curve characteristic (SROC) was also drawn. In the SROC graph, each point comes from a different study. The area under the curve (AUC) reflects the overall performance of the test. The heterogeneity between studies was analyzed with chi-square statistics.

Results

Nine studies evaluating the CAM-ICU and four evaluating the ICDSC were included in the final analysis. Of these, two studies validated both tools simultaneously [9,17]. The main characteristics of the studies are depicted in Tables 1 and 2.

A total of 969 patients were included for the evaluation of the CAM-ICU in the nine studies identified, whereas 391 patients were evaluated in the four validation studies of the ICDSC. All of the studies were conducted in the ICU and, except for the study of van Eijk *et al.* [14], all of the studies used a methodology for the validation of diagnostic tools. The study by van Eijk *et al.* [14] evaluated the CAM-ICU in daily practice.

Studies assessing the CAM-ICU

Of the nine studies evaluating the CAM-ICU, only two were multicenter evaluations [9,14]. A mixed population of critically ill patients was evaluated. Two studies exclusively evaluated patients on mechanical ventilation [7,18], while the other studies evaluated ventilated and non-ventilated patients [4,9,11,14,17,19], and one study exclusively evaluated stroke patients regardless of the ventilatory status [10].

Only the first validation study of the CAM-ICU [19] did not use the sedation scale RASS (Richmond Agitation Sedation Scale), so feature 4 of the CAM-ICU was considered to be positive when the patient presented with an altered level of consciousness (other than alert). In the studies using RASS, patients were excluded if RASS < -3. Only the study by Luetz *et al.* excluded patients with RASS ≤-3 [4].

The accuracy of the CAM-ICU was evaluated in subgroups of patients with RASS < 0 in two studies [4,10]. In a population of patients with stroke, the sensitivity of the CAM-ICU was higher in this subgroup (85% versus 78.9%) [10], and a similar finding was observed in surgical patients (85% versus 78.8%) [4].

The median quality (QUADAS) score was 13 (range 13 to 14). Studies that received a score of 13 were not scored on item 4 of this tool [7,11,14,18]; that is, they did not mention or spent a long time between the application of the CAM-ICU and DSM-IV criteria.

Five studies classified the subtypes of delirium (hypoactive, hyperactive and mixed) [7,9,10,14,17]. In two studies, the accuracy of the CAM-ICU was evaluated in these patient subgroups [14,17], and a lower sensitivity was observed in hypoactive delirium. van Eijk *et al.* showed an overall sensitivity of the CAM-ICU of 64.3% and only of 57% in patients with hypoactive

Table 1 Main characteristics of the included studies (evaluation of the CAM-ICU)

Author	N	Year	ICU	Language	Delirium N (%)	Sensitivity	Specificity	APACHE II	QUADAS
Ely [19]	38	2001	Medical Coronary	English	33 (87)[1]	100 (95.2 to 100)	100 (79.4 to 100)	17.1 ± 8.7#	13
Ely [18]	96	2001	Medical Coronary	English	(25.2)[2]	100 (95.4 to 100)	88.8 (83.8 to 92.7)	23 (18 to 29)*	13
Lin [7]	102	2004	Medical	Chinese	22 (22.4)	95.5 (77.2 to 99.9)	97.5 (91.3 to 99.7)	NR	13
van Eijk [17]	126	2009	General	English Dutch	43 (34)	64.3 (48.0 to 78.4)	88.8 (79.0 to 94.1)	20. 9 ± 7.5#	14
Luetz [4]	156	2010	Surgical	German	63 (40)	78.8 (72.0 to 84.5)	97.1 (94.9 to 98.5)	16 (13 to 19)*	14
Heo [11]	22	2011	Medical	Korean	16 (72.7)	89.5 (78.5 to 98.0)	71.4 (47.8 to 88.7)	25.5 (9 to 39)*	13
van Eijk [14]	181	2011	Medical Surgical	English Dutch	80 (28.3)	46.7 (35.1 to 58.6)	98.1 (93.4 to 99.8)	18.6 ± 7.5#	13
Gusmao-Flores [9]	119	2011	Medical Surgical	Portuguese	46 (38.6)	72.5 (56.1 to 85.4)	96.2 (89.3 to 99.2)	15 ± 6#	14
Mitasova [10]	129	2012	Stroke Unit	Czech	55 (42.6)[1]	78.9 (73.7 to 83.5)	98.3 (97.1 to 99.1)	NR	14

[1]During hospitalization, 2% of daily evaluations, NR, not reported, # mean, * median.

delirium [17]. The same group of researchers, in a multicenter study, showed only 31% sensitivity by the CAM-ICU in these subtypes of delirium, whereas the global sensitivity they obtained was 46.7% [14].

No studies compared the accuracy of the CAM-ICU in ventilated versus non-ventilated patients. However, Ely *et al.* [19] evaluated a subgroup of patients undergoing mechanical ventilation (n = 22 patients) and found a slight increase in the sensitivity (100%) and a slight decrease in the specificity (88%) compared with the overall sample.

Gusmao-Flores *et al.* described 11 evaluations in patients with noninvasive ventilation [9]. These authors reported excellent accuracy for the CAM-ICU: 100% for both sensitivity and specificity.

Studies assessing the ICDSC

Four studies with mixed populations evaluated the ICDSC, only one of which was a multicenter study [9].

All studies that evaluated the ICDSC used the tool as the original study [20]. The ICDSC was rated by the evaluator based on the patient's reports of the previous 24 hours, using a cutoff of 4. Due to these features, the quality (QUADAS) score was 13 for all of the studies.

Two studies suggest an improved accuracy with different cutoffs [9,21]. George *et al.* showed an optimal threshold for screening with a score of 3 [21]. Compared with a cutoff of 4, the sensitivity increased from 75% to 90%; however, the specificity decreased from 74.3% to 61.5%. After excluding cases that were considered to be subsyndromal delirium (a cutoff of 3), Gusmao-Flores *et al.* suggested a better specificity with a cutoff of 5, which identified correctly 86.5% of cases [9].

Only one study evaluated the accuracy of the ICDSC in different subtypes of delirium [17] and this tool presented a lower sensitivity in hypoactive delirium (42.9% versus 32%).

Meta-analysis of studies assessing the CAM-ICU

The pooled values of sensitivity and specificity for the CAM-ICU were 80.0% (95% confidence intervals (CI): 77.1 to 82.6%) and 95.9% (95% CI: 94.8 to 96.8%), respectively (Figure 3). The area under the SROC was 0.97 (Figure 4), suggesting excellent accuracy.

Meta-analysis of studies assessing the ICDSC

The pooled values of sensitivity and specificity for the ICDSC were 74% (95% CI: 65.3 to 81.5%) and 81.9% (95% CI: 76.7 to 86.4%), respectively (Figure 5). The area under the SROC was 0.89 (Figure 6), suggesting good accuracy.

Table 2 Main characteristics of the included studies (evaluation of the ICDSC)

Author	N	Year	ICU	Language	Delirium N (%)	Sensitivity	Specificity	APACHE II	QUADAS
Bergeron [20]	93	2001	Medical Surgical	English	15 (16%)	93.3 (68.1 to 99.8)	80.8 (70.3 to 80.8)	14 (8 to 21)*	13
Van Eijk [17]	126	2009	Medical Surgical	English Dutch	43 (34)	42.9 (27.7 to 59.0)	94.7 (87.1 to 98.5)	20.9 ± 7.5#	13
George [21]	59	2011	Medical Cardiac	English	20 (33.9)	75.0 (50.9 to 91.3)	74.4 (57.9 to 87.0)	NR	13
Gusmao-Flores [9]	119	2011	Medical Surgical	Portuguese	46 (38.6)	95.7 (85.2 to 99.5)	72.6 (60.9 to 82.4)	15 ± 6#	13

NR: not reported, # mean, * median

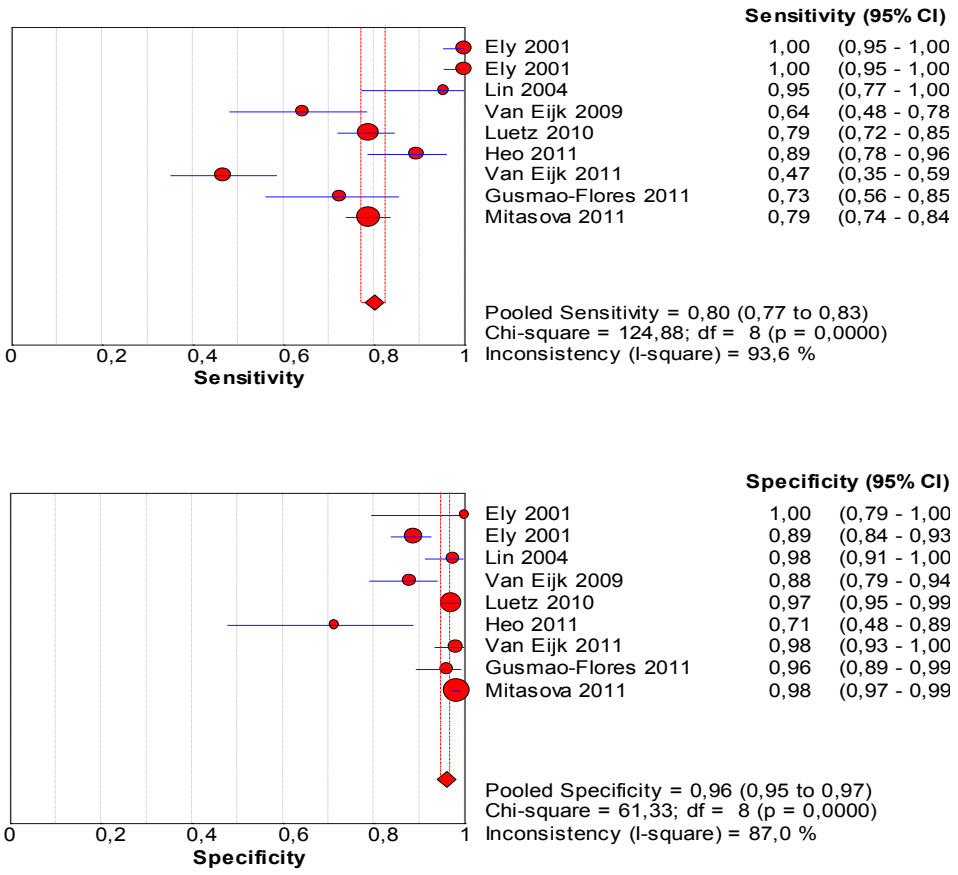


Figure 3 Forest plot of the pooled values of sensitivity and specificity of the CAM-ICU.

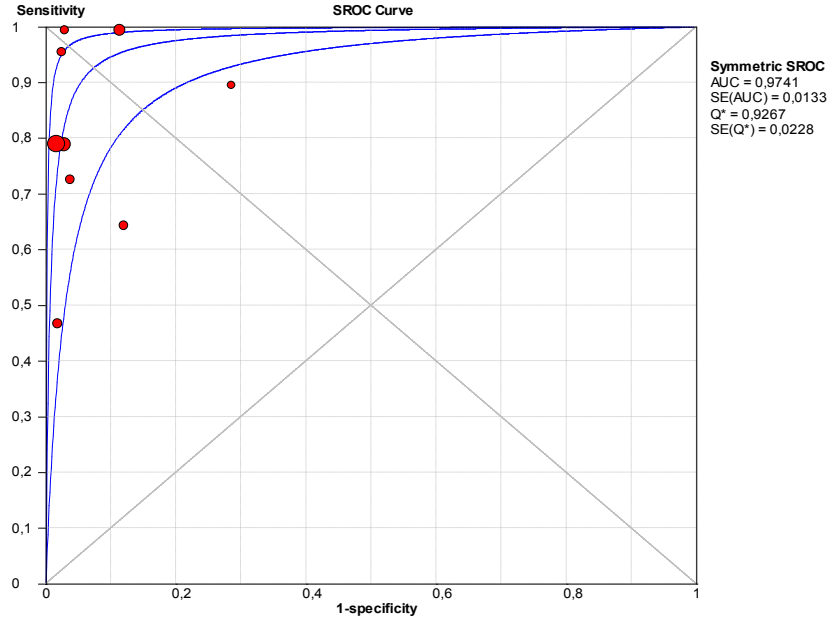


Figure 4 Summary receiver operating characteristics (SROC) obtained from the evaluation studies of the CAM-ICU.

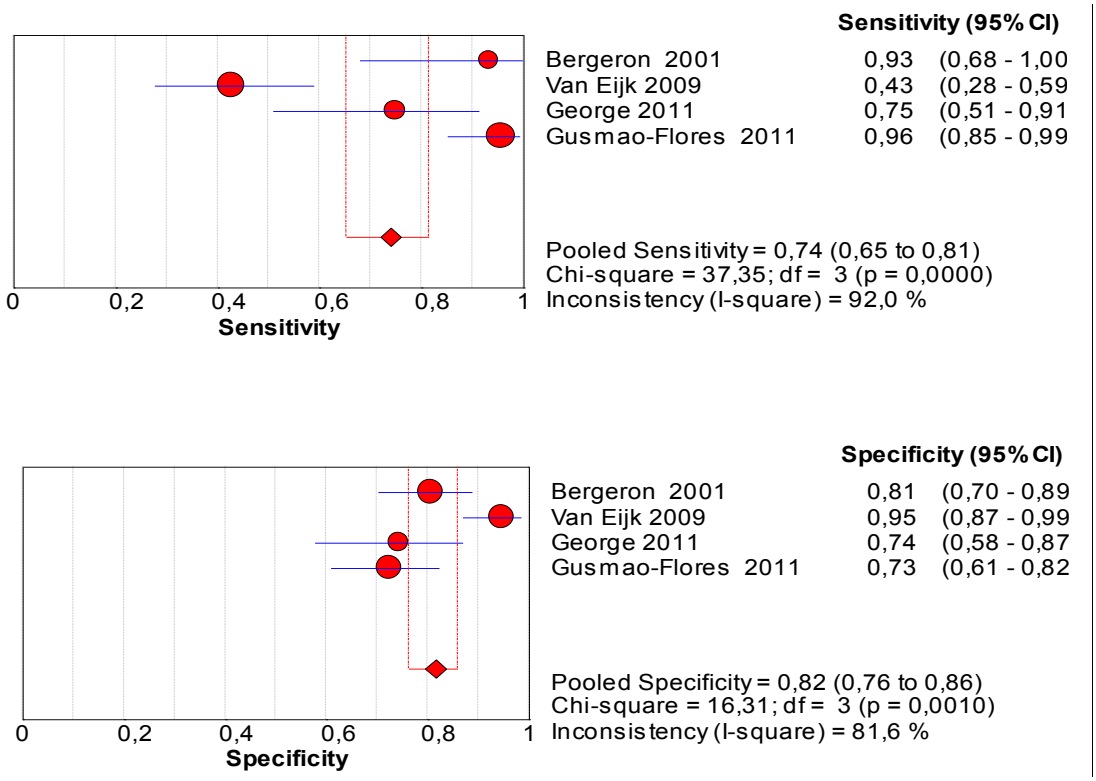


Figure 5 Forest plot of the pooled values of sensitivity and specificity of the ICDSC.

Discussion

This study represents the first attempt to synthesize the validity and added value of the CAM-ICU and ICDSC in ICU patients. Our results showed that the overall accuracy of the CAM-ICU is excellent, with pooled values for sensitivity and specificity of 80% and 95.9%, respectively. In addition, the pooled values for the sensitivity and specificity of the ICDSC were 74% and 81.9%, respectively. Thus, the currently available data support the use of the CAM-ICU or of the ICDSC as screening tools for delirium in critically ill patients. In addition, because of its high specificity, the CAM-ICU is an excellent diagnostic tool to delirium. This is relevant because a validated tool should be used routinely for monitoring critically ill patients and when delirium is present an algorithm to investigate its cause and a therapeutic strategy should be performed.

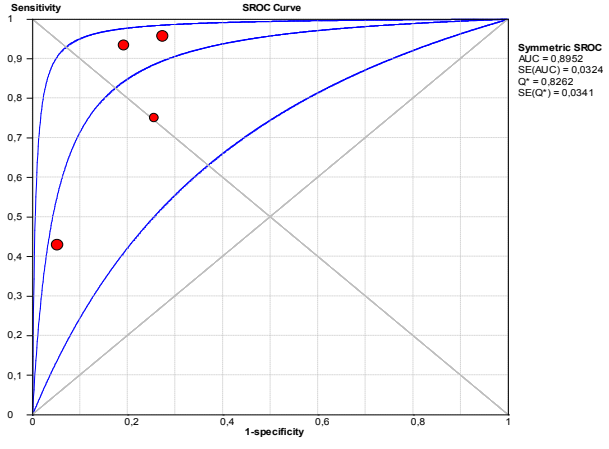


Figure 6 Summary receiver operating characteristics (SROC) obtained from the evaluation studies of ICDSC.

After the first validation study [19], the CAM-ICU was translated into and validated in many languages [6-9,11,22]. Although studies published in non-English languages have been excluded from this systematic review and meta-analysis, some have shown similar accuracy to the CAM-ICU. Tobar *et al.* evaluated 29 ventilated patients in the ICU and showed a sensitivity and specificity of 80% and 96%, respectively [6]. Additionally, Toro *et al.* evaluated 129 patients and observed a sensitivity of 79.4% and a specificity of 97.9% for the CAM-ICU [8]. These same authors performed a subgroup analysis with the ventilated patients (n = 29), and the results suggested better sensitivity (92.9% versus 79.4%) and worse specificity (86.7% versus 97.9%) in this

subgroup of patients. Both studies were published in the Spanish language. Chuang *et al.* validated a Chinese version of the CAM-ICU and again reported high sensitivity (96%) when it was performed by a physician [12].

The present meta-analysis has shown that the pooled sensitivity of the CAM-ICU was 80%, which demonstrates that this tool has good performance for screening patients with delirium in ICU. However, it is also evident that no other validation study has found as high a sensitivity as was observed in the initial studies by Ely *et al.* [18,19]. In addition, there was an even lower sensitivity when the CAM-ICU was used in daily practice, that is, outside of a methodology for validation [14].

Although there is no clear explanation for this loss of sensitivity in the most recent studies, it is possible that the evaluation in cohorts of patients that were less sedated, which is a current trend [23], contributes to decreases in the accuracy of the CAM-ICU. In this systematic review, a higher sensitivity of the CAM-ICU was observed in two studies in subgroups of patients with RASS < 0 [4,10]. Also, a higher sensitivity seems to be present in sedated patients and it is suggested by the differences in accuracy of the CAM-ICU between ventilated and non-ventilated patients. Although no studies compared the accuracy in these subgroups of patients, the study by Toro *et al.* [8] (not included in this systematic review) is consistent with Ely's study [19] and indicates excellent sensitivity in the subgroup of patients undergoing mechanical ventilation. Again, perhaps the sedation effects can contribute to these findings. It is reasonable to hypothesize that feature 2 (inattention) or feature 3 (disorganized thinking) of the CAM-ICU is less likely to be detected when patients are less sedated. Recently, Vasilevskis *et al.* suggested a more intense approach to the detection of inattention when the CAM-ICU is used in daily practice [24]. In addition, feature 1 (an acute onset of mental status changes) may be most frequently considered to be positive in patients with sedation and thus increases the sensitivity of the tool. Of course, more studies are necessary to explain and prove this hypothesis.

The four features of the CAM-ICU - 1) acute onset of mental status changes or fluctuating course; 2) inattention; 3) disorganized thinking; and 4) altered level of consciousness - have objective definitions. This characteristic likely justifies the high inter-rater reliability reported in several studies [4,10,11,18,19].

Moreover, the specificity of the CAM-ICU is high. The pooled value for specificity was 96%, suggesting that when the CAM-ICU is positive, it is not necessary to confirm the diagnosis of delirium by the DSM-IV criteria, improving its feasibility in the ICU. In other words, the CAM-ICU is not only adequate for screening but also a good confirmatory diagnostic tool for delirium in critically ill patients.

Recently, Guenther *et al.* published a study of the accuracy of the CAM-ICU Flowsheet, comparing it with the DSM-IV criteria [25]. Interestingly, they found a sensitivity of 88% to 92% and an excellent specificity of 100%. Clearly, the CAM-ICU and the CAM-ICU Flowsheet are very similar tools. However, our previous study, despite an excellent correlation (kappa: 0.96) between these tools [9], showed that they were not identical, so we decided not to add the Guenther's study in this meta-analysis.

A Canadian group developed and validated the ICDSC [20] motivated by the same challenge: diagnosing delirium in critically ill and mechanically ventilated patients.

The ICDSC checklist is an eight-item screening tool (one point for each item) that is based on DSM criteria and applied to data that can be collected through medical records or to information obtained from the multidisciplinary team.

Bergeron *et al.* developed and validated the ICDSC in a mixed ICU [20]. All of the information used to complete the scale was collected from the patient, the primary nurses' evaluation and the chart in the previous 24 hours. With a cutoff score of four points, they showed a sensitivity of 99% and a specificity of 64%. Similar results were found by our group [9]. However, we observed that the sensitivity of the ICDSC was not consistently high in all studies, and that the pooled value for sensitivity in this meta-analysis was 74%. These results suggest that this tool does not appear to be as accurate as the CAM-ICU for screening purposes. George *et al.*, using a different threshold for positivity (3 rather than 4), showed a higher sensitivity (from 75% to 90%) and, consequently, improved screening characteristics of this tool [21]. However, these changes in the cutoff decreased the specificity of the ICDSC, which was already lower than that observed for the CAM-ICU. The pooled value for specificity of the ICDSC in this meta-analysis was 82%.

Additionally, a recent study by Tomasi *et al.* suggested that the CAM-ICU is a better predictor of outcomes than the ICDSC, which is likely related to the high rate of false positives with the ICDSC [26]. At least two characteristics of the ICDSC might explain its lower sensitivity and specificity. First, the information is collected from the previous 24 hours. Delirium is characterized by its fluctuation, with the possibility of resolution over a long period of evaluation. Additionally, the evaluation of inattention ("easily distracted by external stimuli" [20]), for example, may hinder an effective response by the evaluator.

Despite the limitations described above, the inter-rater reliability of the ICDSC appears to be good. George *et al.* [21] reported an inter-rater agreement of 0.947 (95% confidence interval, 0.870 to 0.979), and in the

study by Bergeron *et al.* [20], the calculated alpha value was between 0.71 and 0.79.

Interestingly, both tools have worse sensitivity when patients with hypoactive delirium are tested. This issue is relevant because this subtype of delirium is the most prevalent [27]. A lower prevalence of delusions and perceptual disturbances in hypoactive delirium does not appear to explain these findings [28].

Despite the observation that no studies compared the accuracy of both tools in ventilated versus non-ventilated patients, most studies included these two types of patients.

Both tools are important in the care of the critically ill patients, each one with features that allow its use at different times or together. The CAM-ICU, to be quite specific, seems to be the ideal tool for the diagnosis of delirium in critically ill patients. In turn, the ICDSC, by its features not dichotomous, allows the diagnosis of subsyndromal delirium, which has potential prognostic implications [29] and can identify patients with potential therapeutic benefit [30].

Our findings should be understood in the context of some limitations. First, studies published in non-English languages were excluded. Unfortunately, a substantial part of the core information was not available from these studies precluding its use in the meta-analysis. However, as described above, the accuracy of the CAM-ICU appears to be consistent with the results of some of these studies. Second, this study cannot explain the findings with different accuracies of these tools in subgroups of patients (ventilated and nonventilated, RASS < 0, subtypes of delirium), but likely, this is a limitation of the tools. Additionally, the use of the CAM-ICU in patients with non-invasive ventilation has an excellent accuracy; however, its data are limited to a single study involving a small number of observations. This reflects the need for studies to evaluate specific groups of patients.

Conclusions

The present meta-analysis demonstrates that the CAM-ICU is an excellent tool for the detection of delirium in critically ill ICU patients regardless of the subgroup of patients evaluated. Despite having a good performance, the ICDSC presents lower sensitivity and specificity as compared to CAM-ICU. The available data suggest that both CAM-ICU and the ICDSC can be used as a screening tool for the diagnosis of delirium in critically ill patients.

Key messages

- The CAM-ICU and the ICDSC are the most studied tools for the diagnosis of delirium in critically ill patients.
- The CAM-ICU and the ICDSC are good screening tools for delirium in ICU patients.
- The CAM-ICU is an excellent diagnostic tool for delirium in critically ill ICU patients

Additional material

Additional file 1: Figure S1. Forest plot of the pooled values of sensitivity and specificity of the CAM-ICU (included pCAM-ICU). Figure S2. Summary receiver operating characteristics (SROC) obtained from the evaluation studies of the CAM-ICU (included pCAM-ICU).

Additional file 2: Table S1. Main characteristics of the included studies (evaluation of the CAM-ICU). Included data from all evaluators.

Abbreviations

AUC: area under the summary receiver operating characteristic curve; CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; ICDSC: Intensive Care Delirium Screening Checklist; ICU: Intensive Care unit; RASS: Richmond Agitation Sedation Scale; SROC: summary receiver operating curve characteristic.

