# DELIRIUM
# v intenzivní medicíně

# Možnosti farmakoterapie

Pavel Ševčík
Marcela Káňová
KARIM FN Ostrava a LF Ostravské univerzity

# Definice, charakteristika I

- Kvalitativní porucha vědomí
- Snížení schopnosti soustředit a udržet pozornost
- Porucha kognitivních funkcí (může přetrvávat měsíce)
  - orientace (čas, místo, jiné osoby)
  - paměť (krátkodobá)
  - zpracování informací
  - vyjadřování (dysartrie, dysnomie, dysgrafie)
- Porucha vnímání
  - porucha interpretace skutečnosti
  - iluze
  - halucinace (zrakové, ev. sluchové, taktilní…)

# Definice, charakteristika II

- Změny rovněž v
  - psychomotorické aktivitě
  - emocích
  - spánkovém cyklu
- Rychlý vznik příznaků (hodiny)
- Proměnlivost v čase

Am Psych Assoc. Diagnostic and Statistical Manual of Mental Disorders 1994