Acknowledgements

This project was partially supported by the National Council of Technological and Scientific Development (CNPq): [474869/2010-5] - Edital Universal MCT/CNPq 14/2010.

Author details

[1]Intensive Care Unit, University Hospital Prof. Edgar Santos, Universidade Federal da Bahia, Rua Augusto Viana, Salvador, 40110-910, Brazil. [2]Programa de Pós-graduação em Processos Interativos dos Órgãos e Sistemas, Instituto de Ciências da Saúde (ICS), Universidade Federal da Bahia, Av. Reitor Miguel Calmon, Salvador, 40110-902, Brazil. [3]D'Or Institute of Research and Education, Rua Diniz Cordeiro, 30, Rio de Janeiro, 22281-100, Brazil. [4]PostGraduate Program, Instituto Nacional do Câncer (INCA), Praça Cruz Vermelha, 23, Rio de Janeiro, 20230-130, Brazil. [5]Department of Neurosciences and Mental Health, University Hospital Prof. Edgar Santos, Universidade Federal da Bahia, Rua Augusto Viana, Salvador, 40110-910, Brazil. [6]Programa de Pós-graduação em Medicina e Saúde (PPgMS) - Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Rua Augusto Viana, Salvador, 40110-910, Brazil.

Authors' contributions

DGF and JIFS conceived the study. DGF and RAC performed the database searches. DGF undertook the statistical analysis. DGF, JIFS and LCQ contributed to the writing of the first draft of the manuscript. All of the authors contributed to and have approved the final manuscript.

Competing interests

There are no conflicts of interest related to this investigation to disclose.

Received: 13 March 2012 Revised: 24 May 2012 Accepted: 3 July 2012
Published: 3 July 2012

References

1. Salluh JI, Soares M, Teles JM, Ceraso D, Raimondi N, Nava VS, Blasquez P, Ugarte S, Ibanez-Guzman C, Centeno JV, Laca M, Grecco G, Jimenez E, Árias-Rivera S, Duenas C, Rocha MG: **Delirium epidemiology in critical care (DECCA): an international study.** *Crit Care* 2010, **14**:R210.
2. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS: **Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.** *JAMA* 2004, **291**:1753-1762.
3. Spronk PE, Riekerk B, Hofhuis J, Rommes JH: **Occurrence of delirium is severely underestimated in the ICU during daily care.** *Intensive Care Med* 2009, **35**:1276-1280.
4. Luetz A, Heymann A, Radtke FM, Chenitir C, Neuhaus U, Nachtigall I, von Dossow V, Marz S, Eggers V, Heinz A, Wernecke KD, Spies CD: **Different**

assessment tools for intensive care unit delirium: which score to use? *Crit Care Med* 2010, **38**:409-418.
5. Salluh JI, Dal-Pizzol F, Mello PV, Friedman G, Silva E, Teles JM, Lobo SM, Bozza FA, Soares M: **Delirium recognition and sedation practices in critically ill patients: a survey on the attitudes of 1015 Brazilian critical care physicians.** *J Crit Care* 2009, **24**:556-562.
6. Tobar E, Romero C, Galleguillos T, Fuentes P, Cornejo R, Lira MT, de la Barrera L, Sanchez JE, Bozan F, Bugedo G, Morandi A, Ely WE: **[Confusion Assessment Method for diagnosing delirium in ICU patients (CAM-ICU): cultural adaptation and validation of the Spanish version].** *Med Intensiva* 2010, **34**:4-13.
7. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, Fang YF, Shieh MH, Kuo HP: **The impact of delirium on the survival of mechanically ventilated patients.** *Crit Care Med* 2004, **32**:2254-2259.
8. Toro AC, Escobar LM, Franco JG, Diaz-Gomez JL, Munoz JF, Molina F, Bejarano J, Yepes D, Navarro E, Garcia A, Ely WE, Esteban A: **[Spanish version of the CAM-ICU (Confusion Assessment Method for the Intensive Care Unit). Pilot study of validation].** *Med Intensiva* 2010, **34**:14-21.
9. Gusmao-Flores D, Salluh JI, Dal-Pizzol F, Ritter C, Tomasi CD, Lima MA, Santana LR, Lins RM, Lemos PP, Serpa GV, Oliveira J, Chalhub RÁ, Pitrowsky MT, Lacerda AL, Koenen KC, Quarantini LC: **The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients.** *Clinics (Sao Paulo)* 2011, **66**:1917-1922.
10. Mitasova A, Kostalova M, Bednarik J, Michalcakova R, Kasparek T, Balabanova P, Dusek L, Vohanka S, Ely EW: **Poststroke delirium incidence and outcomes: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).** *Crit Care Med* 2012, **40**:484-490.
11. Heo EY, Lee BJ, Hahm BJ, Song EH, Lee HA, Yoo CG, Kim YW, Han SK, Shim YS, Lee SM: **Translation and validation of the Korean confusion assessment method for the intensive care unit.** *BMC Psychiatry* 2011, **11**:94.
12. Chuang WL, Lin CH, Hsu WC, Ting YJ, Lin KC, Ma SC: **[Evaluation of the reliability and validity of the Chinese version of the confusion assessment method for the intensive care unit].** *Hu Li Za Zhi* 2007, **54**:45-52.
13. Patel RP, Gambrell M, Speroff T, Scott TA, Pun BT, Okahashi J, Strength C, Pandharipande P, Girard TD, Burgess H, Dittus RS, Bernard GR, Ely EW: **Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals.** *Crit Care Med* 2009, **37**:825-832.
14. van Eijk MM, van den Boogaard M, van Marum RJ, Benner P, Eikelenboom P, Honing ML, van der Hoven B, Horn J, Izaks GJ, Kalf A, Karakus A, Klijn IA, Kuiper MA, de Leeuw FE, de Man T, van der Mast RC, Osse RJ, de Rooij SE, Spronk PE, van der Voort PH, van Gool WA, Slooter AJ: **Routine use of the confusion assessment method for the intensive care unit: a multicenter study.** *Am J Respir Crit Care Med* 2011, **184**:340-344.
15. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J: **The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews.** *BMC Med Res Methodol* 2003, **3**:25.
16. Zamora J, Abraira V, Muriel A, Khan KS, Coomarasamy A: **Meta-DiSc: a software for meta-analysis of test accuracy data.** *BMC Medical Research Methodology* 2006, **6**:31.
17. van Eijk MM, van Marum RJ, Klijn IA, de Wit N, Kesecioglu J, Slooter AJ: **Comparison of delirium assessment tools in a mixed intensive care unit.** *Crit Care Med* 2009, **37**:1881-1885.
18. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R: **Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).** *JAMA* 2001, **286**:2703-2710.
19. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK: **Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).** *Crit Care Med* 2001, **29**:1370-1379.
20. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y: **Intensive Care Delirium Screening Checklist: evaluation of a new screening tool.** *Intensive Care Med* 2001, **27**:859-864.
21. George C, Nair JS, Ebenezer JA, Gangadharan A, Christudas A, Gnanaseelan LK, Jacob KS: **Validation of the Intensive Care Delirium Screening Checklist in nonintubated intensive care unit patients in a resource-poor medical intensive care setting in South India.** *J Crit Care* 2011, **26**:138-143.
22. ICU Delirium and Cognitive Impairment Study Group:[http://www.icudelirium.org].
23. Strom T, Martinussen T, Toft P: **A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial.** *Lancet* 2010, **375**:475-480.
24. Vasilevskis EE, Girard TD, Ely EW: **The bedside diagnosis of ICU delirium: specificity is high, let's optimize sensitivity.** *Am J Respir Crit Care Med* 2012, **185**:107-108; author reply 108.
25. Guenther U, Popp J, Koecher L, Muders T, Wrigge H, Ely EW, Putensen C: **Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients.** *J Crit Care* 2010, **25**:144-151.
26. Tomasi CD, Grandi C, Salluh J, Soares M, Giombelli VR, Cascaes S, Macedo RC, de Souza Constantino L, Biff D, Ritter C, Dal Pizzol F: **Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes.** *J Crit Care* 2011, **27**:212-217.
27. Pandharipande P, Cotton BA, Shintani A, Thompson J, Costabile S, Truman Pun B, Dittus R, Ely EW: **Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients.** *Intensive Care Med* 2007, **33**:1726-1731.
28. Ross CA, Peyser CE, Shapiro I, Folstein MF: **Delirium: phenomenologic and etiologic subtypes.** *Int Psychogeriatr* 1991, **3**:135-147.
29. Ouimet S, Riker R, Bergeron N, Cossette M, Kavanagh B, Skrobik Y: **Subsyndromal delirium in the ICU: evidence for a disease spectrum.** *Intensive Care Med* 2007, **33**:1007-1013.
30. Hakim SM, Othman AI, Naoum DO: **Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial.** *Anesthesiology* 2012, **116**:987-997.

doi:10.1186/cc11407
Cite this article as: Gusmao-Flores *et al.*: The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Critical Care* 2012 **16**:R115.

ARTIGO 3

Título: “Delirium em pacientes sob ventilação mecânica não invasiva".
Autores: Jorge I Salluh, **Dimitri Gusmao-Flores**, Felipe Dal-Pizzol
Jornal: *Lung* Fator de Impacto: 2,062
Ano de publicação: 2012
Número de citações: 0 (fonte: *web of knowledge*)

Carta ao editor com dados originais abordando a possibilidade de utilização da ferramenta CAM-ICU para diagnóstico de delirium nos pacientes em uso de ventilação mecânica não invasiva.

Lung (2012) 190:589–590
DOI 10.1007/s00408-012-9416-6

Diagnosis of Delirium in Patients under Noninvasive Ventilation in the Intensive Care Unit

Jorge I. F. Salluh · Dimitri Gusmao-Flores · Felipe Dal-Pizzol

Received: 9 August 2012 / Accepted: 30 August 2012 / Published online: 13 September 2012

Dear Editor

We read with great interest the recently published paper by Charlesworth et al. [1]. It was a fine contribution about delirium, mainly to show that the data about this disorder in patients with noninvasive ventilation (NIV) are scarce.

Despite the increasing knowledge about delirium, when its diagnosis relies on standard clinical evaluations rather than on the use of validated tools, it remains underdiagnosed. Although several validated tools are available, to the best of our knowledge they have not been validated in the subgroup of patients under noninvasive ventilation. Therefore, we think that the inclusion of the study by Roche Campo et al. [2] in this meta-analysis should be seen with caution. That study evaluated 27 patients with hypercapnic acute respiratory failure (ARF) under NIV and observed that delirium diagnosed by the CAM-ICU occurred in 33 % of the patients and was associated with NIV failure. However, testing the accuracy of this diagnosis was beyond the scope of the study and no gold standard (DSM-IV evaluation) was applied.

We have recently evaluated the performance of the most used tools for the diagnosis of delirium [Intensive Care Delirium Screening Checklist (ICDSC) and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)] in patients under NIV in three ICUs in a multicenter study [3]. Eleven patients under NIV were included, mean age of 61 years (range = 37–70), eight were male (72.7 %), mean APACHE II was 14 (range = 5–23), and SOFA score was 5.5 (range = 3–8). Two patients (18.2 %) died during ICU stay. The main reasons for NIV were cardiovascular ($n = 5$), hypoxemic ARF ($n = 2$), pulmonary embolism ($n = 2$), chronic obstructive pulmonary disease (COPD) exacerbation ($n = 1$), and stroke ($n = 1$). A reference rater (neurologist or psychiatrist) using the DSM-IV criteria diagnosed delirium in two patients (18.2 %). When the CAM-ICU was applied, a diagnosis of delirium was made in the same two patients, whereas the ICDSC identified delirium in three patients. The agreement between the CAM-ICU and DSM-IV was 100 % and the two patients identified by DSM-IV and CAM-ICU also were positive in the ICDSC. The subtypes of delirium were one mixed subtype and one hypoactive.

As NIV is being increasingly employed in the ICU setting and considering the relevance of diagnosing delirium, we believe that our study, despite the small sample size, provides preliminary evidence that the diagnosis is feasible and accurate using the CAM-ICU in this population. However, due to the small number of patients and the need for further characterization regarding the implication of the diagnosis of delirium with respect to the relevant clinical outcomes and success of NIV, we believe that future studies should be performed to validate the accuracy of the CAM-ICU and ICDSC in larger populations of patients under NIV.

Conflict of interest None.

References

1. Charlesworth M, Elliott MW, Holmes JD (2012) Noninvasive positive pressure ventilation for acute respiratory failure in delirious patients: understudied, underreported, or underappreciated?

J. I. F. Salluh
Instituto Nacional do Câncer, Rio de Janeiro, Brazil

D. Gusmao-Flores (✉)
Instituto de Ciências da Saúde (ICS), Universidade Federal da Bahia, Salvador, Brazil
e-mail: dimitrigusmao@gmail.com

F. Dal-Pizzol
Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, Brazil

A systematic review and meta-analysis. Lung 190:000–000. doi: 10.1007/s00408-012-9403-y
2. Roche Campo F, Drouot X, Thille AW et al (2010) Poor sleep quality is associated with late noninvasive ventilation failure in patients with acute hypercapnic respiratory failure. Crit Care Med 38:477–485
3. Gusmao-Flores D, Salluh JI, Dal-Pizzol F et al (2011) The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients. Clinics (Sao Paulo) 66:1917–1922

ARTIGO 4

Título: “Ferramentas para o diagnóstico de delirium nos pacientes graves: é necessário uma calibração para pacientes menos sedados?".

Autores: **Dimitri Gusmao-Flores**, Juliana C S Martins, Daniela Amorim, **Lucas C Quarantini**

Jornal: *Intensive Care Medicine* Fator de Impacto: 5,399

Ano de publicação: 2013

Número de citações: 0 (fonte: *web of knowledge*)

Carta ao editor com dados originais levantando a hipótese que o CAM-ICU tem menor acurácia quando avalia paciente menos sedados. Informação também sugerida na nossa meta-análise publicada na *Critical Care* 2012.

Intensive Care Med
DOI 10.1007/s00134-013-3120-8

Dimitri Gusmao-Flores
Juliana C. S. Martins
Daniele Amorin
Lucas C. Quarantini

Tools for diagnosing delirium in the critically ill: is calibration needed for the less sedated patient?

Received: 6 September 2013
Accepted: 17 September 2013

Dear Editor,

The recent study performed by Haenggi et al. [1] adds important information relating to the diagnosis of delirium in critically ill patients: the effect of sedation. The authors suggest that the prevalence of delirium as assessed using the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) depends on the level of consciousness of the patient at the time of evaluation. These authors found that the proportion of CAM-ICU- and ICDSC-positive evaluations decreased significantly if assessments from patients at Richmond Agitation Sedation Scale (RASS) −2/−3 were excluded.

Interestingly, these findings are in line with what we observe at our medical institution. In our ICU, delirium assessments are performed twice daily using the CAM-ICU. However, we do not evaluate patients at RASS −3 because we believe it is not possible to obtain a reliable result in this group of patients using any of the validated diagnostic tools. This year, we have evaluated 108 consecutive patients admitted to our hospital who were predicted to be admitted to the ICU for >48 h. We observed an overall prevalence of delirium of 34 % (37 patients). However, when only patients with RASS −2 (19 patients) were considered, the incidence of delirium was 89.5 % (17 patients). When the CAM-ICU was performed in these patients the first time they evolved to RASS −1 or higher, only six patients were assessed as being in delirium. Figure 1 shows the 1,873 evaluations performed during this period. The result of applying the CAM-ICU was stratified by the level of sedation; patients with RASS +1 to +4 were excluded from this analysis because they accounted for only 1 % of all assessments.

We also observed that a higher level of RASS is accompanied by a lower frequency of delirium when the evaluation is done with the CAM-ICU. This observation may explain the lower frequency of delirium in non-sedated critically ill patients [2] compared with those on mechanical ventilation and thus under the influence of some kind of sedative [3].

Despite the validation of the CAM-ICU and ICDSC in several languages for their good performance in terms of diagnosis, in the recent meta-analysis conducted by our group we observed that the lower the RASS, the higher the sensitivity of the CAM-ICU [4]. It would appear that more profound sedation determines the convergence of the findings using the various tools to diagnose delirium, including the gold standard [Diagnostic and Statistical Manual of Mental Disorders (DSM) 4th edn]. The opposite trend seem to be true. The sensitivity of the CAM-ICU and ICDSC, for example, in non-critically ill patients is <50 % [5] and therefore not useful for diagnosis.

Hence, we agree with Haenggi et al. [1] that a delirium assessment of patients receiving some form of sedation (RASS −2 or deeper) will likely not provide a proper measurement of delirium and that to insist on applying any of the current delirium screening tools (CAM-ICU or ICDSC) or even the newest version of the DSM (5th edn) to this population will almost always result in a diagnosis of delirium. However, we question whether the frequency of delirium in less sedated patients is in fact lower or whether these tools have a low sensitivity to detect delirium in this population? We believe that the current tools, especially CAM-ICU and ICDSC, require better calibration to properly evaluate patients under light sedation (RASS > −1).

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

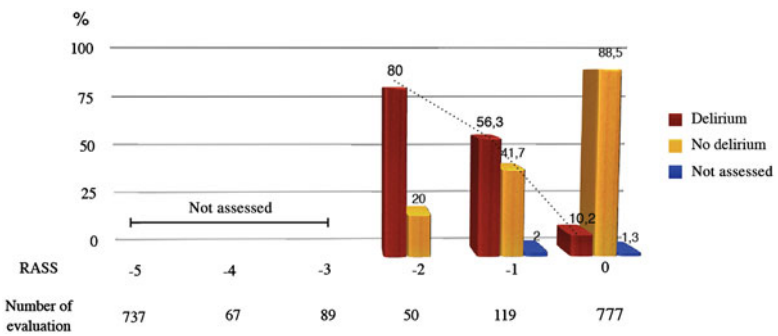


Fig. 1 Frequency of diagnosis of delirium among 1,873 evaluations, stratified by the Richmond Agitation Sedation Scale (*RASS*), determined with the Confusion Assessment Method for the ICU (CAM-ICU)

Published online: 03 October 2013

References

1. Haenggi M, Blum S, Brechbuehl R et al (2013) Effect of sedation level on the prevalence of delirium when assessed with CAM-ICU and ICDSC. Intensive Care Med. doi:10.1007/s00134-013-3034-5
2. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM et al (2008) A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. Crit Care 12:R16
3. Devlin JW, Fong JJ, Fraser GL et al (2007) Delirium assessment in the critically ill. Intensive Care Med 33:929–940
4. Gusmao-Flores D, Figueira Salluh JI, Chalhub RA et al (2012) The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Crit Care 16:R115
5. Neufeld KJ, Hayat MJ, Coughlin JM et al (2011) Evaluation of two intensive care delirium screening tools for non-critically ill hospitalized patients. Psychosomatics 52:133–140

D. Gusmao-Flores
Intensive Care Unit, University Hospital Prof. Edgard Santos, Universidade Federal da Bahia, Salvador, BA, Brazil

D. Gusmao-Flores
Programa de Pós-graduação em Processos Interativos dos Órgãos e Sistemas, Instituto de Ciências da Saúde (ICS), Universidade Federal da Bahia, Salvador, BA, Brazil

D. Gusmao-Flores (✉)
Rua Sabino Silva, 273, Ap. 801, Salvador, BA 40155-250, Brazil
e-mail: dimitrigusmao@gmail.com
Tel.: +55-71-99968535

J. C. S. Martins · D. Amorin
Faculty of Medicine, Universidade Federal da Bahia, Salvador, BA, Brazil

L. C. Quarantini
Department of Psychiatry, University Hospital Prof. Edgard Santos, Universidade Federal da Bahia, Salvador, BA, Brazil

L. C. Quarantini
Programa de Pós-graduação em Medicina e Saúde, Faculdade de Medicina da Bahia, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil

ARTIGO 5

Título: “Escalas de avaliação de *delirium* em pacientes graves: revisão sistemática da literatura”.

Autores: João Pedro LM Carvalho, Antônio RP de Almeida, **Dimitri Gusmao-Flores**

Jornal: Revista Brasileira de Terapia Intensiva

Ano de publicação: 2013

Número de citações: 0 (fonte: *web of knowledge*)

Objetivo: Identificar escalas capazes de estabelecer uma avaliação quantitativa dos sintomas do *delirium* em pacientes graves por meio de uma revisão sistemática.

Métodos: Foram selecionados estudos que avaliaram escalas de estratificação de *delirium* em pacientes internados em unidades de terapia intensiva a partir de busca na base de dados MedLine. Os estudos de validação dessas escalas foram analisados, e foram identificados os pacientes alvos para aplicação, o avaliador, os sinais e sintomas avaliados, a duração da aplicação, além da sensibilidade e da especificidade de cada escala.

Resultados: Seis escalas foram identificadas: o *Delirium Detection Score*, o *Cognitive Test of Delirium*, a *Memorial Delirium Assessment Scale*, o *Intensive Care Delirium Screening Checklist*, a *The Neelon and Champagne Confusion Scale e a Delirium Rating Scale-Revised-98*.

Conclusão: As escalas identificadas permitem estratificação e acompanhamento do paciente grave com *delirium*. Dentre as seis escalas, a mais estudada e que melhor se adequa ao uso em unidade de terapia intensiva foi o *Intensive Care Delirium Screening Checklist*.

João Pedro Lins Mendes Carvalho[1],
Antônio Raimundo Pinto de Almeida[1],
Dimitri Gusmao-Flores[2,3]

Escalas de avaliação de *delirium* em pacientes graves: revisão sistemática da literatura

Delirium rating scales in critically ill patients: a systematic literature review

1. Faculdade de Medicina da Bahia, Universidade Federal da Bahia - UFBA - Salvador (BA), Brasil.
2. Programa de Pós-Graduação em Processo Interativo dos Órgãos e Sistemas, Instituto de Ciência da Saúde, Universidade Federal da Bahia - UFBA - Salvador (BA), Brasil.
3. Unidade de Terapia Intensiva, Hospital Universitário Prof. Edgar Santos, Universidade Federal da Bahia - UFBA - Salvador (BA), Brasil.

RESUMO

Objetivo: Identificar escalas capazes de estabelecer uma avaliação quantitativa dos sintomas do *delirium* em pacientes graves por meio de uma revisão sistemática.

Métodos: Foram selecionados estudos que avaliaram escalas de estratificação de *delirium* em pacientes internados em unidades de terapia intensiva a partir de busca na base de dados MedLine. Os estudos de validação dessas escalas foram analisados, e foram identificados os pacientes alvos para aplicação, o avaliador, os sinais e sintomas avaliados, a duração da aplicação, além da sensibilidade e da especificidade de cada escala.

Resultados: Seis escalas foram identificadas: o *Delirium Detection Score*, o *Cognitive Test of Delirium*, a *Memorial Delirium Assessment Scale*, o *Intensive Care Delirium Screening Checklist*, a *The Neelon and Champagne Confusion Scale e a Delirium Rating Scale-Revised-98*.

Conclusão: As escalas identificadas permitem estratificação e acompanhamento do paciente grave com *delirium*. Dentre as seis escalas, a mais estudada e que melhor se adequa ao uso em unidade de terapia intensiva foi o *Intensive Care Delirium Screening Checklist*.

Descritores: Delírio; Avaliação/métodos; Escalas; Sensibilidade e especificidade; Unidades de terapia intensiva

INTRODUÇÃO

Delirium é uma disfunção orgânica prevalente nas unidades de terapia intensiva (UTI), com incidência variando entre 5 e 92%, de acordo com a população estudada,[1-4] estando associada à alta mortalidade, a maior tempo de internamento em UTI e no hospital, e a maior tempo de ventilação mecânica, além de défice funcional e cognitivo a longo prazo.[1-3,5-7]

Apesar de uma disfunção orgânica importante, o paciente, muitas vezes, não é diagnosticado,[1,3] principalmente aqueles que estão em ventilação mecânica.[3,6,8] Com foco nessa observação, diversas ferramentas foram desenvolvidas, com o objetivo de facilitar o diagnóstico de *delirium* no paciente grave.

Os critérios preconizados pelas ferramentas *Diagnostic and Statistical Manual of Mental Disorders*, 4ª edição (DSM-IV) ou *International Classification of Disease*, 10ª revisão (ICD-10) são os mais usados em indivíduos capazes de se comunicar verbalmente, sendo empregadas principalmente por profissionais especializados na área da neurociência. No paciente grave, as

Conflitos de interesse: Nenhum.

Submetido em 6 de março de 2013
Aceito em 8 de maio de 2013

Autor correspondente:
João Pedro Lins Mendes Carvalho
Rua Waldemar Falcão, 2.106, apto 1.102
CEP: 40296-710 - Salvador (BA), Brasil
E-mail: joaopedro.lmc@gmail.com

DOI: 10.5935/0103-507X.20130026

escalas diagnósticas mais utilizadas, devido à sua simplicidade e à adequada acurácia, são a *Confusion Assessment Method for the Intensive Care Unit* (CAM-ICU) e o *Intensive Care Delirium Screening Checklist* (ICDSC).[9-11] No entanto, tanto o DSM-IV ou o ICD-10 quanto o CAM-ICU são ferramentas dicotômicas, não possibilitando estratificar a gravidade do quadro. O DSM-IV e o ICD-10 baseiam-se na presença de sinais e sintomas para diagnosticar ou não determinada patologia (inclusive o *delirium*). Já o CAM-ICU foi criado, baseado nos critérios do DSM-IV, com o objetivo de facilitar o diagnóstico do *delirium* na UTI e permitir a avaliação de pacientes em ventilação mecânica (impossibilitados de uma comunicação verbal). Assim como as duas outras ferramentas, o CAM-ICU só possibilita a realização do diagnóstico, sem estabelecer uma correlação com a gravidade do quadro.

Este estudo teve por objetivo revisar, de forma sistemática, as escalas capazes de estabelecer uma avaliação quantitativa dos sintomas do *delirium* em pacientes graves.

MÉTODOS

Foi realizada uma extensa pesquisa na base de dados do MEDLINE, a fim de identificar trabalhos que abordassem as escalas de avaliação e estratificação do *delirium* em pacientes internados na UTI. As palavras-chave "*delirium*", "*acute confusion*", "*confusion state*", "*confusional state*", "*acute confusion state*" e "*acute confusional state*" foram pesquisadas e associadas aos termos "*scales*", "*scores*", "*state*", "*measures*", "*measurement*", "*questionnaires*", "*evaluation*", "*levels*", "*indices*", "*assessment*" e "*instrument*". Essa pesquisa foi associada aos termos "ICU", "*critical care*", "ICU *patients*", "*sensitivity*", "*specificity*" e "*accuracy*".

Posteriormente, foram estabelecidos limites e critérios de inclusão. O critério de inclusão principal foi estudos que abordassem escalas para uma avaliação quantitativa do *delirium*. Foram analisados apenas estudos publicados no idioma Inglês e realizados em adultos (acima de 18 anos). Os resultados da aplicação dos filtros de busca, limites e critérios de inclusão de artigos estão descritos na figura 1.

A estratégia de busca final utilizada foi: ((((*ICU*) *OR critical care*) *OR ICU patients*)) *AND* ((((((((((*delirium*) *OR confusional state*) *OR confusion state*) *OR acute confusion*) *OR acute confusion state*) *OR acute confusional state*)) *AND* ((((((((((*scales*) *OR scores*) *OR state*) *OR measurement*) *OR questionnaires*) *OR evaluation*) *OR indices*) *OR levels*) *OR measures*) *OR assessment*) *OR instruments*))) *AND* (((*sensitivity*) *OR specificity*) *OR accuracy*)) *AND* (*Humans*[Mesh] *AND* (*English*[*lang*]) *AND adult*[MeSH]). Dois autores, de forma independente, realizaram a busca dos estudos. Possíveis divergências na seleção dos estudos foram resolvidas com discussão entre todos os autores.

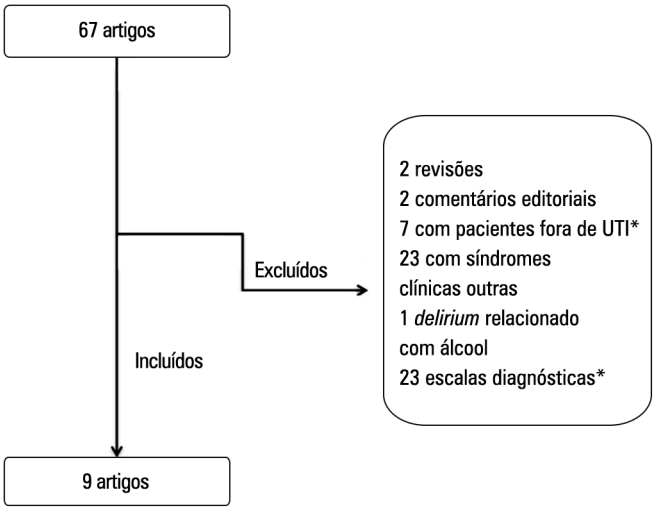


Figura 1 - Diagrama do resultado da aplicação dos filtros de busca, limites e critérios para inclusão de escalas de avaliação de delirium. UTI - unidade de terapia intensiva. * Alguns dos estudos não realizados com paciente em UTI ou que envolveram escalas dicotômicas foram utilizados apenas a título de informações adicionais para o estudo, não estando presente nos resultados apresentados.

Após a análise dos artigos selecionados e a identificação das escalas a serem utilizadas, foi realizada uma nova busca com o nome específico de cada escala, a fim de obter maiores informações.

RESULTADOS

Após a aplicação dos filtros de busca, considerando os limites e critérios de inclusão definidos para este estudo, seis escalas capazes de identificar quantitativamente os sintomas de *delirium* foram selecionadas (cada uma delas é comentada e analisada brevemente a seguir). O quadro 1 descreve os estudos incluídos na revisão. O quadro 2 apresenta um resumo comparativo de todas as escalas incluídas no estudo.

A descrição das variáveis presentes em cada escala pode ser observada no quadro 3.

Delirium Detection Score

O *Delirium Detection Score* (DDS) é uma escala validada, que considera oito dos sintomas do *delirium*, cabendo a cada um desses sintomas uma classificação

Quadro 1 - Artigos incluídos nos resultados da revisão

Autor	Revista	Ano	Tipo de estudo	Escalas abordadas no estudo
Incluídos pelos critérios de busca (N=9)				
Hart et al.[12]	Psychosomatics	1996	Validação	CTD
Hart et al.[13]	J Psychosom Res	1997	Primário	CTD (forma abreviada)
Bergeron et al.[10]	Intensive Care Med	2001	Primário	ICDSC
Otter et al.[14]	Neurocrit Care	2005	Validação	DDS
Van Rompaey et al.[15]	Crit Care	2008	Validação	NEECHAM
Osse et al.[16]	Interact Cardiovasc Thorac Surg	2009	Comparativo	DRS-R-98
Shyamsundar et al.[17]	J Crit Care	2009	Validação	MDAS
Gusmao-Flores et al.[11]	Clinics (São Paulo)	2011	Validação	ICDSC
Neufeld et al.[18]	Psychosomatics	2011	Validação	ICDSC
Incluídos após segunda busca, específica para cada escala (N=7)				
Breitbart et al.[19]	J Pain Symptom Manage	1997	Validação	MDAS
Immers et al.[20]	BMC Nurs	2005	Validação	NEECHAM
Fadul et al.[21]	Support Care Cancer	2007	Validação	MDAS
de Negreiros et al.[22]	Int J Geriatr Psychiatry	2008	Validação	DRS-R-98
Radtke et al.[23]	Br J Anaesth	2008	Comparativo	DDS
Radtke et al.[24]	World J Surg	2010	Comparativo	DDS
Tomasi et al.[25]	J Crit Care	2012	Comparativo	ICDSC

Quadro 2 - Resultados e características das escalas analisadas

Escala	Autor	Tipos de estudo	População alvo	Avaliador	Estratificação	Sensibilidade/ especificidade	Tempo de aplicação	Comentários
Intensive Care Delirium Screening Checklist (ICDSC)	Gusmao-Flores et al.[11]	Validação para uso no Brasil (tradução para português)	UTI	Médico plantonista e enfermeiros	Pontuação de 0 ou 1 para cada item, sendo um escore final mais elevado correlacionado com maior gravidade	96%/72,4% para ponto de corte sugerido de 4 pontos	1-2 minutos	Escala adaptada para o português e validada para o Brasil Escala mais de avaliação do que diagnóstica.
Cognitive Test of Delirium (CTD)	Hart et al.[12]	Validação	UTI	Médico plantonista	Quanto menor o escore, mais grave o paciente	100%/95% para ponto de corte sugerido ≤18 pontos	10-15 minutos	Capaz de diferenciar *delirium* de demência. Uso de linguagem não verbal.
Delirium Detection Score (DDS)	Otter et al.[14]	Avaliação e validação	UTI	Médico plantonista	7-10 = Leve 10-19 = Moderado >19 = Grave	69%/75% para ponto de corte sugerido >7 pontos	3-4 minutos	Só pode ser aplicada para pacientes sob sedação leve (Ramsay ≤3).
Memorial Delirium Assessment Scale (MDAS)	Shyamsundar et al.[17]	Validação para uso em países subdesenvolvidos	UTI e pacientes com câncer em estágios avançados Pacientes não intubados	Médicos residentes ou médicos plantonistas	Pontuação para cada item: 0 = ausente, 1 = leve, 2 = moderado e 3 = grave. Quanto maior o escore final, maior a gravidade	100%/95,5% para ponto de corte sugerido de 10 pontos	10-15 minutos	Validada em estudos de países subdesenvolvidos, com estrutura de UTI e equipe técnica não ideais.
The Neelon and Champagne Confusion Scale (NEECHAM)	Immers et al.[20]	Validação	UTI não intubados	Enfermeiros	27 a 30 - pacientes normais 25 a 26 - grupo de risco para desenvolver *delirium* 20 a 24 - *delirium* leve ≤19 - *delirium* moderado a grave	97,2%/82,8% para um ponto de corte ≤24 pontos	3-4 minutos	Fácil aplicação Deve ser usada como instrumento unicamente de acompanhamento, por estabelecer comparação com as 24 horas anteriores.
Delirium Rating Scale-Revised-98 (DRS-98-R)	de Negreiros et al.[22]	Validação	UTI geral	Médicos psiquiatras	Dos 16 itens, 13 são usados para avaliação de gravidade Quanto maior o escore final, mais grave	92,6%/94,6% para um ponto de corte sugerido de 20		Escala antiga, validada para o português e para o uso no Brasil. A validação foi feita por psiquiatras, em pacientes gerais

UTI - unidade de terapia intensiva.

Quadro 3 - Variáveis presentes em cada escala

Escala	Quantidade de variáveis	Sinais e sintomas avaliados
Delirium Detection Score (DDS)	8 itens	Orientação Agitação Ansiedade Alucinações Convulsões Sudorese paroxística Ciclo sono-vigília Tremores
Cognitive Test of Delirium (CTD)	5 itens	Atenção/Orientação Vigilância Compreensão Memória
Memorial Delirium Assessment Scale (MDAS)	10 itens, subdivididos em 2 grupos (1º com 4 itens e o 2º com 6 itens)	Atenção/Orientação Memória imediata Comportamento Percepção Ciclo sono-vigília Alucinações Delírios Alterações no pensamento
Intensive Care Delirium Screening Checklist (ICDSC)	8 itens	Atenção/Orientação Alucinações Nível de consciência Agitação psicomotora Alteração da linguagem e comportamento Ciclo sono vigília Padrão flutuante dos sintomas
The Neelon and Champagne Confusion Scale (NEECHAM)	9 itens, subdivididos em 3 subescalas	Atenção/Orientação Obediência a comandos Comportamento (padrão motor, verbal e aparência) Condição fisiológica (dados vitais, saturação de oxigênio e incontinência urinária)
Delirium Rating Scale-Revised-98 (DRS-98-R)	16 itens, sendo que 3 deles são usados apenas no diagnóstico e os outros 13 para estratificação	Atenção/Orientação Surgimento dos sintomas Natureza flutuante Fatores associados Ciclo sono-vigília Memória imediata e tardia Ilusões e alucinações Delírios Labilidade emocional Linguagem Distúrbios do pensamento Agitação ou rebaixamento Habilidade visual e espacial

de 0, 1, 4 ou 7 pontos.[14] A escala foi criada pela modificação de um instrumento de avaliação de síndrome de abstinência alcoólica (*Clinical Withdrawal Assessment for Alcohol - CIWA-Ar*).[23,24] Trata-se de uma escala útil para avaliar o grau do *delirium* e guiar um tratamento, podendo também ser uma escala diagnóstica. A escala apresentou uma boa correlação entre avaliadores, desde que previamente treinados para aplicá-la.[24]

Cognitive Test of Delirium

O *Cognitive Test of Delirium* (CTD) avalia cinco itens, cada um deles recebe uma pontuação de 0, 2, 4 ou 6 tendo, desse modo, um total de 30 pontos. Não há uma subdivisão descrita na literatura correlacionando os níveis de gravidade com os respectivos valores do CTD. No entanto, quanto menor o valor do CTD, piores são os desfechos clínicos.[12] A escala é capaz de diferenciar o *delirium* de outras doenças psiquiátricas, como a demência.[12] Devido ao longo tempo de aplicação, foi criada a forma abreviada do CTD, com tempo de aplicação de poucos minutos, porém ainda não foi validada para uso em UTI.[13]

Memorial Delirium Assessment Scale

Escala criada inicialmente para diagnosticar o *delirium* em pacientes com câncer avançado, mas já foi testada e validada para o uso em UTI geral.[17,21] A escala avalia variáveis de dois grandes grupos: cognição e comportamento.[17,21] A *Memorial Delirium Assessment Scale* (MDAS) permite estratificar o *delirium* em diferentes níveis de gravidade, sendo mais grave quanto maior for o escore obtido.[19,21]

Intensive Care Delirium Screening Checklist

O *Intensive Care Delirium Screening Checklist* (ICDSC) é uma escala de estratificação de *delirium*,

mas que pode ser utilizada como diagnóstica,[10] de fácil e rápida aplicação.[18] O ICDSC consiste de uma observação de oito variáveis e uma comparação com a avaliação do dia anterior, sendo níveis crescentes do ICDSC compatíveis com uma estratificação da gravidade;[11] além disso, mostrou-se útil para o diagnóstico do *delirium* subsindrômico.[25] O ICDSC possui a vantagem de ter sido adaptada para o português e validada para o uso no Brasil por Gusmao-Flores et al.[11] O ICDSC mostrou-se uma boa escala para avaliação e acompanhamento do *delirium*.[10,11]

The Neelon and Champagne Confusion Scale

A *The Neelon and Champagne Confusion Scale* (NEECHAM) foi criada como um instrumento para enfermeiros acessarem o *delirium* diariamente, validada para pacientes em UTI,[15] e em ventilação mecânica.[20]

Delirium Rating Scale-Revised-98

A *Delirium Rating Scale-Revised-98* (DRS-R-98) é a escala mais antiga e tradicional, criada exatamente para medir o grau de *delirium* nos pacientes. A DRS-R-98 é uma das mais conhecidas e usadas na terapia intensiva, dentre as que permitem estratificar o *delirium*.[12,16,18] Consiste numa escala de 16 itens (3 deles usados apenas no momento do diagnóstico e 13 usados para estratificação nas sucessivas avaliações). Cada item recebe uma pontuação de 0 a 2 ou de 0 a 3 pontos e, quanto maior a pontuação final, maior a gravidade do quadro.[22] Uma das dificuldades dessa escala é sua complexidade, necessitando que profissionais treinados e capacitados a utilizem e, por vezes, gerando resultados divergentes.[16] A DRS-98-R já foi estudada e validada para o português por de Negreiros et al.[22]

DISCUSSÃO

São muitas as escalas utilizadas para detectar e avaliar pacientes com *delirium*. A presente revisão encontrou seis escalas de estratificação utilizadas para pacientes internados em UTI. As seis escalas já foram adequadamente validadas no idioma original, no entanto, apenas o ICDSC e a DRS-R-68[11,22] foram traduzidas e validadas em português. Outras precisam de validação especificamente para uso no paciente crítico sedado (o DDS), já que só deve ser aplicada em pacientes com escala de Ramsay ≤3.[14] O CTD e o ICDSC apresentam a vantagem de possuírem variáveis dicotômicas (o ICDSC) e que utilizam linguagem não verbal (o CTD), permitindo a avaliação mais simples e acessível para pacientes entubados, por exemplo. No entanto, o grau de sedação pode influenciar na acurácia da escala.[10]

Com relação ao tempo de aplicação de cada instrumento, o CTD e a MDAS apresentam um tempo de aplicação longo para cada paciente, dificultando a adesão para uso eficaz em UTI. A ferramenta ideal seria aquela em que o tempo de aplicação possibilitasse uma avaliação periódica durante cada turno na UTI (devido ao caráter flutuante do *delirium*), como no caso do ICDSC, da NEECHAM ou do DDS.

A maioria das variáveis avaliadas em cada escala foi escolhida com base no diagnóstico pelos critérios do DSM-IV; no entanto, algumas incorporaram outros sintomas menos comuns no quadro do *delirium*, o que diminui a sensibilidade da ferramenta.[23] Um exemplo disso é o DDS, que avalia sinais como tremores e sudorese paroxística, achados que não são frequentes no curso do *delirium*.[23] Outro aspecto importante é que a maioria das escalas possui variáveis que avaliam o *delirium* hiperativo, tais como agitação, ansiedade e alucinações, mas poucas são capazes de avaliar com especificidade o *delirium* hipoativo, subtipo mais comum da doença.[18,23] O caráter hipoativo (sonolência, passividade e inatividade), na maioria dos casos, é uma dificuldade intrínseca da patologia, o que a torna praticamente irreconhecível sem a utilização de uma ferramenta adequada.[18] A avaliação do comportamento (e não apenas da agitação), da atenção, do ciclo sono-vigília e do nível de consciência, como no caso do ICDSC, possibilita uma avaliação dos pacientes com *delirium* hipoativo. No entanto, a alteração do ciclo sono-vigília, presente no DDS, na MDAS e também no ICDSC, dificulta uma avaliação pontual, necessitando de informações longitudinais, o que pode determinar limitações de seu uso.

Escalas como a NEECHAM e o ICDSC possuem a vantagem de terem sido validadas possibilitando a aplicação tanto por enfermeiros como por residentes de enfermagem, desde que devidamente treinados.[11,20] Já a DRS-R-98, em seu estudo de validação para uso no Brasil, foi aplicada apenas por médicos psiquiatras, o que não é a realidade encontrada nas UTI.[22] As outras ferramentas (DDS, MDAS e CTD) foram testadas tendo o médico plantonista como avaliador. Especificamente a MDAS foi validada também com médicos residentes aplicando-a.[17] No entanto, antes da utilização, deve haver treinamento e capacitação para o uso dos diversos instrumentos. Com a capacitação prévia dos profissionais, a maioria das escalas mostrou boa correlação entre avaliadores.[21,26] Outro fator importante a ser

considerado na escolha da escala são os subgrupos de pacientes a serem avaliados. A escolha da ferramenta, baseada no tipo de admissão e na gravidade do paciente, influencia na sua acurácia e na taxa de correlação com outras escalas.[27] O ICDSC se mostrou mais sensível que o CAM-ICU no subgrupo de pacientes cirúrgicos, por exemplo.[27] Fica a critério de cada unidade de cuidado intensivo, portanto, a escolha da escala que vai utilizar, desde que a utilize da forma correta e com profissionais mais indicados.

Hoje, existem diversos métodos diagnósticos consolidados,[28] mas os de avaliação quantitativa ainda são pouco utilizados por parte da equipe médica. A associação de escalas diagnósticas com instrumentos validados para estratificação deveria sempre ser considerada para o melhor entendimento e acompanhamento dos pacientes com *delirium*. O DDS, por exemplo, só deve ser utilizado após o diagnóstico confirmado.[10] O ICDSC, apesar de ter sido estudado como ferramenta diagnóstica, possui especificidade variada[10,29,30] e, consequentemente, pode gerar resultados falso-positivos.[25,27] No entanto, meta-análises e *guidelines* recentes sugerem que o CAM-ICU e o ICDSC são os instrumentos mais bem estudados para diagnóstico do *delirium* e, portanto, sugeridos como ferramentas de escolha para essa finalidade.[28,30,31]

O ICDSC foi a ferramenta mais bem estudada diante dos trabalhos encontrados,[10,11,25,28-30] sugerindo que, apesar de não existir uma ferramenta ideal, é a que melhor se adequa à avaliação da estratificação do *delirium*. Outra característica importante dessa ferramenta é a possibilidade de diagnosticar o *delirium* subsindrômico,[25] condição clínica com desfechos intermediários entre pacientes com e sem *delirium*.[32]

O diagnóstico do *delirium* já está bem estabelecido na literatura, no entanto, sua estratificação ainda é um aspecto não adequadamente determinado, o que dificultou a realização da presente revisão. Os estudos são bastantes heterogêneos quanto a população alvo, profissional avaliador, grau de sedação dos pacientes incluídos, e sinais e sintomas avaliados, impossibilitando, assim, uma comparação entre as diferentes escalas. Dessa forma, foi possível apenas uma análise descritiva. No entanto, a presente revisão permitiu mostrar as características, e os pontos positivos e negativos de cada escala disponível na literatura, para estratificação dos pacientes com *delirium* internados em UTI.

CONCLUSÃO

Foram identificadas seis escalas validadas (porém apenas duas para a língua portuguesa), tendo como população alvo pacientes internados em unidades de terapia intensiva sob diferentes graus de sedação (entubados ou não). Todas apresentaram boa acurácia para a estratificação do *delirium*. A escala mais estudada e que melhor se adequa ao uso em unidade de terapia intensiva foi o ICDSC, por sua praticidade, acurácia e validação para a língua portuguesa.

ABSTRACT

Objective: To identify scales that can establish a quantitative assessment of delirium symptoms in critically ill patients through a systematic review.

Methods: Studies that evaluated delirium stratification scales in patients hospitalized in intensive care units were selected in a search performed in the MedLine database. Validation studies of these scales and their target patient populations were analyzed, and we identified the examiner and the signs and symptoms evaluated. In addition, the duration of the application and the sensitivity and specificity of each scale were assessed.

Results: Six scales were identified: the Delirium Detection Score, the Cognitive Test of Delirium, the Memorial Delirium Assessment Scale, the Intensive Care Delirium Screening Checklist, The Neelon and Champagne Confusion Scale and the Delirium Rating Scale-Revised-98.

Conclusion: The scales identified allow the stratification and monitoring of critically ill patients with delirium. Among the six scales, the most studied and best suited for use in the intensive care units was the Intensive Care Delirium Screening Checklist.

Keywords: Delirium; Evaluation/methods; Scales; Sensitivity and specificity; Intensive Care Units

REFERÊNCIAS

1. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35(7):1276-80.
2. Kishi Y, Iwasaki Y, Takezawa K, Kurosawa H, Endo S. Delirium in critical care unit patients admitted through an emergency room. Gen Hosp Psychiatry. 1995;17(5):371-9.
3. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med. 2004;32(11):2254-9.
4. Guenther U, Popp J, Koecher L, Muders T, Wrigge H, Ely EW, et al. Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients. J Crit Care. 2010;25(1):144-51.
5. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703-10.
6. Mistarz R, Eliott S, Whitfield A, Ernest D. Bedside nurse-patient interactions do not reliably detect delirium: an observational study. Aust Crit Care. 2011;24(2):126-32.
7. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420.
8. Han JH, Zimmerman EE, Cutler N, Schnelle J, Morandi A, Dittus RS, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. Acad Emerg Med. 2009;16(3):193-200.
9. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29(7):1370-9.
10. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27(5):859-64.
11. Gusmao-Flores D, Salluh JI, Dal-Pizzol F, Ritter C, Tomasi CD, Lima MA, et al. The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients. Clinics (Sao Paulo). 2011;66(11):1917-22.
12. Hart RP, Levenson JL, Sessler CN, Best AM, Schwartz SM, Rutherford LE. Validation of a cognitive test for delirium in medical ICU patients. Psychosomatics. 1996;37(6):533-46.
13. Hart RP, Best AM, Sessler CN, Levenson JL. Abbreviated cognitive test for delirium. J Psychosom Res. 1997;43(4):417-23.
14. Otter H, Martin J, Bäsell K, von Heymann C, Hein OV, Böllert P, et al. Validity and reliability of the DDS for severity of delirium in the ICU. Neurocrit Care. 2005;2(2):150-8.
15. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Elseviers M, Bossaert L. A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. Crit Care. 2008;12(1):R16.
16. Osse RJ, Tulen JH, Hengeveld MW, Bogers AJ. Screening methods for delirium: early diagnosis by means of objective quantification of motor activity patterns using wrist-actigraphy. Interact Cardiovasc Thorac Surg. 2009;8(3):344-8; discussion 348.
17. Shyamsundar G, Raghuthaman G, Rajkumar AP, Jacob KS. Validation of memorial delirium assessment scale. J Crit Care. 2009;24(4):530-4.
18. Neufeld KJ, Hayat MJ, Coughlin JM, Huberman AL, Leistikow NA, Krumm SK, et al. Evaluation of two intensive care delirium screening tools for non-critically ill hospitalized patients. Psychosomatics. 2011;52(2):133-40.
19. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. J Pain Symptom Manage. 1997;13(3):128-37.
20. Immers HE, Schuurmans MJ, van de Bijl JJ. Recognition of delirium in ICU patients: a diagnostic study of the NEECHAM confusion scale in ICU patients. BMC Nurs. 2005;4:7.
21. Fadul N, Kaur G, Zhang T, Palmer JL, Bruera E. Evaluation of the memorial delirium assessment scale (MDAS) for the screening of delirium by means of simulated cases by palliative care health professionals. Support Care Cancer. 2007;15(11):1271-6.
22. de Negreiros DP, da Silva Meleiro AM, Furlanetto LM, Trzepacz PT. Portuguese version of the Delirium Rating Scale-Revised-98: reliability and validity. Int J Geriatr Psychiatry. 2008;23(5):472-7.
23. Radtke FM, Franck M, Schneider M, Luetz A, Seeling M, Heinz A, et al. Comparison of three scores to screen for delirium in the recovery room. Br J Anaesth. 2008;101(3):338-43.
24. Radtke FM, Franck M, Schust S, Boehme L, Pascher A, Bail HJ, et al. A comparison of three scores to screen for delirium on the surgical ward. World J Surg. 2010;34(3):487-94.
25. Tomasi CD, Grandi C, Salluh J, Soares M, Giombelli VR, Cascaes S, et al. Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes. J Crit Care. 2012;27(2):212-7.
26. Devlin JW, Fong JJ, Fraser GL, Riker RR. Delirium assessment in the critically ill. Intensive Care Med. 2007;33(6):929-40. Review.
27. Fagundes JA, Tomasi CD, Giombelli VR, Alves SC, de Macedo RC, Topanotti MF, et al. CAM-ICU and ICDSC agreement in medical and surgical ICU patients is influenced by disease severity. PloS One. 2012;7(11):e51010.
28. Neto AS, Nassar AP Jr, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, et al. Delirium screening in critically ill patients: a systematic review and meta-analysis. Crit Care Med. 2012;40(6):1946-51. Review.
29. George C, Nair JS, Ebenezer JA, Gangadharan A, Christudas A, Gnanaseelan LK, et al. Validation of the Intensive Care Delirium Screening Checklist in nonintubated intensive care unit patients in a resource-poor medical intensive care setting in South India. J Crit Care. 2011;26(2):138-43.
30. Gusmao-Flores D, Figueira Salluh JI, Chalhub RA, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Crit Care. 2012;16(4):R115.
31. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263-306. Review.
32. Cole M, McCusker J, Dendukuri N, Han L. The prognostic significance of subsyndromal delirium in elderly medical inpatients. J Am Geriatr Soc. 2003;51(6):754-60.

ARTIGO 6

Título: “Delirium: Uma disfunção orgânica como outra qualquer".

Autores: **Dimitri Gusmao-Flores**, **Lucas C Quarantini**

Jornal: *Critical Care Medicine* Fator de Impacto: 6,124

Ano de publicação: 2012

Número de citações: 0 (fonte: *web of knowledge*)

Carta ao Editor comentando o estudo original “*Delirium in critically ill patients: Impact on long-term health-related quality of life and cognitive functioning*” de van den Boogaard M e col. publicado na *Critical Care Medicine*, 2012.

model of Lagu et al remains superior to the customized versions of the Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II models.

Dr. van der Veen is the Director of the Praktijk Index, a company that sells real-time monitoring tools in which the Hospital Standardized Mortality Ratio model is implemented (not the customized Hospital Standardized Mortality Ratio in the article). The remaining authors have not disclosed any potential conflicts of interest.

Sylvia Brinkman, MSc, Ameen Abu-Hanna, PhD, André van der Veen, Evert de Jonge, MD, PhD, Nicolette F. de Keizer, PhD, Academic Medical Center, Amsterdam, The Netherlands

REFERENCES

1. Lagu T, Higgins TL, Nathanson BH, et al: Incorporating initial treatments improves the performance of a mortality prediction model based on administrative data. *Crit Care Med* 2012; 40:2268–2269
2. Brinkman S, Abu-Hanna A, van der Veen A, et al: A comparison of the performance of a model based on administrative data and a model based on clinical data: Effect of severity of illness on standardized mortality ratios of intensive care units*. *Crit Care Med* 2012; 40:373–378

DOI: 10.1097/CCM.0b013e31820eb763

Delirium: A organ dysfunction like any other

To the Editor:

The intensive care units appeared in response to the need for better monitoring of critically ill patients. The intensivist physicians were involved very early, and many of them fell in love, in identification and care of organ dysfunction ... but only few dysfunctions. For too long the focus on studies in the intensive care unit was directed to understanding and treating states of circulatory shock, renal, and respiratory failure. Only in the last 10 yrs, delirium, a form of presentation of the acute brain dysfunction, has been the focus on research. During this period, a major step was taken at the description and validation of accurate diagnostic tools (1), but little is known about how the best way to prevent and treat delirium in critically ill patients with its different forms of presentation (hyperactive, hypoactive, and mixed). The recently published study by van den Boogaard et al (2) was a Dutch contribution aimed to assess the significance of delirium on the quality of life and cognitive function of patients after 18 months of the intensive care discharge. They found greater cognitive impairment in those patients who had delirium, and an association between the duration of delirium and loss of memory.

However, two aspects that were not commented by the authors deserve special attention. First, a cognitive assessment was not performed prior to admission in the intensive care unit. This seems to be a major limitation in most studies with similar objectives. Thus, it is unclear if previous cognitive or memory changes could predispose the emergence of delirium in hospitalized patients.

Furthermore, despite adjustments for covariates, no other description of organ dysfunction was reported in the results. All covariates were described at hospital admission. Nothing was mentioned about medications and other organ dysfunctions that arose during hospitalization. Patients with acute respiratory distress syndrome, for example, have an important impact on long-term cognitive functioning (3), and in addition, these changes may occur even in patients without delirium (4).

It is plausible to imagine that an acute brain injury presenting as delirium can leave several sequels, including cognitive impairment or loss of memory (5). In fact, it is not a surprise that a patient with an episode of acute renal failure develops a reduction in creatinine clearance chronically or even with the need for dialysis. Or that a patient with an acute lung injury develops functional respiratory failure in the long term. Thus, it is easy to take as true results as shown by van den Boogaard et al. But, take care. We need more evidence.

The design of future studies needs to consider these observations. An edge of doubt still exist about if episodes of delirium during the intensive care unit stay determines future cognitive impairment or it is just a marker of severity, as well as other organ dysfunction.

The authors have not disclosed any potential conflicts of interest.

Dimitri Gusmao-Flores, MD, Lucas C. Quarantini, MD, Programa de Pós-graduação em Processos Interativos dos Órgãos e Sistemas, Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, Bahia, Brazil

REFERENCES

1. Ely EW, Margolin R, Francis J, et al: Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; 29:1370–1379
2. van den Boogaard M, Schoonhoven L, Evers AW, et al: Delirium in critically ill patients: Impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med* 2012; 40:112–118
3. Hopkins RO, Weaver LK, Collingridge D, et al: Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005; 171:340–347
4. Jones C, Griffiths RD, Slater T, et al: Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. *Intensive Care Med* 2006; 32:923–926
5. MacLullich AM, Beaglehole A, Hall RJ, et al: Delirium and long-term cognitive impairment. *Int Rev Psychiatry* 2009; 21:30–42

DOI: 10.1097/CCM.0b013e31825149e9

The authors reply:

We thank Gusmao-Flores and Quarantini for their interest in and response to our long-term quality-of-life study in intensive care unit (ICU) survivors who did and did not suffer from delirium during their ICU stay (1). Their response focuses on two important issues: cognitive assessments prior to ICU admission and organ dysfunction.

Regarding their first argument, we indeed did not perform cognitive function measures prior to the ICU admission. As described in the Discussion section, this could be considered as a limitation of our study. However, we did ask patients to rate the change in their cognitive functioning (range: much better [1-point] to much worse [5-points]) compared to the period prior to the ICU admission. Patients with delirium experienced significantly more long-term problems with memory and concentration after ICU discharge than before when compared with nondelirium patients (score 3.4 ± 1.2 vs. 2.3 ± 1.1; $p < .01$). Although this may be considered a crude and not validated measure, it does indicate how patients perceive a possible change in their cognitive functioning.

The second argument concerns the fact that we did not adjust out data for

ARTIGO 7

Título: “Benzodiazepinos e Delirium: a melhor opção para o paciente certo."
Autores: **Dimitri Gusmao-Flores**, João Pedro LM Carvalho, **Lucas C Quarantini**
Jornal: *Critical Care Medicine* Fator de Impacto: 6,124
Ano de publicação: 2013
Número de citações: 0 (fonte: *web of knowledge*)

Carta ao Editor comentando o estudo original “*Factors Predisposing to Coma and Delirium: Fentanyl and Midazolam Exposure; CYP3A5, ABCB1,and ABCG2 Genetic Polymorphisms; and Inflammatory Factors*” de van den Boogaard M e colaboradores publicado na *Critical Care Medicine*, 2013.

Kusum Menon, MD, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Canada

REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. *Crit Care Med* 2013; 41:580–637
2. Valoor HT, Singhi S, Jayashree M: Low-dose hydrocortisone in pediatric septic shock: An exploratory study in a third world setting. *Pediatr Crit Care Med* 2009; 10:121–125
3. Pizarro CF, Troster EJ, Damiani D, et al: Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med* 2005;33:855–859
4. De Kleijn ED, Joosten KF, Van Rijn B, et al: Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in children with severe meningococcal disease. *Pediatr Infect Dis J* 2002; 21:330–336
5. Riordan FA, Thomson AP, Ratcliffe JM, et al: Admission cortisol and adrenocorticotrophic hormone levels in children with meningococcal disease: Evidence of adrenal insufficiency? *Crit Care Med* 1999; 27:2257–2261
6. Widya MS, Martoatmodjo: Clinical observations on dengue shock syndrome (an evaluation of steroid treatment). *Paediatr Indones* 1975; 15:151–160
7. Sumarmo, Talogo W, Asrin A, et al: Failure of hydrocortisone to affect outcome in dengue shock syndrome. *Pediatrics* 1982; 69:45–49

DOI: 10.1097/CCM.0b013e31828cf478

The authors reply:

We first want to recognize the contributions of Menon (1) to the field of pediatric sepsis and in particular to the topic of the use of steroids in pediatric sepsis. We will take this opportunity to use her input to add more clarity to our recommendation and rationale as to steroid therapy of pediatric septic shock.

The adult guidelines recommend that 200 mg of hydrocortisone should be considered in an adult with continued hemodynamic instability despite adequate fluid loading and vasopressor infusion. *We have made more restrictive pediatric recommendations.*

We *only* recommend giving hydrocortisone for catecholamine-resistant shock in pediatric patients with infection-associated Addison's disease. This is because it is standard of care to give hydrocortisone for Addisonian shock. The prevalence of infection-associated Addison's disease depends on the patient population with at-risk groups including *Waterhouse Friederichsen* purpura fulminans, hypopituitary/hypothalamic syndromes, and patients on chronic steroid therapies such as cancer and transplantation populations being higher than 25% and other low-risk patient groups being lower than 10%. Addison's disease is defined by either a baseline cortisol less than 4 mg/dL or an adrenocorticotropic hormone-stimulated cortisol less than 18 mg/dL (2). This was graded 1A. It was graded a strong recommendation because it is standard to treat Addisonian shock of any cause with hydrocortisone. We agree that an argument could be made for a lower letter grade as to quality of evidence.

The stress dose recommended in children is 50 mg/m2 (2 mg/kg) daily with shock doses as high as 50 mg/kg/d having been reported (2–4).

The authors have disclosed that they do not have any potential conflicts of interest.

Joseph A. Carcillo, MD, Children's Hospital of Pittsburg, Pittsburgh, PA; **Adrienne G. Randolph, MD**, Children's Hospital Boston, MA; **Jan A. Hazelzet, MD**, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands; **R. Phillip Dellinger, MD**, Cooper Health Systems, Camden, NJ

REFERENCES

1. Menon K: Use of Hydrocortisone for Refractory Shock in Children. *Crit Care Med* 2013; 41:e294–e295
2. Aneja R, Carcillo JA: What is the rationale for hydrocortisone treatment in children with infection-related adrenal insufficiency and septic shock? *Arch Dis Child* 2007; 92:165–169
3. McEvoy G: Hormones and synthetic substitutes. *In:* The American Hospital Formulary. Bethesda, MD, American Society of Health-System Pharmacists, 1998, pp 68:04–68:08
4. Drugs.com website: Hydrocortisone dosage. Available at: http://www.drugs.com/dosage/hydrocortisone.html. Accessed August 6, 2013

DOI: 10.1097/CCM.0b013e3182a51cf0

Benzodiazepines and Delirium: The Best Option for the Right Patient

To the Editor:

In a recent issue of *Critical Care Medicine,* Skrobik et al (1) published an elegant study on predisposing factors for coma and delirium in critically ill patients. With a very careful methodology, this study surprised us with the results that showed no association between benzodiazepines and delirium. More surprising was to observe that patients with delirium had lower serum levels of midazolam compared with those without delirium. These findings differ from previously published literature (2). There are at least three ways to explain these results. First, it is possible that patients who had fewer episodes of delirium with higher levels of midazolam were, in fact, in a coma, making it impossible to evaluate them with the specific diagnostic tools for delirium. If Skrobik et al (1) had used the variable "delirium free without coma," perhaps the message from the result would be clearer. On the other hand, the serum level of benzodiazepine (mean) in the group of comatose patients and in the patients without delirium was quite different, suggesting that patients without delirium were indeed a distinct population from those in a coma at the time of assessment. Second, the diagnostic tool used (the Intensive Care Delirium Screening Checklist [ICDSC]) may not have good accuracy in assessing patients using sedation. However, the ICDSC was validated in different languages, where in a recent meta-analysis, the pooled sensitivity was 74% and, more important for this study, the pooled specificity was 84% (3). Therefore, this tool has a good diagnostic accuracy. So, maybe the problem is not there. Third, and what we believe to be the reason why the results were a surprise, is that the prevalence of drinkers was high (around 35%). This population clearly benefits from the use of benzodiazepine, either to prevent cases of alcohol withdrawal, which can meet the clinical criteria for delirium,

or as a first-line treatment for abstinence (4). Other studies with different methodology, that is, observational, validation of a diagnostic tool for delirium and clinical trials, which had episodes of delirium as an outcome, usually exclude patients with a history of alcohol abuse (5). Thus, the results of the study by Skrobik et al (1) should be interpreted as based on their particular profile of the sample. Although a well-done study, this feature may hinder the external validation of the results.

The authors have disclosed that they do not have any potential conflicts of interest.

Dimitri Gusmao-Flores, MD, Programa de pós graduação em Processo Interativo dos Órgãos e Sistemas, Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, Bahia, Brazil; **João Pedro L. M. Carvalho, AM**, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, Bahia, Brazil; **Lucas C. Quarantini, MD, PhD** Programa de pós graduação em Medicina e Saúde, Universidade Federal da Bahia, Salvador, Bahia, Brazil

REFERENCES

1. Skrobik Y, Leger C, Cossette M, et al: Factors Predisposing to Coma and Delirium: Fentanyl and Midazolam Exposure; CYP3A5, ABCB1, and ABCG2 Genetic Polymorphisms; and Inflammatory Factors. *Crit Care Med* 2013; 41:999–1008
2. Pandharipande P, Shintani A, Peterson J, et al: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; 104:21–26
3. Gusmao-Flores D, Figueira Salluh JI, Chalhub RA, et al: The confusion assessment method for the intensive care unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) for the diagnosis of delirium: A systematic review and meta-analysis of clinical studies. *Crit Care* 2012; 16:R115
4. Ungur LA, Neuner B, John S, et al: Prevention and therapy of alcohol withdrawal on intensive care units: Systematic review of controlled trials. *Alcohol Clin Exp Res* 2013; 37:675–686
5. Pandharipande PP, Pun BT, Herr DL, et al: Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA* 2007; 298:2644–2653

DOI: 10.1097/CCM.0b013e31829824f0

Continuous Electroencephalographic Monitoring and Vasospasm

To the Editor:

We have read with interest the review article by Sutter et al (1) recently published in *Critical Care Medicine* about the utilization of continuous electroencephalography (cEEG) in ICU patients. In the section dedicated to subarachnoid hemorrhage (SAH), Sutter et al (1) refer mainly to the monitoring of seizures. However, one of the major complications of SAH is represented by vasospasm; it contributes to delayed cerebral ischemia (DCI) resulting in substantial disability and mortality (2). The diagnosis of vasospasm is very challenging (2). Focal electroencephalographic slowing may indicate ischemia rendering cEEG a potential useful tool in the monitoring of vasospasm in patients with SAH (1). In this regard, small studies have been published.

Vespa et al (3) studied prospectively 32 acute SAH patients with quantitative cEEG, testing the hypothesis that decreased relative alpha (RA) variability is a marker of early brain dysfunction accompanying vasospasm. During the course of ICU stay, vasospasm developed in 19 of 32 patients; in these patients, RA was decreased and it improved after vasospasm resolution. In 10 of 19 patients, RA reduction preceded the diagnosis of vasospasm by a mean of 2,9 days (SD, 1.73). In seven of 13 patients, decreased RA was not related to vasospasm but to intracranial hypertension. Vespa et al (3) concluded that RA variability is a sensitive but nonspecific predictor of the development of vasospasm and that RA can be monitored continuously allowing an early therapy.

Claassen et al (4) evaluated prospectively 34 poor-grade SAH patients with cEEG to identify quantitative electroencephalography variables that are most sensitive and specific for the detection of DCI. DCI developed in nine of 34 patients; the alpha/delta ratio demonstrated the strongest association with DCI allowing a quick diagnosis and therapy to prevent cerebral infarction.

Rathakrishnan et al (5) studied prospectively 12 SAH patients (Hunt-Hess grades I–V) to determine whether cEEG permits the prediction of DCI related to clinical changes. A novel cEEG variable measuring alpha power and variability, termed composite alpha index, was graphically displayed and analyzed. Fifty-nine predictions were made in 12 patients. They concluded that quantitative cEEG supplements clinical data in patients with SAH allowing to detect DCI in an early stage.

From these preliminary studies, with a small number of patients, it emerges that cEEG may become a useful tool in the monitoring of vasospasm (allowing rapid diagnosis and therapy before irreversible brain damage occurs).

The review article by Sutter et al (1) allows intensivists to increase their skills about cEEG. We hope also that new studies involving a greater number of patients with SAH will begin to better delineate the role of cEEG in the early diagnosis of vasospasm.

The authors have disclosed that they do not have any potential conflicts of interest.

Edoardo Picetti, MD, Ilaria Rossi, MD, Maria Luisa Caspani MD, I Servizio Anestesia Rianimazione, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

REFERENCES

1. Sutter R, Stevens RD, Kaplan PW: Continuous Electroencephalographic Monitoring in Critically Ill Patients: Indications, Limitations, and Strategies. *Crit Care Med* 2013; 41:1124–1132
2. Komotar RJ, Schmidt JM, Starke RM, et al: Resuscitation and critical care of poor-grade subarachnoid hemorrhage. *Neurosurgery* 2009; 64:397–411
3. Vespa PM, Nuwer MR, Juhász C, et al: Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring. *Electroencephalogr Clin Neurophysiol* 1997; 103:607–615
4. Claassen J, Hirsch LJ, Kreiter KT, et al: Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. *Clin Neurophysiol* 2004; 115:2699–2710
5. Rathakrishnan R, Gotman J, Dubeau F, et al: Using continuous electroencephalography in the management of delayed cerebral ischemia following subarachnoid hemorrhage. *Neurocrit Care* 2011; 14:152–161

DOI: 10.1097/CCM.0b013e3182995784

ARTIGO 8

Título: “Triagem para diagnóstico de delirium no paciente grave".
Autores: **Dimitri Gusmao-Flores**, Jorge I Salluh, **Lucas C Quarantini**
Jornal: *Critical Care Medicine* Fator de Impacto: 6,124
Ano de publicação: 2013
Número de citações: 0 (fonte: *web of knowledge*)

Carta ao Editor comentando o estudo original “*Delirium screening in critically ill patients: A systematic review and meta-analysis*.” de Neto AS e colaboradores publicado na *Critical Care Medicine*, 2013.

esophageal pressure (P_{ES}) (3). This indeed is not surprising because the abdominal "extra weight" is not uniformly applied throughout the chest wall surface. Lacking definitive experimental data, one might speculate that the nondependent lung regions could be over distended by a PEEP level titrated to counterbalance the abdominal "extra weight," particularly if the discrepancy between P_{ES} and E_{CW} is marked (i.e., in patients with higher P_{ES} and lower E_{CW}).

The aim of our transpulmonary approach was perhaps less ambitious; we waived the task of quantifying the abdominal "extra weight" through esophageal manometry, whereas we trusted on the traditional view that PEEP should be titrated (after an adequate lung recruiting maneuver) to maximize alveolar recruitment and minimize tidal alveolar overdistension. To do so, we applied a modified version of the Express trial strategy (4)—maximal PEEP compatible with end-inspiratory airway opening plateau pressure ($P_{AO,PLAT}$) of 30 cm H_2O—by substituting $P_{AO,PLAT}$ with $P_{L,PLAT}$. We used esophageal manometry to obtain tidal P_{ES} swings and calculated chest wall and lung elastance (E_{CW}, E_L) from tidal P_{ES} excursions, not taking into account absolute P_{ES} values (5). Subsequently we used the ratio between E_{CW} and E_L to evaluate the percentage of pressure applied to the airway opening effectively applied to the lung and to the chest wall. Chiumello and coworkers (6) found in patients with acute respiratory distress syndrome that the contribution of chest wall elastance to the whole respiratory system elastance was between 7% and 67%. Indeed, our P_{LPLAT} target (26 cm H_2O) is the lung distending pressure resulting by applying 30 cm H_2O to the airway opening in patients with the lowest contribution of E_{CW} to the whole respiratory system elastance. Of note, as underscored by Drs. Talmor and Loring, hemodynamic parameters were not affected by this approach (7, 8).

In conclusion, we agree with Drs. Talmor and Loring that it is time to target P_L when setting the ventilator. At the same time, we are convinced that further work is needed to set up the ideal (or perhaps less erroneous) method for interpreting and using esophageal manometry.

Dr. Grasso received payment for lectures/education presentations for Maquet, Solna, Sweden. Dr. Staffieri received payment for lectures/education presentations for Novartis. Dr. Stripoli has not disclosed any potential conflicts of interest.

Salvatore Grasso, MD, Dipartimento dell'Emergenza e Trapianti d'Organo, Sezione di Anestesiologia e Rianimazione, Università degli Studi Aldo Moro, Bari, Italy; **Francesco Staffieri, VD, PhD,** Dipartimento dell'Emergenza e Trapianti d'Organo, Sezione di Chirurgia Veterinaria, Università degli Studi Aldo Moro, Bari, Italy; **Tania Stripoli, PhD,** Dottorato in Scienze Chirurgiche Sperimentali e Terapie Cellulari, Università degli Studi Aldo Moro, Bari, Italy

REFERENCES

1. Talmor D, Sarge T, Malhotra A, et al: Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359:2095–2104
2. Hedenstierna G: Esophageal pressure: Benefit and limitations. *Minerva Anestesiol* 2012; 78:959–966
3. Loring SH, O'Donnell CR, Behazin N, et al: Esophageal pressures in acute lung injury: Do they represent artifact or useful information about transpulmonary pressure, chest wall mechanics, and lung stress? *J Appl Physiol* 2010; 108:515–522
4. Mercat A, Richard JC, Vielle B, et al; Expiratory Pressure (Express) Study Group: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646–655
5. Gattinoni L, Chiumello D, Carlesso E, et al: Bench-to-bedside review: Chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. *Crit Care* 2004; 8:350–355
6. Chiumello D, Carlesso E, Cadringher P, et al: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008; 178:346–355
7. Grasso S, Terragni P, Birocco A, et al: ECMO criteria for influenza A (H1N1)-associated ARDS: Role of transpulmonary pressure. *Intensive Care Med* 2012; 38:395–403
8. Staffieri F, Stripoli T, De Monte V, et al: Physiological effects of an open lung ventilatory strategy titrated on elastance-derived end-inspiratory transpulmonary pressure: Study in a pig model. *Crit Care Med* 2012; 40:2124–2131

DOI: 10.1097/CCM.0b013e3182741c24

Delirium Screening in Critically Ill Patients

To the Editor:

In the past 10 yrs, several methods have been developed and validated to diagnose delirium in critically ill patients. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are most commonly used for this purpose. The recent article by Neto et al was a worthy attempt to review, systematically, and to conduct a meta-analytical approach of these studies (1). However, despite a comprehensive search in the databases, there are shortcomings in the selection of studies and on the extraction of data that, unfortunately, compromised the final results and their interpretation.

First, we believe that the inclusion of the study by Guenther et al was inadequate (2). This study evaluated the CAM-ICU Flowsheet and not the CAM-ICU. Although these tools are quite similar, with the only difference being the change in the order of the features 3 and 4, they are not identical. Recently, in a multicenter study, we observed differences in the diagnostic accuracy when these tools were compared in a sample of critically ill patients (3). Thus, we believe that the mentioned study should not be included for the final calculation of the meta-analysis. Second, and what we consider the most serious flaw, the extraction of some data from the selected studies, particularly in the studies that evaluated the ICDSC, was not appropriate. The original study of this tool disclosed in its abstract and discussion sensitivity of 99%, using the cutoff of four (4). And this was the data used in this meta-analysis (1). But this value refers to the upper limit of the confidence interval of 95%. In Table 5 of the study by Bergeron et al, we can calculate the accuracy and the fact that the sensitivity was 93.3% (95% confidence interval 68.1–99.8). Another issue occurred in the extraction of data from the study by George et al (5), but in this case, the difference of the values used in the meta-analysis and the actual value was even more significant. Neto

et al used the values concerning the accuracy of the tool when the cutoff used was three and not four as is generally accepted. With the usually employed cutoff, the sensitivity of ICDSC in the study by George et al is 75% and not 90%. All other articles that validated the ICDSC used the cutoff of four. Thus we do not agree with Neto et al who conclude in the discussion of their study that ICDSC has high sensitivity. Probably, with the use of appropriate data, the pooled sensitivity of the ICDSC is lower than the pooled sensitivity of the CAM-ICU.

Finally, in a recent study of the validation of the CAM-ICU in the Portuguese language, included in this meta-analysis, we described in the methodology that the interval between the evaluation with the CAM-ICU and the Diagnostic and Statistical Manual of Mental Disorders-IV criteria was 30 mins (3), so we cannot understand why item 4 of the QUality Assessment of studies of Diagnostic Accuracy included in Systematic reviews scale (in the supplementary material) identified our study as "unclear."

The authors have not disclosed any potential conflicts of interest.

Dimitri Gusmao-Flores, MD, Programa de Pós-graduação em Processos Interativos dos Órgãos e Sistemas, Instituto de Ciências da Saúde (ICS), Universidade Federal da Bahia, Canela, Salvador, Bahia, Brazil; **Jorge Ibrain Filgueira Salluh, MD,** Instituto Nacional do Câncer, Rio de Janeiro, RJ, Brazil; **Lucas C. Quarantini, MD,** Programa de Pós-graduação em Medicina e Saúde, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, Bahia, Brazil

REFERENCES

1. Neto AS, Nassar AP Jr, Cardoso SO, et al: Delirium screening in critically ill patients: A systematic review and meta-analysis. *Crit Care Med* 2012; 40:1946–1951
2. Guenther U, Popp J, Koecher L, et al: Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients. *J Crit Care* 2010; 25:144–151
3. Gusmao-Flores D, Salluh JI, Dal-Pizzol F, et al: The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients. *Clinics (Sao Paulo)* 2011; 66:1917–1922
4. Bergeron N, Dubois MJ, Dumont M, et al: Intensive Care Delirium Screening Checklist: Evaluation of a new screening tool. *Intensive Care Med* 2001; 27:859–864
5. George C, Nair JS, Ebenezer JA, et al: Validation of the Intensive Care Delirium Screening Checklist in nonintubated intensive care unit patients in a resource-poor medical intensive care setting in South India. *J Crit Care* 2011; 26:138–143

DOI: 10.1097/CCM.0b013e31826be806

The authors reply:

First of all, we would like to thank Gusmao-Flores et al for the comments on our article. Regarding the question of the inclusion of the study by Guenther et al (1), the Confusion Assessment Method for the ICU (CAM–ICU) flowsheet switches the original numbering of features 3 and 4 for simplicity because most ICU patients with delirium are positive in the order of the flowsheet, thus allowing the CAM-ICU flowsheet to be completed in just three features. The sensitivity, specificity, positive predictive value, and negative predictive value for the CAM-ICU flowsheet found in the study cited by Gusmao-Flores and colleagues were identical to those of the CAM-ICU (72.5%, 96.2%, 90.6%, and 87.4%, respectively) (2). So we think that the study by Guenther et al (1) can be included without any bias. Besides we recalculated our data without this study and found similar results.

Indeed, if one calculates the sensitivity from Table 5 of the study from Bergeron et al (3), one will find a value of 93% as stated by Gusmao-Flores et al. However, in the text of the article they state that "With a cut-off value of 4 points, sensitivity is 99% and specificity 64%..." and we used this value for analysis. However, when we recalculated our data with a sensitivity of 93% instead of 95%, we found similar results.

Finally, in the study by George et al (4), they found that the best cut-off value for diagnosis of delirium was 3 and not 4 as stated before in another study (2). We choose to use this value because, in the population studied by these authors, it demonstrated the best sensitivity and specificity. Also, the study by Bergeron et al (3) excluded mechanical-ventilated patients, which weakens the extrapolation of its cut-off value for studies that evaluated patients on mechanical ventilation as by George et al (4). Finally, we agree and we apologize for the mistake in the item four of the Quality Assessment of Diagnostic Accuracy Studies scale. Really, the study by Gusmao-Flores et al (2) stated that the time interval between each evaluation was 30 mins.

The authors have not disclosed any potential conflicts of interest.

Ary Serpa Neto, MD, ABC Medical School, Santo André, São Paulo, Brazil; **Arjen J. Slooter, MD, PhD,** Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

REFERENCES

1. Guenther U, Popp J, Koecher L, et al: Validity and reliability of the CAM-ICU flowsheet to diagnose delirium in surgical ICU patients. *J Crit Care* 2010; 25:144–151
2. Gusmao-Flores D, Salluh JI, Dal-Pizzol F, et al: The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients. *Clinics (Sao Paulo)* 2011; 66:1917–1922
3. Bergeron N, Dubois MJ, Dumont M, et al: Intensive Care Delirium Screening Checklist: Evaluation of a new screening tool. *Intensive Care Med* 2001; 27:859–864
4. George C, Nair JS, Ebenezer JA, et al: Validation of the Intensive Care Delirium Screening Checklist in nonintubated intensive care unit patients in a resource-poor medical intensive care setting in South India. *J Crit Care* 2011; 26:138–143

DOI: 10.1097/CCM.0b013e3182741ec0

Hospitalist Path to Critical Care Fellowship Is Uneven and Narrow

To the Editor:

As the organization representing more than 150 pulmonary critical care and internal medicine critical care training program directors, we commend the efforts of the authors to address our field's workforce shortage and improve the training of the many hospitalists who currently manage critically ill patients (1). However, we also share their concerns about

ARTIGO 9

Título: “Inibidores da colinesterase para tratamento do *delirium*”.
Autores: **Dimitri Gusmao-Flores**, Ricardo A Challhub, **Lucas C Quarantini**
Jornal: *The Lancet* Fator de Impacto: 39,06
Ano de publicação: 2011
Número de citações: 0 (fonte: *web of knowledge*)

Carta ao Editor comentando o estudo original “*Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial*” de van Eijk MMJ e colaboradores publicado no *The Lancet*, 2010.

Correspondence

Cholinesterase inhibitor treatment in patients with delirium

Maarten van Eijk and co-workers (Nov 27, p 1829)[1] report a possible higher risk of mortality in critically ill patients with delirium who received rivastigmine oral solution and haloperidol than in those who received placebo and haloperidol (p=0·07), a finding that led to early trial termination.

Given our own interest in delirium trials, we were curious about the conclusions from this prospective study, for which the population was only 25% of the target size. Data provided a signal to the Safety Monitoring Board to terminate the trial, but were underpowered for comparisons. Van Eijk and colleagues acknowledge that the findings could be due to chance because of the heterogeneous causes of death with no apparent relation to rivastigmine's mechanism of action.[1] An imbalance of health status was also notable: 46 (85%) of 54 rivastigmine-treated patients, versus 32 (64%) of 50 on placebo, were "emergency admissions", and rivastigmine-treated patients had been in intensive care for longer (15 days *vs* 8 days, p<0·0001) and had spent longer in comatose states (69/659 days *vs* 16/459 days, p<0·0001) than those on placebo.[1] Analyses were not adjusted for these differences.

There is evidence that confusional states represent a cholinergic deficit.[2] Preliminary studies of cholinesterase inhibitors in patients with delirium seemed promising,[3,4] so it is disappointing that this controlled study had methodological problems. We still expect more robust evidence for the efficacy or risk in delirium of cholinesterase inhibitors which—unlike neuroleptic treatment—might ameliorate the key pharmacological problem underlying confusional states. A large proportion of elderly patients with delirium already have, or will develop, dementia in due course.[5] Therefore, this condition may allow not only an early identification of patients at risk, but also the introduction of early and targeted intervention.

We have previously received honoraria from companies that manufacture and sell cholinesterase inhibitors.

*Lutz Frölich, Hans Förstl
Lutz.Froelich@zi-mannheim.de

Central Institute of Mental Health, Ruprecht-Karls University of Heidelberg and Technische Universität, 68159 Munich, Germany

1 van Eijk MMJ, Roes KCB, Honing MLH, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010; **376:** 1829–37.
2 Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging* 1993; **3:** 335–48.
3 Gamberini M, Bolliger D, Lurati Buse GA, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery—a randomized controlled trial. *Crit Care Med* 2009; **37:** 1762–68.
4 Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G. Cholinesterase inhibition as a possible therapy for delirium in vascular dementia: a controlled, open 24-month study of 246 patients. *Am J Alzheimers Dis Other Demen* 2004; **19:** 333–39.
5 Bickel H, Gradinger R, Kochs E, Forstl H. High risk of cognitive and functional decline after postoperative delirium: a three-year prospective study. *Dement Geriatr Cogn Disord* 2008; **26:** 26–31.

Maarten van Eijk and colleagues[1] postulated that use of the cholinesterase inhibitor rivastigmine to increase acetylcholine concentrations might attenuate inflammatory responses in the brain and thus improve the outcome of critically ill patients with delirium. However, they found a threefold higher mortality rate in patients treated with rivastigmine compared with patients treated with placebo.

Delirium is thought to be caused by the immunological response of the brain to signals of systemic inflammation, particularly when this involves infection.[2] This immunological response consists of cell proliferation, stimulation of the hypothalamus-pituitary-adrenal axis, and production of cytokines such as tumour necrosis factor (TNF) α and interleukin 6. Acetylcholine is able to suppress the production of pro-inflammatory cytokines through a specific action on α7 cholinergic receptors on macrophages.[3]

Perhaps the negative outcome seen by van Eijk and colleagues is not so surprising. Elderly people are more prone to delirium since their immunity is weaker, rendering them more prone to infections.[2] When these patients are treated with rivastigmine, their immunity is compromised even further, since the cytokine response is inhibited by higher acetylcholine concentrations. Moreover, the cytokine response is just a single aspect of the inflammatory response as a whole. In this respect, inhibition of the TNFα response by rivastigmine in patients with delirium might be similar to the inhibition of TNFα with monoclonal antibodies in patients with sepsis: it does not improve survival.[4]

We declare that we have no conflicts of interest.

*Anne-Cornélie J M de Pont, Michael A van Geer, Marcus J Schultz
a.c.depont@amc.uva.nl

Adult Intensive Care Unit, Academic Medical Centre, 1105 AZ Amsterdam, Netherlands

1 Van Eijk MMJ, Roes KCB, Honing MLH, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind placebo-controlled randomised trial. *Lancet* 2010; **376:** 1829–37.
2 Cerejeira J, Firmino H, Vaz Serra A, et al. The neuroinflammatory pathway of delirium. *Acta Neuropathol* 2010; **119:** 737–54.
3 Van der Poll T, Opal S. Host pathogen interactions in sepsis. *Lancet Infect Dis* 2008; **8:** 32–43.
4 Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. *Lancet* 1998; **351:** 929–33.

We have some doubts about the study by Maarten van Eijk and colleagues[1] on the use of rivastigmine in critically ill patients with delirium.

First, we could not understand the delay in starting therapy for delirium (12 h on average). There are several theories about the pathophysiology of delirium and few randomised studies, but, as with any other organ dysfunction, the promptness of


Science Photo Library

treatment can make a difference to its effectiveness. Second, mortality in the placebo group was very low (8%), which is surprising in a group of older patients (mean age 70 years) with a high risk of death (mean APACHE II score 19·6).[2]

Third, van Eijk and colleagues used the delirium severity index to measure severity of delirium; however, this instrument has been used only once previously (to report on the cost of hospital admission) and has not been validated for assessment of severity.[3] Finally, delirium is characterised by its fluctuating course, with episodes of normality between those of mental confusion, inattention, or disorganised thinking. With this in mind, to assess delirium only one or two times per day is unacceptable. Delirium should be viewed as an organ dysfunction, assessed four to six times per day, and with more robust methods (eg, the intensive care delirium screening checklist[4]).

We declare that we have no conflicts of interest.

Dimitri Gusmao-Flores, Ricardo Ávila Chalhub, Lucas C Quarantini
dimitrigusmao@gmail.com

Intensive Care Unit, University Hospital Prof Edgar Santos, Universidade Federal da Bahia, Salvador, BA, Brazil (DGF); and Programa de Pós-graduação em Processos Interativos dos Orgãos e Sistemas, Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, BA, Brazil (DGF, RAC, LCQ)

1 van Eijk MMJ, Roes KCB, Honing MLH, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010; **376:** 1829–37.

2 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13:** 818–29.

3 Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004; **32:** 955–62.

4 Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive care delirium screening checklist: evaluation of a new screening tool. *Intensive Care Med* 2001; **27:** 859–64.

The study by Maarten van Eijk and co-workers[1] suggests a detrimental effect of the cholinesterase inhibitor rivastigmine on both the severity of delirium and on survival after admission to the intensive-care unit (ICU).

At least 11 of the 16 patients who died in van Eijk and colleagues' study succumbed to sepsis or multiple-organ failure.[1] This finding raises the suspicion that rivastigmine is particularly deleterious in sepsis, which is a common risk factor for delirium in the ICU. Indeed, decreased rather than increased serum cholinesterase concentrations have been described in patients with septic shock.[2] In these patients, cholinesterase concentrations progressively decreased, and the patients with the very lowest levels tended to die.[2] Thus, further cholinesterase inhibition by means of rivastigmine treatment might not be desirable under these circumstances.

We suggest that, although rivastigmine treatment might have favourable effects on cerebral inflammation by enhancing cholinergic inhibition of microglial activity (thereby preventing neurodegeneration[3]), this process might be in vain in patients with sepsis because of concurrent excessive systemic cholinergic activity. Although the so-called cholinergic anti-inflammatory pathway has been promoted as potentially beneficial in sepsis,[4] increased anti-inflammatory activity has been associated with mortality in febrile patients.[5] Thus unrestrained acetylcholine signalling could cause immune paralysis, new episodes of sepsis, and persistent organ failure with an increased risk of death, and through these mechanism also provide a continual stimulus for delirium.

We declare that we have no conflicts of interest.

Ronan M G Berg, Kirsten Møller
ronan@dadlnet.dk

Centre of Inflammation and Metabolism, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, 2100 Copenhagen Ø, Denmark (RMGB); and Intensive Care Unit, Department of Anaesthesiology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark (KM)

1 van Eijk MMJ, Roes KCB, Honing MLH, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010; **376:** 1829–37.

2 al-Kassab AS, Vijayakumar E. Profile of serum cholinesterase in systemic sepsis syndrome (septic shock) in intensive care unit patients. *Eur J Clin Chem Clin Biochem* 1995; **33:** 11–14.

3 van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet* 2010; **375:** 773–75.

4 Tracey TJ. Reflex control of immunity. *Nat Rev Immunol* 2009; **9:** 418–28.

5 van Dissel JT, van Langevelde P, Westendorp RG, Kwappenberg K, Frölich M. Anti-inflammatory cytokine profile and mortality in febrile patients. *Lancet* 1998; **351:** 950–53.

The finding by Maarten van Eijk and colleagues[1] that the cholinesterase inhibitor rivastigmine increases the severity of delirium and might increase mortality in critically ill patients surprised van Eijk and colleagues and the medical community alike. It could be argued that delirium in patients with Alzheimer's disease is different from that in critically ill patients. An even more likely hypothesis is that the action of rivastigmine is different in the two groups of patients.

Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase via hydrolysis, resulting in increased cholinergic transmission. The major route of rivastigmine metabolism is by its own target enzymes. Plasma cholinesterase activity was reported to be lower in a small series of intensive-care patients,[2] a finding that has been confirmed in a larger cohort.[3] Standard doses of rivastigmine in patients with lower cholinesterase activity might, therefore, lead to accumulation of rivastigmine and acetylcholine. Toxic effects result from excess stimulation of central, peripheral muscarinic, and nicotinic receptors, but symptoms vary in cases of overdose. Bradycardia was not specifically seen in the critically ill patients treated with rivastigmine.[1] Intoxication however, has been reported in the absence of bradycardia.[4]

Considering the above, data on circulating concentrations of rivastigmine and cholinesterase activity

ARTIGO 10

Título: “Biomarcadores na encefalopatia séptica: revisão sistemáticas dos estudos clínicos”.

Autores: Paula V Zenaide, **Dimitri Gusmao-Flores**.

Jornal: Revista Brasileira de Terapia Intensiva

Ano de publicação: 2013

Número de citações: 0 (fonte: *web of knowledge*)

Objetivo: O objetivo deste estudo foi revisar sistematicamente a importância da enolase específica neuronal e S100B para diagnóstico e monitorização da encefalopatia séptica. Métodos: Foi realizada uma busca no banco de dados PubMed selecionando estudos que avaliaram níveis séricos de S 100 B e enolase específica neuronal em pacientes com sepse, publicados entre Janeiro de 2000 e Abril de 2012. Apenas estudos em humanos e que utilizaram um método adicional de avaliação neurológica foram selecionados. Resultados: Foram identificados nove estudos, dos quais sete associaram concentrações elevadas de S100 beta e enolase específica neuronal ao desenvolvimento de encefalopatia séptica; quarto também as associaram ao aumento de mortalidade. Entretanto, dois trabalhos não encontraram essa associação quando avaliaram S100 beta e um deles não observou correlação entre a enolase específica neuronal e encefalopatia séptica. Conclusão: A S100 beta e enolase específica neuronal são biomarcadores promissores para diagnóstico e monitorização de pacientes com encefalopatia séptica, mas é necessária uma maior investigação.

Paula Veriato Zenaide[1], Dimitri Gusmao-Flores[2,3]

Biomarkers in septic encephalopathy: a systematic review of clinical studies

Biomarcadores na encefalopatia séptica: revisão sistemática dos estudos clínicos

1. Academic Medical Course, Escola Bahiana de Medicina e Saúde Pública - Salvador (BA), Brazil.
2. Post-graduate Program in Interactive Processes of Organs and Systems, Instituto de Ciência da Saúde, Universidade Federal da Bahia - UFBA - Salvador (BA), Brazil.
3. Intensive Care Unit, Hospital Universitário Professor Edgar Santos - HUPES - Salvador (BA), Brazil.

ABSTRACT

Objective: The aim of this study was to systematically review the importance of neuron-specific enolase and S100 beta for diagnosing and monitoring septic encephalopathy.

Methods: A PubMed database search was performed to identify studies that evaluated S100 beta and neuron-specific enolase serum levels in patients with sepsis and that were published between January 2000 and April 2012. Only human studies that employed an additional method of neurological assessment were selected.

Results: Nine studies were identified, seven of which associated high concentrations of S100 beta and neuron-specific enolase with the development of septic encephalopathy. Four studies also associated these concentrations with increased mortality. However, two studies did not find such an association when they evaluated S100 beta levels, and one of these studies did not observe a correlation between neuron-specific enolase and septic encephalopathy.

Conclusion: S100 beta and neuron-specific enolase are promising biomarkers for diagnosing and monitoring patients with septic encephalopathy, but more research is necessary.

Keywords: Sepsis/complications; Brain diseases/etiology; Biological markers; S100 proteins; Phosphopyruvate hydratase; Intensive care

INTRODUCTION

Septic encephalopathy (SE) is a common but not well-understood complication of sepsis that affects between 9% and 71% of septic patients,[1-4] depending on the diagnostic criteria used. SE may be defined as a cerebral disorder resulting from metabolic and cellular signaling changes that are mediated by inflammatory components.[2] SE is typically an early event during the natural evolution of the disease and often appears prior to the failure of other organs.[2,5] Moreover, SE is associated with a worse prognosis.[6]

SE not only is associated with high hospital mortality (16%-63%),[2] but also can lead to long-term cognitive and functional limitations in those patients who survive.[7] Because of the possible consequences associated with this organ dysfunction, early diagnosis of brain injury can help identify those patients with more severe disease who require increased surveillance and immediate intervention. However, the clinical signs can vary based on the patient's degree of sedation; moreover, the clinical signs may be nonspecific, as several diseases are commonly associated with a reduced level of consciousness or agitation, disorientation, poor concentration, delirium, and coma.[1,4,5,8] Together, these factors render SE a diagnosis of exclusion.[1,2,9] Thus, clinical criteria, which

Conflicts of interest: None.

Submitted on January 30, 2013
Accepted on March 20, 2013

Corresponding author:
Paula Veriato Zenaide
Avenida Cardeal da Silva, 2.272, apto. 306
CEP: 41950-495 - Salvador (BA), Brazil
E-mail: pvzenaide@hotmail.com

are based on electrophysiological and biochemical tests, should be used in diagnosing SE.[3] In this context, SE biomarkers[2] would be useful for monitoring brain dysfunction and predicting mortality,[10] although the exact function of these markers in managing septic patients remains unclear.[11] Among the various biomarkers currently in use, neuron-specific enolase (NSE) and S100 beta are the most promising.

NSE is a γγ isomer of the cytoplasmic glycolytic enzyme that is found in neurons and neuroendocrine cells.[12] NSE is released into the blood and cerebrospinal fluid during brain damage.[13] S100 beta is a calcium-binding protein that belongs to the S100 family, which is composed of low-molecular-weight, multigene proteins.[14] S100 beta is produced by astrocytes in the central nervous system (CNS) but has both a neuroectodermal and mesodermal origin[15] and can therefore be expressed by other cells such as chondrocytes, adipocytes, and melanocytes. The exact mechanism by which S100 beta is excreted is still unknown but appears to be related to the oxidative stress[16] produced when neural tissue is attacked.

The aim of this systematic review is to highlight the importance of the biomarkers S100 beta and NSE in diagnosing and monitoring SE.

METHODS

A systematic PubMed search was performed for scientific articles related to SE biomarkers, employing the following search terms:

"((((((S-100beta) OR S-100 beta) OR S100beta) OR s100b) OR neuron-specific enolase) OR NSE) AND sepsis".

In addition to this search strategy, the keyword "septic encephalopathy" was used, and abstracts of all the resultant publications were evaluated to identify possibly relevant studies.

For the initial analysis, studies published in English between January 1, 2000 and April 31, 2012 were selected.

To select the studies, the following inclusion criteria were used: prospective cohort studies, clinical trials that used biomarkers as evaluation parameters, and cross-sectional studies. Furthermore, studies were selected that used at least one method of neurological assessment, such as the Glasgow coma scale (GCS), the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), computed tomography (CT), magnetic resonance imaging (MRI), electroencephalography (EEG), and intracranial pressure (ICP) or direct measurements of cerebral spinal fluid (CSF) markers. Studies were excluded from this review if the methodology did not fit the inclusion criteria, did not assess SE, did not measure NSE or S100 beta levels, included pregnant women in the patient cohort, or employed non-human experimental models.

The references in these selected articles were also used to identify additional studies.

The search for articles was performed independently and blindly by all of the present authors, who strictly adhered to the defined inclusion and exclusion criteria. The results obtained by each author were subsequently compared. In the case of disagreement over the selected articles, the publications were reassessed together by the authors, who deliberated on the relevance of the studies and whether to include them in the present review.

RESULTS

Using the predefined search strategies, 130 studies were identified. Of these studies, 121 were excluded, as shown in figure 1. Some of the excluded studies fulfilled more than one exclusion criterion but were grouped into only one category. No relevant studies were found in the reference sections of the selected articles.

Among the studies included in this review (Table 1), the majority had a non-probabilistic sampling design and included patients who were treated at their respective health services for sepsis,[17-20] severe sepsis,[10,17,19-21] and septic shock.[10,17,20,22,23] The diagnoses for these studies were based on the criteria established by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM). Only one study was conducted using initially healthy individuals.[23] Three studies analyzed children[18,19,22] who were 15 years of age or younger,[22] whereas the other investigations only included adults older than 18 years in their cohorts. The most frequently encountered exclusion criteria in these studies were primary

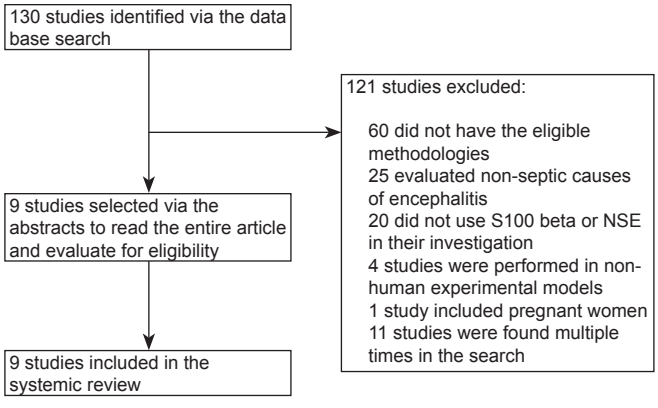


Figure 1 - Flowchart of the studies selected for systematic review. NSE - neuron-specific enolase.

CNS diseases (i.e., meningitis, encephalitis, stroke, epilepsy, and tumors),[10,17-20,22,23] metabolic neurological disorders secondary to non-septic causes,[10,17,20,22] recent surgery for cardiac revascularization,[10,22,23] and neurosurgery.[10,19,23] Five studies used control groups to compare their results,[10,18,19,22,24] whereas three studies compared their results between subgroups of septic patients formed based on other evaluation criteria, such as GCS[21,23] and CAM-ICU.[17] One group of researchers performed transcranial Doppler ultrasonography on their patients and used indirect measurements of ICP and cerebral perfusion pressure to compare their results.[20]

The biomarker analyses were performed using different types of tests. Some studies used enzyme immunoassays (ELISAs),[18,19,22] one used the LIAISON Sangect 100 commercial kit,[21] two used radioimmunoassays,[10,23] one used a luminometric assay,[23] and two studies[17,20] did not specify the type of assay that was used. Furthermore, different maximum values for normal blood concentrations of S100 beta were observed in the adults (0.105 μg/L, 0.12 μg/L, <0.15 μg/L, and 0.5 μg/L).[10,17,20,21,23,24] Serum levels of NSE that were ≤12.5 μg/L were considered normal in three studies.[10,23,24]

NSE

Among the selected studies, four[10,18,22,24] evaluated NSE. In the pediatric populations, one study demonstrated elevated NSE serum concentrations in patients with septic shock compared with the control group (96.6 μg/L±8.9 versus 4.0 μg/L±1.3, p<0.001).[22] EEGs performed on six children with shock indicated a 100% incidence of neurological alterations suggesting encephalopathy. The study by Rodríguez-Núñez et al.[18] analyzed the CSF of children with sepsis, who presented higher biomarker concentrations than the control group did (1.58ng/ml±0.81 versus 1.52ng/ml±1.01), but this difference was not significant.

One study of adults with severe sepsis and septic shock revealed elevated levels of NSE in 70% of patients diagnosed with encephalopathy, which was based on persistent neurological changes for at least 72 hours after weaning from sedation.[10] In the study by van den Boogaard, who analyzed a previously healthy population, blood samples collected during the induction of systemic inflammation by administering *Escherichia coli* lipopolysaccharide (LPS) presented decreasing concentrations of NSE in the short term (11.1 μg/L±0.47 to 7.7 μg/L±0.39; p<0.0001).[24]

One study correlated increased patient mortality with higher NSE concentrations,[22] whereas another study revealed no correlation between these variables, despite having demonstrated that patients who had NSE levels >30 μg/L died.[10]

Table 1 - Characteristics of the studies investigating biomarkers of septic encephalopathy

Author	Year	Study design	Population studied	Sample	Biomarker used	Evaluation criteria	Clinical significance
Rodríguez-Nuñez et al.[18]	2001	Cross-sectional cohort	Children 1 to 15 years of age with sepsis	182	NSE	None	The time or intensity of hypoxia was not sufficient to cause neuronal damage
Nguyen et al.[10]	2006	Prospective cohort	Patients 18 to 89 years of age with severe sepsis and septic shock	220	S100 beta NSE	GCS, MRI and CT	S100 beta levels are predictors of mortality in the ICU and more accurately reflect the development of encephalopathy and brain damage
Piazza et al.[21]	2007	Prospective cohort	Patients between 49 and 84 years of age with severe sepsis	21	S100 beta	GCS, EEG, CT	The increased S100 beta levels were not related to the severity of neurological dysfunction
Hsu et al.[22]	2008	Prospective cohort	Children between 3 months and 21 years of age with septic shock	56	S100 beta NSE	EEG	Increased S100 beta and NSE levels strongly suggest neurological injury
Pfister et al.[17]	2008	Prospective cohort	Patients between 18 and 90 years of age with sepsis, severe sepsis, or septic shock	16	S100 beta	CAM-ICU	S100 beta levels are correlated with sepsis associated with delirium, but its diagnostic role needs further study
Pfister et al.[20]	2008	Prospective cohort	Adults with an average age of 67 years, who had sepsis, severe sepsis, or septic shock	15	S100 beta	PPC and ICP	The increased concentration of S100 beta is related to low cerebral perfusion pressures
Hamed et al.[19]	2009	Prospective cohort	Septic children between 1 and 180 months of age	75	S100 beta	GCS, EEG, MRI and CT	S100 beta levels suggest a direct involvement of this biomarker in septic encephalopathy
Spapen et al.[23]	2010	Clinical trial	Patients between 56 and 82 years of age with septic shock	54	S100 beta	GCS	S100 beta is a potential biomarker for diagnosing and monitoring septic encephalopathy
van den Boogaard et al.[24]	2010	Clinical trial	Previously healthy males between 1 and 25 years of age who volunteered for the administration of LPS,	25	S100 beta NSE	EEG	There were no signs that acute systemic inflammation increases the levels of specific proteins in the brain or alters cognitive function

NSE - neuron-specific enolase; GCS - Glasgow Coma Scale; EEG - electroencephalogram; ICU - intensive care unit; MRI - magnetic resonance imaging; CT - computed tomography; CAM-ICU - confusion assessment method for the intensive care unit; CPP - cerebral perfusion pressure; ICP - intracranial pressure.

S100 beta

The association between S100 beta and SE was investigated in eight studies,[10,17,19-24] five of which correlated elevated biomarker levels with the development of SE.[10,17,19,22,23] One study identified high serum concentrations of S100 beta in patients with low cerebral perfusion pressure.[20] The four studies that used GCS to clinically diagnose SE revealed elevated levels of S100 beta in the patients with the lowest scores.[10,17,19,23] Of the studies that used EEG as an evaluation criterion, two associated electroencephalographic abnormalities with increased serum concentrations of S100 beta.[19,22] Additionally, four studies correlated elevated biomarker levels with increased mortality,[10,17,20,22] and two studies confirmed the use of S100 beta as a method of monitoring brain damage during sepsis.[10,23]

However, two studies found no correlation between the increased S100 beta serum concentrations and the development of SE.[21,24] Both studies used EEG as an evaluation criterion and revealed no correlation between the test standards and the biomarker levels. Moreover, the study that used GCS showed no correlation between the GCS scores and the serum concentrations of S100 beta, suggesting that the severity of brain damage cannot be defined based on the levels of this protein.[21]

DISCUSSION

The present review identified a positive association between elevated levels of NSE and S100 beta and the development of encephalopathy secondary to sepsis. The findings suggest that these biomarkers may facilitate diagnosis of this complication, which is common but often undiagnosed.[6]

The pathophysiology of SE appears to be multifactorial. The disease results from the interaction and overlapping of various mechanisms related to the systemic inflammatory response,[5] including oxidative stress, proinflammatory and anti-inflammatory mediators, the complement cascade, endothelial dysfunction, blood-brain barrier disruption, and microvascular failure.[1,25] This entire process leads to dysfunction, apoptosis, and cell death. Therefore, the development of this disease is more closely related to the inflammatory response than to the infectious agent alone.

Various clinical tools have been used to diagnose SE. CAM-ICU is a validated scale for identifying *delirium* and is capable of accessing different aspects of a person's mental state, including attention, thought organization, and consciousness.[26] GCS is another scale that is used to diagnose SE and, although initially designed to assess the level of consciousness in trauma patients, is now used in patients with a variety of disorders[4,27] However, during identification of an altered level of consciousness, the clinical findings are frequently nonspecific and cannot specify the cause of the neurological syndrome.

The use of sedation, a practice that is still common in intensive care units, may also contribute to an inaccurate assessment of a patient's state of consciousness. Imaging methods may serve as alternatives; however, CT does not identify definitive changes in SE cases, whereas MRI is often useful for diagnosing brain abnormalities and may eventually facilitate the determination of a prognosis.[28] Furthermore, these imaging methods are expensive, and the transport of patients to undergo the exam has been a major limitation for use.[28] Young et al. investigated EEG and concluded that it is a sensitive method for evaluating brain function in SE,[29] but again, sedation is a limiting factor in employing this method.[4,21] Thus, in the absence of well-defined criteria for diagnosing SE,[1] additional and more accurate methods must be examined.

In this context, the search for biochemical markers appears to be a natural process. Once the sensitivities and specificities of these biomarkers have been established, their application is generally easy because they can be measured when samples are collected from patients (regardless of the clinical status) and because there is no requirement for patient transport or for a specialized professional to perform the procedure. Different studies have used S100 beta and NSE as biomarkers that can correlate patient outcomes with severe traumatic brain injury.[30] Stein et al. found elevated concentrations of S100 beta in patients who were admitted with brain damage following trauma and who had a worse prognosis.[30] Other researchers have identified a correlation between the biomarkers and nontraumatic ischemic brain injury, such as cardiac arrest (CA)[31-33] and surgical cases of cardiac revascularization.[34,35] González-García et al. found significantly elevated serum concentrations of NSE and S100 beta in patients with arterial ischemic stroke (AIS) compared with the control group (NSE: 11.2 µmol/L versus 9.5 µmol/L, with p=0.0135; S100 beta: 127 nmol/L versus 84.6 nmol/L, with p=0.0000).[36]

Few studies have attempted to directly associate S100 beta and NSE with SE. Six studies included in the present review correlated these biomarkers with the development of SE[10,17,19,20,22,23] and thus analyzed distinct populations. The studies by Hsu et al.[22] and Hamed et al.[19] focused on the pediatric population, whereas the remaining studies[10,17,20,23] included adults and seniors. This variation

in cohorts associated with similar clinical findings suggests that S100 beta and NSE may be used as biomarkers for SE in the general population. Most of these studies included only patients with severe sepsis and septic shock, i.e., in advanced stages of infection, during which organ dysfunction already exists. Because SE is usually an early event in the natural evolution of sepsis,[3,6] patients in this phase of the disease most likely have already developed encephalopathy, and the use of biomarkers would be one way to confirm this clinical suspicion.

In their study, Hamed et al.[19] also included septic patients who did not display any clinical or EEG evidence of neurological damage. Notably, this group had S100 beta serum concentrations that were higher than in the non-septic patients, suggesting the early occurrence of brain damage during sepsis and highlighting the limited sensitivity of other tests in diagnosing this pathology. Another important finding in the study by Hamed et al. was that the biomarker concentrations in the CSF are higher than those in the blood, which corroborates the theory of increased intrathecal production of S100 beta during sepsis. Conversely, several authors have argued that S100 beta may not be a specific cerebral biomarker,[22] as extracranial foci of elevated levels of this protein (such as in the heart, skeletal muscle, and kidney) have been described.[17,20] Nevertheless, Nguyen et al.[10] used postoperative patients who had undergone surgical revascularization as a control group in their study and did not find elevated concentrations of NSE or S100 beta in this group.

The primary objective of the studies conducted by Spapen[23] and Pfister[20] was not to evaluate the use of S100 beta as a biomarker of SE; however, in the first investigation, high concentrations of this protein were found in patients with GCS scores <13, which is consistent with the results reported in other studies that evaluated S100 beta as a diagnostic criterion for SE. Furthermore, this clinical trial is a good example of using this protein to monitor patients. In addition, Pfister[20] correlated low cerebral perfusion pressures with elevated serum S100 beta levels in patients with sepsis, severe sepsis, and septic shock. Although brain perfusion is not a proven diagnostic method for SE, low perfusion pressure is one of the pathophysiological mechanisms of SE that has been previously cited, and low perfusion pressure may be an indirect signal of CNS injury. Therefore, this finding strengthens the association between S100 beta and SE.

Three other studies included in the present review did not associate SE with elevated concentrations of these biomarkers.[18,21,24] One such study was conducted by Rodríguez-Núñez et al.,[18] who analyzed the CSF concentrations of NSE in children with sepsis. This cross-sectional study model may be considered a limiting factor because the duration of the disease might not have been sufficient for ischemia and neuronal damage to develop.

Based on the close relationship between the inflammatory response and the pathophysiology of SE, van den Boogaard et al.[24] studied the behavior of NSE and S100 beta in previously healthy subjects with a transient systemic inflammatory response induced by the administration of *E. coli* lipopolysaccharide (LPS). Serum concentrations of cortisol, inflammatory cytokines, NSE, and S100 beta, as well as electroencephalographic abnormalities, were the parameters used to evaluate the results. However, no evidence was found indicating that acute inflammation causes increased serum concentrations of specific cerebral proteins. However, such findings cannot be considered definitive. The timing of the experiment may be a limiting factor in the study because, after 8 hours of monitoring, the inflammatory cytokines, which had increased significantly, returned to their basal levels; therefore, the inflammatory response, which is a key element in the development of encephalopathy, was not perpetuated. However, it is possible that the quantity of LPS administered was one factor responsible for these findings. Viral load is a major determinant of the inflammatory response during infection; thus, the amount of LPS administered might not have been sufficient to produce an inflammatory response that could cause brain damage and consequently increase the serum concentrations of these biomarkers.

Of the studies included in this systematic review, four used GCS as a parameter for correlating biomarker levels in the evaluation of encephalopathy.[10,19,21,23] Piazza et al.[21] reported that S100 beta could not indicate brain injury in septic patients upon admission because the protein concentrations did not correlate with the GCS findings. However, the study did not demonstrate that all patients with a GCS score ≤8 had elevated serum concentrations of S100 beta, with the exception of one patient who had a Glasgow score of 8. Adequate weaning from sedation might also have influenced the results, but because the study did not report the type of sedation used or the interval between the discontinuation of sedation and application of GCS, there is no way of determining how much the sedation interfered with the patient assessment.

Regarding the use of NSE and S100 beta in monitoring these patients, the studies yielded conflicting results, especially for S100 beta. Seven studies performed serial assessments of the levels of these biomarkers,[10,17,20-24] but only four of them correlated the NSE and S100 beta concentrations with time.[21-24]

Hsu et al.[22] presented an adjusted biomarker curve in which the highest concentrations were found between the fifth and seventh day following admission. Piazza et al.[21] also found elevated levels of S100 beta by the end of the seventh day of hospitalization, and Spapen et al.[23] noted peak levels of S100 beta between the second and third days of monitoring. However, a common thread in these studies is that, after the initiation of monitoring, patients develop higher-than-normal levels of these markers. This finding suggests that these substances should be assessed upon admission; thereafter, it is still unclear how often the marker levels should be determined for monitoring these patients. Irrespective of the method, it is proposed that monitoring should be performed because of the association between elevated levels of these biomarkers and increased mortality. Thus, it would be possible to establish a prognosis and stratify patients according to their disease severity.

A common feature observed in the studies in this systematic review is the small number of evaluated patients. The largest study included 220 patients, but only 27 patients were diagnosed with SE, thus decreasing the external validation of the results. Furthermore, various studies employed different laboratory assays to measure the S100 beta and NSE concentrations, thereby eliminating the possibility of quantitatively analyzing the results from these investigations. Another relevant fact is that most of the studies evaluated S100 beta, whereas only four studies included the analysis of NSE.[10,18,21,22]

This systematic review has certain limitations that should be noted. The present authors only utilized the PubMed database to search for relevant articles and only included articles that were written in English, which might have limited the findings of this study.

CONCLUSION

NSE and especially S100 beta are potential serum biomarkers for diagnosing and monitoring SE. However, additional studies with a larger number of patients are necessary to establish more definitive outcomes.

RESUMO

Objetivo: O objetivo deste estudo foi revisar sistematicamente a importância da enolase específica neuronal e S100B para diagnóstico e monitorização da encefalopatia séptica.

Métodos: Foi realizada uma busca no banco de dados PubMed selecionando estudos que avaliaram níveis séricos de S100 B e enolase específica neuronal em pacientes com sepse, publicados entre Janeiro de 2000 e Abril de 2012. Apenas estudos em humanos e que utilizaram um método adicional de avaliação neurológica foram selecionados.

Resultados: Foram identificados nove estudos, dos quais sete associaram concentrações elevadas de S100 beta e enolase específica neuronal ao desenvolvimento de encefalopatia séptica; quatro também as associaram ao aumento de mortalidade. Entretanto, dois trabalhos não encontraram essa associação quando avaliaram S100 beta e um deles não observou correlação entre a enolase específica neuronal e encefalopatia séptica.

Conclusão: A S100 beta e enolase específica neuronal são biomarcadores promissores para diagnóstico e monitorização de pacientes com encefalopatia séptica, mas é necessária uma maior investigação.

Descritores: Sepse/complicações; Encefalopatias/etiologia; Marcadores biológicos; Proteínas S100; Fosfopiruvato hidratase; Terapia intensiva

REFERENCES

1. Ringer TM, Axer H, Romeike BF, Zinke J, Brumkhorst F, Witte OW, et al. Neurological sequelae of sepsis: I) Septic encephalopathy. Open Crit Care Med J. 2011;4:2-7.
2. Pytel P, Alexander JJ. Pathogenesis of septic encephalopathy. Curr Opin Neurol. 2009;22(3):283-7.
3. Ebersoldt M, Sharshar T, Annane D. Sepsis associated delirium. Intensive Care Med. 2007;33(6):941-50.
4. Szatmári S, Végh T, Csomós A, Hallay J, Takács I, Molnár C, et al. Impaired cerebrovascular reactivity in sepsis-associated encephalopathy studied by acetazolamide test. Crit Care. 2010;14(2):R50.
5. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED. Pathophysiology of septic encephalopathy: a review. Crit Care Med. 2000;28(8):3019-24.
6. Zampieri FG, Park M, Machado FS, Azevedo LC. Sepsis-associated encephalopathy: not just delirium. Clinics (Sao Paulo). 2011;66(10):1825-31.
7. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. JAMA 2010;304(16):1787-94.
8. Lamar CD, Hurley RA, Taber HK. Sepsis-associated encephalopathy: review of the neuropsychiatric manifestations and cognitive outcome. J Neuropsychiatry Clin Neurosci. 2011;23(3):236-41.
9. Davies NW, Sharief MK, Howard RS. Infection-associated encephalopathies: their investigation, diagnosis, and treatment. J Neurol. 2006;253(7):833-45.
10. Nguyen DN, Spapen H, Su F, Schiettecatte J, Shi L, Hachimi-Idrissi S, et al. Elevated serum levels of S-100beta protein and neuron-specific enolase are associated with brain injury in patients with severe sepsis and septic shock. Crit Care Med. 2006;34(7):1967-74.
11. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit Care. 2010;14(1):R15.
12. Shinozaki K, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Abe R, et al. S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review. Crit Care. 2009;13(4):R121.
13. Zhou J, Lei L, Shi Y, Wang J, Jiang H, Shen L, et al. Serum concentrations of NSE and S100B in spinocerebellar ataxia type 3/ Machado-Joseph disease. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2011;36(6):504-10.

14. Peric B, Zagar I, Novakovic S, Zgajnar J, Hocevar M. Role of serum S100B and PET-CT in follow-up of patients with cutaneous melanoma. BMC Cancer. 2011;11:328.
15. Kruijff S, Bastiaannet E, Kobold AC, van Ginkel RJ, Suurmeijer AJ, Hoekstra HJ. S-100B concentrations predict disease-free survival in stage III melanoma patients. Ann Surg Oncol. 2009;16(12):3455-62. Erratum in Ann Surg Oncol. 2011;18 Suppl 3:S331.
16. Hamed SA, Hamed EA, Zakary MM. Oxidative stress and S-100B protein in children with bacterial meningitis. BMC Neurol. 2009;9:51.
17. Pfister D, Siegemund M, Dell-Kuster S, Smielewski P, Rüegg S, Strebel SP, et al. Cerebral perfusion in sepsis-associated delirium. Crit Care. 2008;12(3):R63.
18. Rodríguez-Núñez A, Cid E, Rodríguez-García J, Camiña F, Rodríguez-Segade S, Castro-Gago M. Concentrations of nucleotides, nucleosides, purine bases, oxypurines, uric acid, and neuron-specific enolase in the cerebrospinal fluid of children with sepsis. J Child Neurol. 2001;16(9):704-6.
19. Hamed SA, Hamed EA, Abdella MM. Septic encephalopathy: relationship to serum and cerebrospinal fluid levels of adhesion molecules, lipid peroxides and S-100B protein. Neuropediatrics. 2009;40(2):66-72.
20. Pfister D, Schmidt P, Smielewski P, Siegemund M, Strebel SP, Rüegg S, et al. Intracranial pressure in patients with sepsis. Acta Neurochir Suppl. 2008;102:71-5.
21. Piazza O, Russo E, Cotena S, Esposito G, Tufano R. Elevated S100B levels do not correlate with the severity of encephalopathy during sepsis. Br J Anaesth. 2007;99(4):518-21.
22. Hsu AA, Fenton K, Weinstein S, Carpenter J, Dalton H, Bell MJ. Neurological injury markers in children with septic shock. Pediatr Crit Care Med. 2008;9(3):245-51.
23. Spapen H, Nguyen DN, Troubleyn J, Huyghens L, Schiettecatte J. Drotrecogin alfa (activated) may attenuate severe sepsis-associated encephalopathy in clinical septic shock. Crit Care. 2010;14(2):R54.
24. van den Boogaard M, Ramakers BP, van Alfen N, van der Werf SP, Fick WF, Hoedemaekers CW, et al. Endotoxemia-induced inflammation and the effect on the human brain. Crit Care. 2010;14(3):R81.
25. Sharshar T, Hopkinson NS, Orlikowski D, Annane D. Science review: The brain in sepsis--culprit and victim. Crit Care. 2005;9(1):37-44.
26. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29(7):1370-9.
27. Siami S, Annane D, Sharshar T. The encephalopathy in sepsis. Crit Care Clin. 2008;24(1):67-82, viii.
28. Piazza O, Cotena S, De Robertis E, Caranci F, Tufano R. Sepsis associated encephalopathy studied by MRI and cerebral spinal fluid S100B measurement. Neurochem Res 2009;34(7):1289-92.
29. Young GB, Bolton CF, Archibald YM, Austin TW, Wells GA. The electroencephalogram in sepsis-associated encephalopathy. J Clin Neurophysiol. 1992;9(1):145-52.
30. Stein DM, Lindell AL, Murdock KR, Kufera JA, Menaker J, Bochicchio GV, et al. Use of serum biomarkers to predict cerebral hypoxia after severe traumatic brain injury. J Neurotrauma. 2012;29(6):1140-9.
31. Dauberschmidt R, Zinsmeyer J, Mrochen H, Meyer M. Changes of neuron-specific enolase concentration in plasma after cardiac arrest and resuscitation. Mol Chem Neuropathol. 1991;14(3):237-45.
32. Martens P. Serum neuron-specific enolase as a prognostic marker for irreversible brain damage in comatose cardiac arrest survivors. Acad Emerg Med. 1996;3(2):126-31.
33. Meynaar IA, Oudemans-van Straaten HM, van der Wetering J, Verlooy P, Slaats EH, Bosman RJ, et al. Serum neuron-specific enolase predicts outcome in post-anoxic coma: a prospective cohort study. Intensive Care Med. 2003;29(2):189-95.
34. Basile AM, Fusi C, Conti AA, Paniccia R, Trefoloni G, Pracucci G, et al. S-100 protein and neuron-specific enolase as markers of subclinical cerebral damage after cardiac surgery: preliminary observation of a 6-month follow-up study. Eur Neurol. 2001;45(3):151-9.
35. Astudillo R, Van der Linden J, Radegran K, Hanson LO, Aberg B. Elevated serum levels of S-100 after deep hypothermic arrest correlate with duration of circulatory arrest. Eur J Cardiothorac Surg. 1996;10(12):1107-12; discussion 1113.
36. González-García S, González-Quevedo A, Fernández-Concepción O, Peña-Sánchez M, Menéndez-Saínz C, Hernández-Díaz Z, et al. Short-term prognostic value of serum neuron specific enolase and S100B in acute stroke patients. Clin Biochem. 2012;45(16-17):1302-7.

5 DISCUSSÃO

O adequado diagnóstico de *delirium* nos pacientes graves internados em unidades de terapia intensiva é etapa essencial para uma melhor compreensão deste transtorno. Após os primeiros estudos de validação do CAM-ICU (ELY; MARGOLIN; et al., 2001) e do ICDSC (BERGERON et al., 2001), duas das mais estudadas ferramentas diagnósticas para *delirium*, diversos outros as reavaliaram em diferentes idiomas (GUSMAO-FLORES et al., 2011) e com populações distintas. O resultado destes estudos, agrupados em duas meta-análises (GUSMAO-FLORES et al., 2012; NETO et al., 2012), permitiu concluir que estes dois instrumentos possibilitam, com boa acurácia, a realização do diagnóstico de *delirium*.

Na meta-análise publicada pelo nosso grupo, a sensibilidade e especificidade conjunta do CAM-ICU foi de 80% e 96%, respectivamente (GUSMAO-FLORES et al., 2012). Desta forma, a razão de probabilidade positiva calculada é igual a 20, o que representa uma excelente acurácia para, quando o resultado for positivo, realmente o paciente estar com *delirium*. Por outro lado, a razão de probabilidade negativa é de 0,20 identificando assim uma acurácia moderada para, quando o resultado for negativo, identificar realmente o paciente sem *delirium.* Fica claro, assim, que o CAM-ICU é uma excelente ferramenta para identificar pacientes com *delirium* mas pode falhar quando informa que o paciente não tem *delirium.*

Utilizando um raciocínio similar para o ICDSC, com os dados da mesma meta-análise, encontra-se um conjunto de sensibilidade e especificidade de 74% e 82%, respectivamente. Assim, a razão de probabilidade positiva é de 4,11 e a negativa de 0,31 sugerindo que o ICDSC tem uma acurácia menor.

Avaliando apenas os dados encontrados nesta meta-análise, sugere-se que o CAM-ICU possui melhor acurácia para o diagnóstico quando comparado ao ICDSC. Além disto, é uma escala de fácil aplicação e que permite mais objetividade diferentemente do ICDSC que possibilita, em alguns pontos tais como avaliação da atenção, variadas interpretações.

As análises das propriedade psicométricas destas duas ferramentas, considerando características tais como confiabilidade e validade, determinaram uma pontuação ponderada de 19,6 para o CAM-ICU e 16,8 para o ICDSC (BARR et al., 2013). A pontuação total varia de 0 a 20, sendo que ferramentas diagnósticas que alcançam valores maior ou igual a doze são consideradas válida e confiáveis para uso em unidades de terapia intensiva (STREINER DL, 2008).

Desta forma, a recente diretriz sobre analgesia, dor e delirium publicada sob os cuidados da *Society of Critical Care Medicine* (BARR et al., 2013) recomendam o uso do CAM-ICU ou do ICDSC para diagnóstico de *delirium* no paciente grave internado na UTI.

Porém, é importante considerar que as propriedade psicométricas de instrumentos diagnósticos não pertencem, intrinsecamente, às ferramentas e sim ao conjunto formado pela ferramenta, população avaliada e o contexto clínico onde esta população está inserida (AMERICAN EDUCATIONAL RESEARCH ASSOCIATION (AERA), 1999). Assim, um mesmo instrumento pode ter diferentes acurácias quando muda-se a população ou o contexto onde ele é aplicado.

Esta observação parece relevante pois é possível que os pacientes graves internados na UTI atualmente tenham uma condução distinta quando comparado com aqueles dos estudos de validação. Um exemplo é a prática de sedação, que vem sendo reduzida com o passar dos anos (STROM; MARTINUSSEN; TOFT, 2010) e que parece influenciar na adequada avaliação de *delirium* nos pacientes quando utiliza-se o CAM-ICU e o ICDSC (HAENGGI et al., 2013).

Em uma publicação com 1873 avaliações realizadas em uma única unidade, observamos que a positividade do CAM-ICU reduz quanto mais alerta encontra-se o paciente (GUSMAO-FLORES et al., 2013). Este achado pode ser interpretado de duas formas: de fato há menos incidência de delirium em pacientes mais alerta ou existe uma diminuição de acurácia do CAM-ICU neste grupo de doentes. É possível que esta última assertiva seja verdadeira pois a acurácia do CAM-ICU e do ICDSC, quando comparada com o DSM-IV, em paciente não graves e internados fora da UTI, é ruim (NEUFELD et al., 2011).

Da mesma forma, a avaliação do CAM-ICU e do ICDSC não foi ainda adequadamente realizada em pacientes em uso de ventilação não invasiva (VNI). O único estudo que incluiu pacientes em VNI foi o nosso estudo de validação em língua portuguesa (GUSMAO-FLORES et al., 2011). Com análise de apenas 11 pacientes observamos uma excelente acurácia destas ferramentas, com sensibilidade e especificidade próxima a 100% (SALLUH; GUSMAO-FLORES; DAL-PIZZOL, 2012).

6 CONCLUSÃO

O diagnóstico de *delirium* utilizando o padrão ouro, os critérios do DSM, exige tempo e conhecimento específicos que inviabiliza o seu uso regular nas unidades de terapia intensiva. Portanto, o uso de instrumentos que permitem fazer o diagnóstico, de forma acurada e rápida, faz-se necessário. Esta linha de pesquisa possibilitou, após a finalização dos estudos anteriormente mencionados, chegarmos as seguintes conclusões:

- O diagnóstico de *delirium* no paciente grave pode ser realizado, com boa acurácia, utilizando o *Confusion Assessment Method for the Intensive Care Unit* (CAM-ICU*)* e o *Intensive Care Delirium Screening Checklist* (ICDSC).
- O CAM-ICU está validado para o uso no idioma português brasileiro. A sua versão modificada, o CAM-ICU *Flowsheet* também pode ser utilizada, com a vantagem de permitir a conclusão da avaliação de forma mais rápida.
- O CAM-ICU pode ser considerado com instrumento diagnóstico para *delirium* nos pacientes em uso de suporte ventilatório não invasivo.
- Uma década após a publicação do estudo original de validação do CAM-ICU, observamos que a sensibilidade da ferramenta vem diminuindo; é possível considerar que a utilização desta ferramenta em pacientes com níveis de sedação mais superficial não permita o diagnóstico de *delirium* com precisão.
- Apesar de diversas escalas terem sido criadas para estratificação de *delirium*, inclusive nos pacientes graves, não há consistência nos estudos para selecionarmos uma escala que permita claramente diferenciar *delirium* mais grave de menos grave.

6 PERSPECTIVA FUTURA

Atualmente, a avaliação do paciente com *delirium* utilizando o CAM-ICU é realizada regularmente na UTI Geral do Hospital Universitário Prof. Edgar Santos, da Universidade Federal da Bahia. No entanto, acreditamos que o CAM-ICU perde sensibilidade quando utilizado em pacientes com níveis menores de sedação. Esta observação ocorre com alguma frequência quando, após a avaliação da atenção utilizando o teste visual e auditivo recomendado pelo CAM-ICU percebemos que mesmo nos casos onde não ocorreram erros nas questões o paciente está claramente desatento. Diante desta observação, e considerando que esta perda de sensibilidade ocorre principalmente por falha na detecção da desatenção, encontra-se em planejamento o projeto de modificar a forma de avaliação da atenção desta ferramenta. Em parceria com um grupo de neuropsicólogos, a proposta inicial é, além de buscar uma forma mais sensível de avaliação da atenção, também quantificá-la. Para tanto, a ideia é utilizar um dispositivo eletrônico conectado a um computador permitindo avaliar a quantidade de acertos além da velocidade das respostas para uma determinada questão, com maior precisão.

Outro ponto que já foi concluído e iniciaremos em breve a fase das análise, foi um questionário internacional sobre a percepção dos profissionais que trabalham em UTI, sobre a importância e forma de diagnosticar *delirium* nos pacientes em uso de suporte ventilatório não invasivo. A etapa de resposta já foi finalizada com cerca de 500 questionários respondidos. Segue-se a esta etapa um projeto de avaliação do *delirium* como possível marcador de falência com o uso da VNI.

Numa linha similar, e já com aprovação do Comitê de Ética e Pesquisa local, avaliaremos a relevância clínica do diagnóstico de *delirium* no momento da extubação orotraqueal. Existe uma percepção por parte dos profissionais que trabalham na UTI que *delirium* é um preditor de falência de extubação, mas há carência de dados consistentes na literatura.

O nosso banco de dados atual consta com cerca de 3000 avaliações utilizado o CAM-ICU. Este número permite diversos estudos exploratórios, que vem sendo realizado e apresentado em congressos nacionais e internacionais, com objetivo de identificar padrões de *delirium* que tenham associação com desfecho. Por exemplo, é possível que cursar com *delirium* em dias alternados tenha mais importância clínica que em dias consecutivos, apesar de totalizar o mesmo número de dias de *delirium.* Mas ainda é necessário uma análise mais cuidadosa destes dados.

Por fim, pretendemos com brevidade testar uma intervenção terapêutica nos quadros de *delirium* em paciente graves, particularmente os hipoativos, com técnicas padronizadas de mobilização do sujeito com apoio da equipe de fisioterapia. Finalizamos um estudo piloto de intervenção em 12 casos que evoluíram com melhora do quadro imediatamente após uma estratégia de mobilização, sugerindo resultados promissores. Estamos, neste momento, preparado o manuscrito com este relato. Buscaremos a partir deste estudo exploratório, estruturar um ensaio clínico randomizado, multicêntrico e controlado. Ainda está pendente a determinação do método ótimo de controle.

REFERÊNCIAS

AMERICAN EDUCATIONAL RESEARCH ASSOCIATION (AERA), A. P. A. A., NATIONAL COUNCIL IN MEASUREMENT IN EDUCATION (NCME). **Standards for Educational and Psychological Testing**. Washington, DC: American Educational Research Association, 1999.

APA. **Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5**. 5. American Psychiatric Publishing, 2013. 991 ISBN 0890425558.

BARR, J. et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. **Crit Care Med,** v. 41, n. 1, p. 263-306, Jan 2013.

BARR, J.; PANDHARIPANDE, P. P. The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 Pain, Agitation, and Delirium Guidelines in an integrated and interdisciplinary fashion. **Crit Care Med,** v. 41, n. 9 Suppl 1, p. S99-115, Sep 2013.

BERGERON, N. et al. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. **Intensive Care Med,** v. 27, n. 5, p. 859-64, May 2001.

CEREJEIRA, J. et al. The neuroinflammatory hypothesis of delirium. **Acta Neuropathol,** v. 119, n. 6, p. 737-54, Jun 2010.

ELY, E. W. et al. The impact of delirium in the intensive care unit on hospital length of stay. **Intensive Care Med,** v. 27, n. 12, p. 1892-900, Dec 2001.

ELY, E. W. et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). **Crit Care Med,** v. 29, n. 7, p. 1370-9, Jul 2001.

FOLSTEIN, M. F.; FOLSTEIN, S. E.; MCHUGH, P. R. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. **J Psychiatr Res,** v. 12, n. 3, p. 189-98, Nov 1975.

GUENTHER, U. et al. Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients. **J Crit Care,** v. 25, n. 1, p. 144-51, Mar 2010.

GUSMAO-FLORES, D. et al. Tools for diagnosing delirium in the critically ill: is calibration needed for the less sedated patient? **Intensive Care Med**, Oct 3 2013.

GUSMAO-FLORES, D. et al. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. **Crit Care,** v. 16, n. 4, p. R115, Jul 3 2012.

GUSMAO-FLORES, D. et al. The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients. **Clinics (Sao Paulo),** v. 66, n. 11, p. 1917-22, 2011.

HAENGGI, M. et al. Effect of sedation level on the prevalence of delirium when assessed with CAM-ICU and ICDSC. **Intensive Care Med,** v. 39, n. 12, p. 2171-9, Dec 2013.

HART, R. P. et al. Abbreviated cognitive test for delirium. **J Psychosom Res,** v. 43, n. 4, p. 417-23, Oct 1997.

HART, R. P. et al. Validation of a cognitive test for delirium in medical ICU patients. **Psychosomatics,** v. 37, n. 6, p. 533-46, Nov-Dec 1996.

INOUYE, S. K. et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. **Ann Intern Med,** v. 113, n. 12, p. 941-8, Dec 15 1990.

KHAN, B. A. et al. Comparison and agreement between the Richmond Agitation-Sedation Scale and the Riker Sedation-Agitation Scale in evaluating patients' eligibility for delirium assessment in the ICU. **Chest,** v. 142, n. 1, p. 48-54, Jul 2012.

LINDESAY, J. The concept of delirium. **Dement Geriatr Cogn Disord,** v. 10, n. 5, p. 310-4, Sep-Oct 1999.

LIPTZIN, B. What criteria should be used for the diagnosis of delirium? **Dement Geriatr Cogn Disord,** v. 10, n. 5, p. 364-7, Sep-Oct 1999.

LIPTZIN, B. et al. An empirical study of diagnostic criteria for delirium. **Am J Psychiatry,** v. 148, n. 4, p. 454-7, Apr 1991.

MARCANTONIO, E. R. et al. A clinical prediction rule for delirium after elective noncardiac surgery. **JAMA,** v. 271, n. 2, p. 134-9, Jan 12 1994.

MILBRANDT, E. B. et al. Costs associated with delirium in mechanically ventilated patients. **Crit Care Med,** v. 32, n. 4, p. 955-62, Apr 2004.

NETO, A. S. et al. Delirium screening in critically ill patients: a systematic review and meta-analysis. **Crit Care Med,** v. 40, n. 6, p. 1946-51, Jun 2012.

NEUFELD, K. J. et al. Evaluation of two intensive care delirium screening tools for non-critically ill hospitalized patients. **Psychosomatics,** v. 52, n. 2, p. 133-40, Mar-Apr 2011.

PANDHARIPANDE, P. P. et al. Long-term cognitive impairment after critical illness. **N Engl J Med,** v. 369, n. 14, p. 1306-16, Oct 3 2013.

PISANI, M. A. et al. Days of delirium are associated with 1-year mortality in an older intensive care unit population. **Am J Respir Crit Care Med,** v. 180, n. 11, p. 1092-7, Dec 1 2009.

SALLUH, J. I.; GUSMAO-FLORES, D.; DAL-PIZZOL, F. Diagnosis of delirium in patients under noninvasive ventilation in the intensive care unit. **Lung,** v. 190, n. 6, p. 589-90, Dec 2012.

SPRONK, P. E. et al. Occurrence of delirium is severely underestimated in the ICU during daily care. **Intensive Care Med,** v. 35, n. 7, p. 1276-80, Jul 2009.

STREINER DL, N. G. **Health Measurement Scales: A Practical Guide to Their Development and Use.** Fourth. Oxford University Press, 2008.

STROM, T.; MARTINUSSEN, T.; TOFT, P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. **Lancet,** v. 375, n. 9713, p. 475-80, Feb 6 2010.

TUCKER, G. J. The diagnosis of delirium and DSM-IV. **Dement Geriatr Cogn Disord,** v. 10, n. 5, p. 359-63, Sep-Oct 1999.

WILD, D. et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. **Value Health,** v. 8, n. 2, p. 94-104, Mar-Apr 2005.

APÊNDICE

APÊNDICE A

Termo de consentimento livre e esclarecido

Projeto: Validação do instrumento *Confusion Assessment Method – Intensive Care Unit (CAM – ICU)* para o idioma português brasileiro em pacientes críticos com *delirium*

Solicitamos o consentimento para que seu familiar participe deste estudo que procura validar para o idioma português brasileiro o método conhecido como CAM-ICU. Este é um instrumento desenvolvido com finalidade de facilitar o diagnóstico de delirium em pacientes internado nas Unidades de Terapia Intensiva. Consta apenas de avaliação clínica breve. Este método já foi validado em vários idiomas (por exemplo: inglês, espanhol e chinês). Foi traduzida para o idioma português brasileiro e agora decidimos validar, pois a tradução somente não é suficiente para sua utilização. Antes de concordar que seu familiar participe desta pesquisa é importante que você leia este documento. Por favor, dedique um tempo para ler cuidadosamente as informações seguintes e discutir isto, se achar necessário, com familiares, amigos ou outro médico. Se você desejar, pode levar esta folha para casa para pensar melhor. Pergunte-nos se houver qualquer coisa que não está clara ou se você precisar de mais informações. Utilize o tempo que for necessário para decidir se deseja liberar seu familiar para participar do estudo.

Esta validação consiste somente em um breve questionário, com duração de 5 a 30 minutos.

Algumas exigências para participar deste estudo são:

- Ter idade maior que 18 anos.
- Estar internado em unidade de terapia intensiva
- Ter apresentado alteração súbita (ou flutuante) do comportamento.
- Conhecer o idioma português brasileiro.

O seu familiar estará ajudando na compreensão do delirium em pacientes críticos. Os investigadores não são remunerados para a realização dessa pesquisa, assim como os pacientes analisados não receberão benefícios financeiros para sua participação no mesmo.

Todas as informações coletadas sobre o seu familiar durante a pesquisa serão mantidas em sigilo. Qualquer informação que saia do hospital terá o nome e endereço do pacientes removidos, de forma que ele não poderá ser identificado (a).

Dúvidas poderão ser esclarecidas, a qualquer momento, com Dr. Dimitri Gusmão (responsável pelo projeto e médico intensivista), por telefone (71-9996-8535), ou no Hospital Universitário Prof. Edgard Santos, quarto andar, Unidade de Terapia Intensiva.

O seu familiar pode ou não participar da pesquisa. Se concordar com sua participação deverá assinar este formulário em duas vias e manter uma cópia com você. Fique claro que se não concordar com a participação isto não afetará o cuidado e a atenção que o médico dará ao paciente.

_____ _____

Nome do Paciente Nome do Familiar/Responsável

_____ _____

Assinatura do Familiar / Responsável Data

_____ _____

Assinatura do investigador Data

APÊNDICE B

Termo de consentimento livre e esclarecido

Projeto: Avaliação de *delirium* em pacientes graves – aspectos epidemiológicos e perspectivas terapêuticas

Solicitamos o consentimento para que seu familiar participe deste estudo que procura avaliar os pacientes com delirium durante o internamento em unidade de terapia intensiva do Complexo Hospitalar Professor Edgard Santos. Delirium é um estado confusional agudo, ou seja o paciente pode ficar agitado, confuso, desatento e, às vezes, ter alucinações visuais – vê imagens que não existem. Apesar de hoje entendermos melhor sobre como diagnosticar e sobre a importância dos episódios de delirium nos pacientes graves questões ainda continuam sem respostas. Por exemplo, não há evidência na literatura médica sobre a importância do diagnóstico do delirium durante o processo de extubação. Ou seja, os pacientes que estão respirando com a ajuda de respirador mecânica e estão prontos para serem extubados, não se sabe se estar em delirium é indicação de não extubar. As últimas diretrizes sobre extubação no paciente grave não recomendam a avaliação do delirium antes deste procedimento. Outra clara limitação dos estudos que avaliam perspectivas terapêuticas em pacientes com delirium é a ausência de ferramentas validadas para estratificar esta entidade. Atualmente utilizamos um instrumento para diagnóstico para delirium dicotômico, ou seja, informa se o paciente apresenta ou não delirium. No entanto, existe possibilidade dos pacientes apresentarem melhora em alguns domínios cognitivos, ou seja, melhora parcial do quadro, diminuir os episódios de alucinação ou recuperar parte da memória, e estar ainda em delirium. Fica evidente assim a necessidade de métodos de estratificação. Por fim, à despeito de recentes estudos clínicos com tratamento farmacológico para o delirium, o melhor tratamento ainda não está definido. Alguns dados sugerem que estímulos cognitivos (realizar algumas questões e cálculos) e motores, tais como sentar no leito, podem promover melhora aguda da memória em pacientes com Depressão e benefícios em pacientes com Doença de Parkinson. A proposta também é avaliar o papel destas intervenções não farmacológicas em

pacientes com o diagnóstico recente de delirium, além de acompanhar todos os casos diagnosticado com uma ferramenta de estratificação ainda não validada, que é a *Delirium Index for the Intensive Care Unit.*

Esta ferramenta é constituída por um pequeno questionário de rápida aplicação. A estratégia não farmacológica (o estímulo motor e cognitivo) é constituída de atividades motoras, tais como sentar o paciente na cama ou numa poltrona, ficar em pé ou até mesmo deambular e estímulos cognitivos. Neste estudo, avaliaremos o papel da atividade motora nos pacientes com delirium. É importante ficar claro que toda a atividade motora será realizada seguindo o nosso protocolo (já utilizado como rotina na nossa UTI) e supervisionado por médico e fisioterapeutas. Assim, esta intervenção além da avaliação diária para a presença de delirium não acarretará nenhum risco para o paciente.

Antes de concordar que seu familiar participe desta pesquisa é importante que você leia este documento. Por favor, dedique um tempo para ler e reler, se necessário, cuidadosamente as informações apresentadas, discutir com familiares, amigos ou outro médico se assim desejar. Você também pode levar esta folha para casa para pensar melhor. Pergunte-nos se houver qualquer coisa que não está clara ou se você precisar de mais informações. Utilize o tempo que for necessário para decidir se deseja liberar seu familiar para participar do estudo.

Por outro lado, todas estas intervenções podem não trazer nenhum benefício imediato para o paciente, mas o seu familiar estará ajudando na compreensão do delirium nos pacientes graves. Ou seja, ao final da pesquisa esperamos saber mais sobre o valor deste quadro (delirium) nos pacientes e se medidas simples como a mobilização pode ajudar na recuperação.

Os investigadores não são remunerados para a realização dessa pesquisa, assim como os pacientes analisados não receberão benefícios financeiros para sua participação no mesmo.

Todas as informações coletadas sobre o seu familiar durante a pesquisa serão mantidas em sigilo. Qualquer informação que saia do hospital terá o nome e endereço do pacientes removidos, de forma que ele não poderá ser identificado (a).

Dúvidas poderão ser esclarecidas, a qualquer momento, com Dr. Dimitri Gusmão (responsável pelo projeto e médico intensivista), por telefone (71-9996-8535), ou no Hospital Universitário Prof. Edgard Santos, quarto andar, Unidade de Terapia Intensiva. Outro contato é o Comitê de Ética em Pesquisa no endereço Rua Augusto Viana, s/nº, 1º andar – Canela, Hospital Universitário Professor Edgard Santos, Canela, Salvador- Bahia, que possui um grupo de profissionais independentes que analisaram este estudo.

O seu familiar pode ou não participar da pesquisa. Se concordar com sua participação deverá assinar este formulário em duas vias e manter uma cópia com você. Fique claro que se não concordar com a participação isto não afetará o cuidado e a atenção que o médico dará ao paciente.

_____ _____

Nome do Paciente Nome do Familiar/Responsável

_____ _____

Assinatura do Familiar / Responsável Data

_____ _____

Assinatura do investigador Data

APÊNDICE C

Validação da CAM – ICU (Português)

Identificação
Nome: _____Idade:_____
Gênero: ( ) Masculino ( ) Feminino
Hospital: _____Rg.:_____ Leito: ___
Reinternação na UTI: ( ) Sim ( ) Não Reinternação < 48 horas: ( ) Sim ( ) Não
Data internação (hospital): ___/___/___ Data de internação (UTI): ___/___/___
Hora internação: ___:___

Comorbidades

( ) ICC	( ) DM	( ) Demência
( ) IRC	( ) HAS	( ) Doença psiquiátrica
( ) Cirrose (Child A-B-C)	( ) IAM prévio	( ) Tabagismo
( ) DPOC	( ) Alcoolismo	( ) Imunossupressão
( ) Tumor hematológico	( ) AVC	( ) SIDA
( ) Tumor locoregional	( ) Tumor metastático	( ) Doença Reumática
( ) Parkinson		

Origem:

( ) Enfermaria	( ) Emergência
( ) Centro cirúrgico	( ) Home Care
( ) Semi intensiva	( ) Outro hospital

Tipo de internação:
( ) Clínica
( ) Cirurgia emergência/urgência
( ) Cirurgia eletiva

Categoria diagnóstica (clínica):

( ) Sepse	( ) Hepático	( ) Pós PCR
( ) Renal	( ) Cardiovascular	( ) Insf. Respiratória (exceto sepse)
( ) Neurológico	( ) Digestivo	( ) Hematológico
( ) Trauma	( ) Monitorização	( ) Choque (exceto sepse)

( ) Outra: _____

Categoria diagnóstica (cirurgia):

( ) Cirurgia torácica	( ) Cirurgia abdominal	( ) Cirurgia urológica
( ) Neurocirurgia	( ) Cirurgia ortopédica	( ) Cirurgia Vascular
( ) Cirurgia cardíaca	( ) Cirurgia de coluna	( ) Outra: _____

Escores:
APACHE II: _____

Sedação / Analgesia (antes da avaliação – todos que se aplicam):

( ) Morfina	( ) Dexmedetomidina	( ) Ketamina
( ) Fentanil	( ) Propofol	( ) Outro benzodiazepínico
( ) Diazepam	( ) Midazolam	( ) Haldol

( ) Outra: _____

Ventilação:
( ) Mecânica ( ) Espontânea ( ) VNI

Diagnóstico delirium:
RASS: _____ (no momento da avaliação)
CAM – ICU: ( )Sim ( )Não Avaliador: _____ Duração: _____
DSM IV: ( )Sim ( )Não Avaliador: _____ Duração: _____
Flowsheet: ( )Sim ( ) Não
Avaliador:_____Duração:_____

Checklist:

Alteração do nivel da consciência	( )	Total: _____
Desatenção	( )	
Desorientação	( )	Avaliador: _____
Alucinação-psicose	( )	
Agitação psicomotora ou lentificação	( )	
Linguagem ou humor inapropriado	( )	
Alteração do ciclo sono/vigília	( )	
Flutuação dos sintomas	( )	

Tipos de delirium:
( ) Hipoativo ( ) Hiperativo ( ) Misto

Desfecho:
Tempo de VM: _____ (dias)
Tempo na UTI: _____ (dias)
Saída da UTI: ( ) vivo ( ) Morto Data: ___/___/___
Evolução em 30 dias: ( ) Alta ( ) Óbito ( ) Ainda hospitalizado

Pior Resultado Observado no Dia (24h) da Inclusão no Estudo.

Variáveis Fisiológicas			Laboratoriais		
Variável	**Maior valor**	**Menor valor**	**Variável**	**Maior valor**	**Menor val**
PA (mmHg)			Hematócrito (%)		
Freq. cardíaca (bpm)			Hemoglobina (g/dL)		
Freq. respiratória (irpm)			Leucócitos (x10^3/mm^3)		
Temperatura (ºC)			Plaquetas (x10^3/mm^3)		
E. Coma Glasgow (pontos)			INR		
Diurese (ml/24h)			Creatinina (mg/dL)		
			Uréia (mg/dL)		
Gasometria arterial			Sódio (mEq/L)		
pH			Potássio (mEq/L)		
PaO_2 (mmHg)			Bilirrubinas totais (mg/dL)		
$PaCO_2$ (mmHg)			Albumina (g/dL)		
HCO_3 (mEq/L)			PCR (mg/dL)		
FiO_2 (%)			**Aminas Vasoativas (maior dose em mcg/Kg/min)**		
Lactato arterial (mmol/L)			Noradrenalina/Adrenalina		
			Dobutamina		
			Dopamina		

ANEXOS

ANEXO A

CAM-ICU: ORIENTAÇÕES PARA APLICAÇÃO

CARACTERÍSTICA 1: Flutuação do estado mental basal
a) Há evidência de mudança aguda do estado mental basal?
b) Essa mudança tem caráter flutuante nas últimas 24h?

CARACTERÍSTICA 2: Desatenção
a) O paciente tem dificuldade de manter a atenção?
Obs.: Realizar o teste das letras (Vide *). Caso necessário poderá ser realizado o teste das figuras.

CARACTERÍSTICA 3: Alteração do nível de consciência
a) O paciente está sonolento, comatoso ou agitado?
Obs.: Realizar avaliação com escalas de sedação (RASS ou SAS).

CARACTERÍSTICA 4: Pensamento desorganizado
a) O paciente tem um discurso incoerente?
b) O paciente é incapaz de responder aos comandos corretamente?
Obs.: Realizar sequência de perguntas dicotômicas. Caso o paciente acerte todas as perguntas, deve-se realizar o teste do comando (Vide #).

Delirium é diagnosticado quando ambas as características 1 e 2 são positivas e as características 3 ou 4 estão presentes..

* Teste das letras:
Diga ao paciente que irá falar dez letras e que ao ouvir a letra "A", ele devererá apertar a sua mão. Leia a seguinte sequência com intervalo de três segundos para cada letra: S A V E H A A R T.
Considera-se alterada a atenção quando o paciente errar mais de duas vezes.

Sequência de perguntas dicotômicas:

Pergunte ao paciente se:

a) Uma pedra flutua na água? Resposta esperada: Não.

b) Há peixes no mar? Resposta esperada: Sim.

c) Um quilo pesa mais que dois quilos? Resposta esperada: Não.

d) Você pode bater um prego com um martelo? Resposta esperada: Sim.

Considera-se pensamento desorganizado, caso ele erre mais de uma respostas.

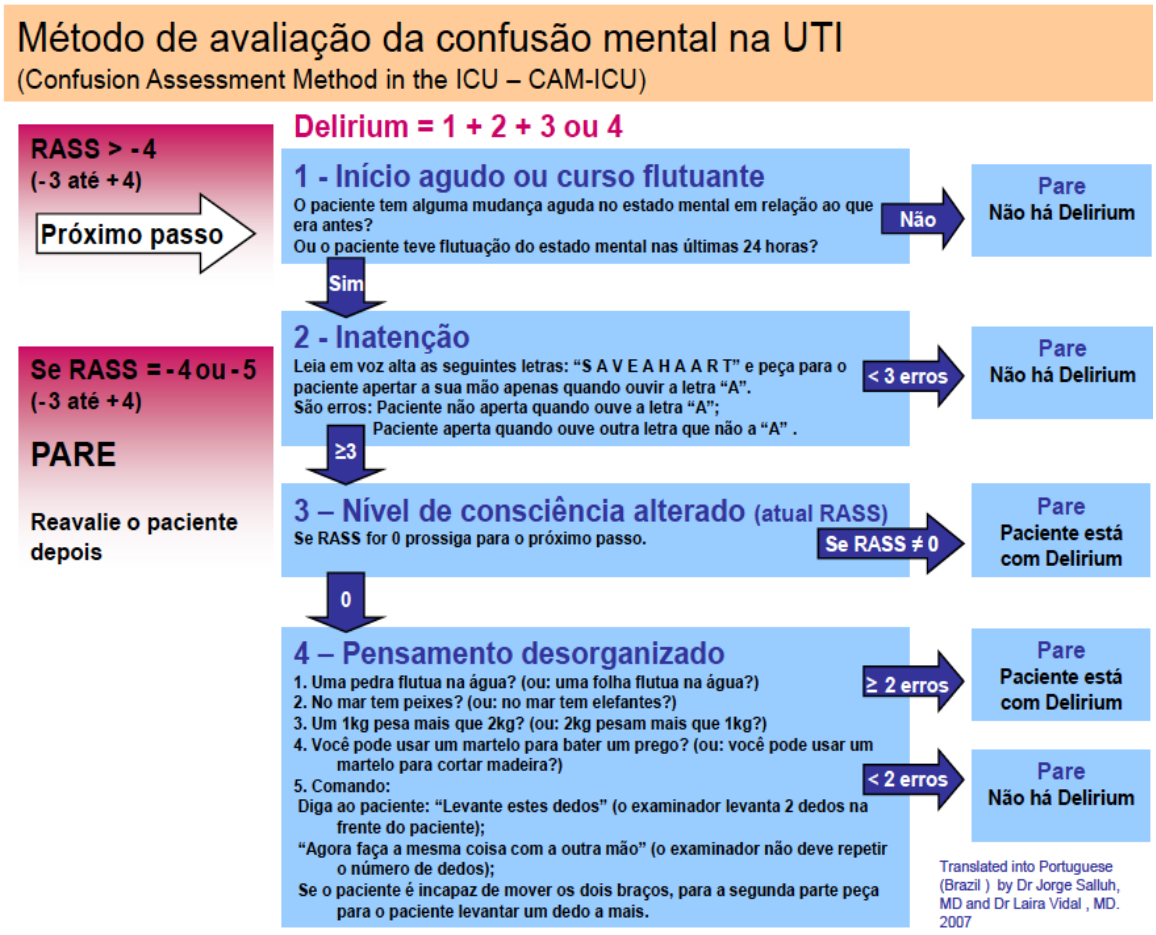
Teste do comando:

Mostre dois dedos ao paciente por alguns segundos e peça para ele repetir. Após isto, peça para que ele faça com a outra mão. Caso o paciente esteja impossibilitado de utilizar a outra mão, peça que ele adicione um dedo a mão inicialmente testada.

Considera-se pensamento desorganizado, caso ele não execute os comandos corretamente.

ANEXO B

CAM-ICU *Flowsheet*



ANEXO C

Intensive Care Delirium Screening Checklist (ICDSC)

A escala é concluída com base em informações coletadas em cada turno de 8 horas ou a partir das 24 horas anteriores. Manifestação óbvia de um item = 1 ponto; nenhuma manifestação de um item ou nenhuma avaliação possível = 0 ponto. A pontuação de cada item é inserida na caixa vazia correspondente, como 0 ou 1.

1. Alteração do nível de consciência
   A/B: Nenhuma resposta (A) ou a necessidade de estimulação vigorosa (B) de modo a obter qualquer resposta significa uma alteração grave no nível de consciência impedindo a avaliação. Se houver coma (A) ou estupor (B) a maior parte do período de tempo, então um traço (–) é incluído, e não há qualquer avaliação adicional durante esse período.
   C: Sonolência ou exigência de leve a moderada estimulação para uma resposta implica em uma alteração do nível de consciência e pontua 1.
   D: Estado de vigília ou dormindo, que poderia facilmente ser despertado é considerado normal e pontua 0.
   E: Hipervigilância é classificada como um nível de consciência anormal e pontua 1.
2. Desatenção: dificuldade em acompanhar uma conversa ou instruções. Facilmente distraído por estímulos externos. Dificuldade em mudar o foco. Qualquer destes estados pontua 1.
3. Desorientação: qualquer erro evidente no tempo, lugar ou pessoa pontua 1.
4. Alucinação, ilusão ou psicose: a inequívoca manifestação clínica de alucinação ou de comportamento provavelmente devido à alucinação (p. ex., tentar pegar um objeto inexistente) ou ilusão. Qualquer um destes pontua 1.
5. Agitação ou retardo psicomotor: hiperatividade exigindo o uso adicional de medicamentos sedativos ou contenção a fim de controlar o perigo potencial a si próprio ou a outros (p. ex., retirando acessos venosos, agressão à equipe); hipoatividade ou lentidão psicomotora clinicamente perceptível. Qualquer um destes pontua 1.
6. Fala ou humor inadequados: fala inapropriada, desorganizada ou incoerente; apresentação imprópria de emoções relacionada a eventos ou situação. Qualquer um destes pontua 1.
7. Alteração do ciclo sono/vigília: dormir menos de 4 h ou acordar com frequência durante a noite (não considerar despertar iniciado pelo pessoal médico ou ambiente barulhento); dormir durante a maior parte do dia. Qualquer um destes pontua 1.
8. Flutuação dos sintomas: flutuação na manifestação de qualquer item ou sintoma durante 24 h (p. ex., à partir de um turno para outro) pontua 1.

ANEXO D

Richmond agitation-sedation scale (RASS)

Pontos	Termos	Descrição
+4	Combativo	Claramente combativo, violento, representando risco para a equipe
+3	Muito agitado	Puxa ou remove tubos ou cateteres, agressivo verbalmente
+2	Agitado	Movimentes despropositados frequentes, briga com o ventilador
+1	Inquieto	Apresenta movimentos, mas que não são agressivos ou vigorosos
0	Alerta e calmo	
-1	Sonolento	Adormecido, mas acorda ao ser chamado (estímulo verbal) e mantém os olhos abertos por mais de 10 segundos
-2	Sedação leve	Despertar precoce ao estímulo verbal, mantém contato visual por por menos de 10 segundos
-3	Sedação moderada	Movimentação ou abertura ocular ao estímulo verbal (mas sem contato visual)
-4	Sedação intensa	Sem resposta ao ser chamado pelo nome, mas apresenta movimentação ou abertura ocular ao toque (estímulo físico)
-5	Não desperta	Sem resposta ao estímulo verbal ou físico

ANEXO E

Sedation Agitation Scale

Escala de sedação SAS (*Sedation - Agitation Scale*)
7. Agitação perigosa
6. Muito agitado
5. Agitado
4. Calmo e cooperativo
3. Sedado
2. Muito sedado
1. Coma

Parecer do CEP 1

HOSPITAL UNIVERSITÁRIO PROF. EDGARD SANTOS- UFBA - HUPES

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação de delirium em pacientes graves ¿ aspectos epidemiologicos e perspectivas terapeuticas

Pesquisador: DIMITRI GUSMÃO FLORES

Área Temática:

Versão: 2

CAAE: 12180213.6.0000.0049

Instituição Proponente: Hospital Universitário Prof. Edgard Santos-UFBA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 276.339

Data da Relatoria: 22/03/2013

Apresentação do Projeto:

Trata-se de um estudo observacional para verificar o papel do delirium (estado confusional agudo e flutuante da consciência e cognição frequentemente identificado em pacientes graves internados nas unidades de terapia intensiva) na falha da extubação em pacientes criticamente doentes, definido como reintubação do paciente em até 72 horas. Nesta ótica, o mesmo tem três hipóteses: 1)o delirium prediz o sucesso da extubação; 2) A atividade motora pode contribuir na resolução do delirium em paciente grave; 3) A escala Delirium Index for the Intensive Care Unit (DI-ICU)pode ser utilizada para estratificação do delirium grave. Será realizado em UTI com duas fontes de dados: 1) retrospectiva, baseada em cadastros de pacientes de dados sócio-demográficos, clínicos,laboratoriais e indicadores de assistência; 2) prospectiva, com a adoção do uso do instrumento Confusion Assessment Method for the Intensive Care Unit (CAM-UCI) para detecção de delirium duas vezes por dia, aplicada por equipe médica treinada e com um protocolo (já em uso) de mobilização passiva ou ativa dos pacientes internados pela equipe de fisioterapia. Em todos os pacientes em programação de extubação será aplicado a CAM-UCI antes do procedimento e o mesmo será realizado independente do resultado desta escala, uma vez que a mesma não é um critério para a decisão de extubação (este é um dos objetivos do estudo - verificar o papel do delirium, mensurado pela CAM-UCI, na flaha da

Endereço: Rua Augusto Viana, s/nº - 1º Andar
Bairro: Canela **CEP:** 40.110-060
UF: BA **Município:** SALVADOR
Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

extubação). O mesmo procedimento (aplicação da CAM-UCI) será feito antes e depois dos procedimentos de mobilização do paciente. Em pacientes com diagnóstico de delirium, também será aplicada outra escala, a Delirium Index for the Intensive Care Unit (DI-UCI), para avaliar a gravidade do delirium..
Serão incluídos todos os pacientes internados na UTI, com idade superior a 18 anos, avaliados diariamente para identificar possível quadro de delirium.

Objetivo da Pesquisa:

- Avaliar a importância do delirium no sucesso de extubação dos pacientes em ventilação mecânica.
- Avaliar a associação da delirium index modificada com o tempo de delirium, mortalidade, tempo de ventilação mecânica e de internamento hospitalar.
- Avaliar o curso dos pacientes com delirium após a instituição de atividades físicas e cognitivas combinadas - dual task.

Avaliação dos Riscos e Benefícios:

Os procedimentos propostos já foram incorporados a rotina da UTI e são realizados da prática diária de assistência. A proposta de pesquisa visa avaliar se essas intervenções são efetivas e poderiam modificar a rotina de intervenção da indicação de extubação, o que poderia beneficiar pacientes futuros. Não há benefício imediato para o sujeito da pesquisa.
Os riscos são mínimos, uma vez que os protocolos propostos já são realizados de rotina na UTI e não modificam as condutas da equipe multidisciplinar no momento atual.

Comentários e Considerações sobre a Pesquisa:

Todos os procedimentos propostos pelos autores foram incorporados como rotina da UTI na qual ocorrerá o estudo. Independente da autorização do familiar/responsável do paciente internado os procedimentos serão realizados. Solicita-se autorização para que os dados sejam coletados e utilizados na pesquisa. A pesquisa é realizada em ambiente hospitalar que não altera a rotina de atendimento dos pacientes e busca avaliar melhor os procedimentos adotados pelo serviço.

Considerações sobre os Termos de apresentação obrigatória:

NDN

Recomendações:

No TCLE revisado, página 3, trecho "Se concordar com sua participação deverá assinar este formulário em duas vias e manter uma cópia com você", substituir a palavra cópia por via, uma vez que o responsável pelo paciente recebe um das vias do TCLE e não uma cópia.

HOSPITAL UNIVERSITÁRIO PROF. EDGARD SANTOS- UFBA - HUPES

Continuação do Parecer: 276.339

Conclusões ou Pendências e Lista de Inadequações:

1) Os anexos 2,3 e 4 não se encontram no texto;
Pendência RESOLVIDA;

DO TCLE, os seguintes aspectos merecem esclarecimento e/ou correção:

2) Redação do TCLE ("resolução 196/96, IV.1 - Exige-se que o esclarecimento dos sujeitos se faça em linguagem acessível")
O TCLE contém alguns termos, presumivelmente, de difícil compreensão da população leiga:
a) "a importância dos episódios de delirium nos pacientes graves (que é um ESTADO CONFUSIONAL AGUDO)". Sugerimos descrever o quadro clínico com palavras de simples compreensão, em acréscimo ao termo destacado;
Pendência RESOLVIDA na versão 2 do TCLE;

b) "existe possibilidade dos pacientes apresentarem melhora em alguns DOMINIOS COGNITIVOS".
Sugerimos descrever com exemplos;
"ESTÍMULOS COGNITIVOS E MOTORES(estratégicas não farmacológicas) pode promover melhora aguda da memória". Solicitamos descrever os estimulos cognitivos e motores a serem realizados de maneira simples. Isso foi feito adiante no texto. Colocá-lo logo na primeira citação facilita a compreensão do leitor;
Pendência RESOLVIDA na versão 2 do TCLE;

c) Colocar o contato do CEP do HUPES no TCLE.
Pendência RESOLVIDA na versão 2 do TCLE;

3) Segundo a Resolução 196/96 artigo IV.1b, " Exige-se que o esclarecimento dos sujeitos se faça em linguagem acessível e que inclua necessariamente os seguintes aspectos: os desconfortos e riscos possíveis e os benefícios esperados".
a) Assim. o TCLE deve informar que não há nenhum benefício imediato para o sujeito da pesquisa, mas pode auxiliar em tratamentos futuros. A frase "O seu familiar estará ajudando na compreensão do delirium em pacientes críticos" pode ser mais clara em informar os benefícios esperados futuramente. Qual o benefício de "compreender o delirium em pacientes críticos"?
Pendência RESOLVIDA na versão 2 do TCLE;

Endereço: Rua Augusto Viana, s/nº - 1º Andar
Bairro: Canela **CEP:** 40.110-060
UF: BA **Município:** SALVADOR
Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

4) Segundo a resolução 196/96, artigo V, "Considera-se que toda pesquisa envolvendo seres humanos envolve risco".
a) Assim, deixar claro que os riscos são mínimos pois todos os protocolos não alteram a rotina de atendimento do doente internado. Apenas se quer avaliar melhor o resultados dessas intervenções já utilizadas.
Pendência RESOLVIDA na versão 2 do TCLE;

Fica subentendido que o Termo de Dispensa do TCLE se aplica aos dados da vertente retrospectiva (dados em prontuários e em banco de dados) e o TCLE aos novos pacientes a serem incluídos no estudo, para que autorizem a inclusão de seus familiares.

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

Considerações Finais a critério do CEP:
O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 - Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.

O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária ¿ ANVISA ¿ junto com seu posicionamento.

HOSPITAL UNIVERSITÁRIO PROF. EDGARD SANTOS- UFBA - HUPES

Continuação do Parecer: 276.339

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas.

Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em _____/_____/_____ e ao término do estudo.

Situação: Projeto Aprovado.

SALVADOR, 20 de Maio de 2013

Assinador por:
Roberto José da Silva Badaró
(Coordenador)

Endereço: Rua Augusto Viana, s/nº - 1º Andar
Bairro: Canela **CEP:** 40.110-060
UF: BA **Município:** SALVADOR
Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

Parecer do CEP 2

Parecer Consubstanciado de Projeto

Título do Projeto: Validação do instrumento Confusion Assessment Method/Intensive Care Unit (CAM/ICU) para o idioma português brasileiro em pacientes críticos com delirium

Pesquisador Responsável Dimitri Gusmão Flôres

Data da Versão 08/07/2010	Cadastro 54/2010	Data do Parecer 09/08/2010

Grupo e Área Temática III - Projeto fora das áreas temáticas especiais

Objetivos do Projeto

1 TEMA DA PESQUISA

Avaliação do método CAM-ICU (Confusion Assesment Method for Intensive Care Unit) em pacientes internados em unidades de terapia intensiva no Brasil.

2 PERGUNTA DA INVESTIGAÇÃO

Qual a acurácia do método CAM-ICU traduzido para o idioma português no diagnóstico de delirium em pacientes críticos?

3 OBJETIVO GERAL

Validar a CAM-ICU para o idioma português brasileiro em pacientes críticos com delirium.

3.1OBJETIVO ESPECÍFICO

Avaliar a acurácia da versão em português brasileiro do instrumento CAM-ICU para o diagnóstico de delirium em pacientes de UTI no Brasil

3.2OBJETIVOS SECUNDÁRIOS

Avaliar a correlação inter-observadores da versão em língua portuguesa da CAM-ICU.

Identificar a freqüência de delirium nas UTIs incluídas no estudo e descrever suas características clínicas e sócio-demográficas.

Sumário do Projeto
O estudo de validação será realizado nas Unidades de Terapia Intensiva do Hospital Universitário professor Edgar Santos e do Hospital Geral Roberto Santos, Salvador-Ba e no Instituto Nacional do Câncer (Inca), Rio de Janeiro-RJ. O familiar ou o representante legal. *Serão avaliados pacientes internados em unidade de terapia intensiva de forma consecutiva* com idade superior a 18 anos, após o segundo dia de admissão, estando ou não em uso de suporte ventilatório invasivo. Será necessário que o paciente encontre-se com uma pontuação do RASS (Richmond Agitation Sedation Scale), que é uma escala de sedação e analgesia já utilizada rotineiramente em unidades de terapia intensiva maior igual a -3. Esta pontuação na escala RASS implica interação do paciente com o meio externo.
Um intensivista utilizará a CAM-ICU e os critérios do DSM IV serão utilizados por um profissional da área de neurociências (neurologista, psiquiatra, geriatria). O intervalo entre as avaliações será de 30 minutos. Nenhum dos avaliadores terá acesso à avaliação do outro. A avaliação realizada em Salvador será feita por um único intensivista (Dimitri Gusmão Flôres, que aplicará a CAM-ICU) e por dois psiquiatras (Patrícia Pimenta Lemos e Gisele Vasconcelos Serpa, que aplicarão o DSM VI). No Rio de Janeiro, um único intensivista fará a avaliação com a CAM-ICU (Melissa Tassano Pitrowsky) e um neurologista (Marco Antônio Sales Dantas de Lima) aplicará a DSM IV.
A CAM–ICU é um instrumento adaptado para pacientes internados em terapia intensiva, com resposta não verbal, através de reconhecimento de figuras, resposta simples tipo sim/não e comandos simples (apêndice 2). DSM IV é um sistema de classificação dos transtornos mentais categórico adotado pela Associação Psiquiátrica Americana.

6 ANÁLISE ESTATÍSTICA
Médias e proporções serão utilizadas para descrever as características clínicas e demográficas da amostra analisada. A correlação dos dois testes (DSM IV e CAM-ICU) serão analisadas utilizando uma tabela 2X2. Para a validação da versão em português seguiremos o método utilizado por Ely et al, no qual, em um estudo piloto, encontrou uma sensibilidade de 95% entre observadores e uma especificidade de 88%. Assumindo que a prevalência de delirium em UTI na América Latina é de 32%, na população geral, e de 60% em pacientes na ventilação mecânica (Salluh et al, dados não publicados),, , precisaríamos de 60 pacientes para a análise. Utilizaremos o software SPSS.

Aspectos relevantes para avaliação	*Situação*
Título	Adequado
Relação dos Pesquisadores	Adequada
Local de Origem na Instituição	Adequado
Projeto elaborado por patrocinador	Não
Local de Realização	Outro (citar no comentário)
Outras instituições envolvidas	Sim
Condições para realização	Adequadas
Introdução	Adequada
Objetivos	Adequados
Método	
Tipo de projeto	Pesquisa em Seres Humanos
Delineamento	Adequado
Tamanho de amostra	Total 60 Na Instituição 20
Cálculo do tamanho da amostra	Adequado
Participantes pertencentes a grupos especiais	Não
Seleção eqüitativa dos indivíduos participantes	Adequada
Critérios de inclusão e exclusão	Adequados
Relação risco- benefício	Adequada
Uso de placebo	Não utiliza
Período de suspensão de uso de drogas (wash out)	Não utiliza
Monitoramento da segurança e dados	Adequado
Armazenamento de material biológico	Não se aplica
Instrumentos de coleta de dados	Adequados
Avaliação dos dados	Adequada - quantitativa

PROJETO APROVADO

O estudo será realizado nas Unidades de Terapia Intensiva do Hospital Universitário professor Edgar Santos e do Hospital Geral Roberto Santos, Salvador-Ba e no Instituto Nacional do Câncer (Inca), Rio de Janeiro-RJ.

• O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de *retirar seu consentimento em qualquer fase da pesquisa, sem penalização* alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 - Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.

• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

• Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprovatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, item III.2.e).

• Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em ___/___/___ e ao término do estudo. dezembro 2010

ROBERTO BADARÓ, MD PHD
Coordenador CEP
CHUPES

54/10

Privacidade e confidencialidade	Adequada
Termo de Consentimento	Adequado
Adequação às Normas e Diretrizes	Sim
Cronograma	Adequado
Data de início prevista	Após aprovação pelo CEP
Data de término prevista	3 meses após aprovação pelo CEP
Orçamento	Adequado
Solicita recursos à instituição	Não
Fonte de financiamento externa	Outras fontes
Referências Bibliográficas	Adequadas

Recomendação

Aprovar

Comentários Gerais sobre o Projeto

Instituto de Ciências da Saúde
Programa de Pós Graduação
Processos Interativos dos Órgãos e Sistemas
Avenida Reitor Miguel Calmon s/n - Vale do Canela. CEP: 40110-100
Salvador, Bahia, Brasil

http://www.ppgorgsistem.ics.ufba.br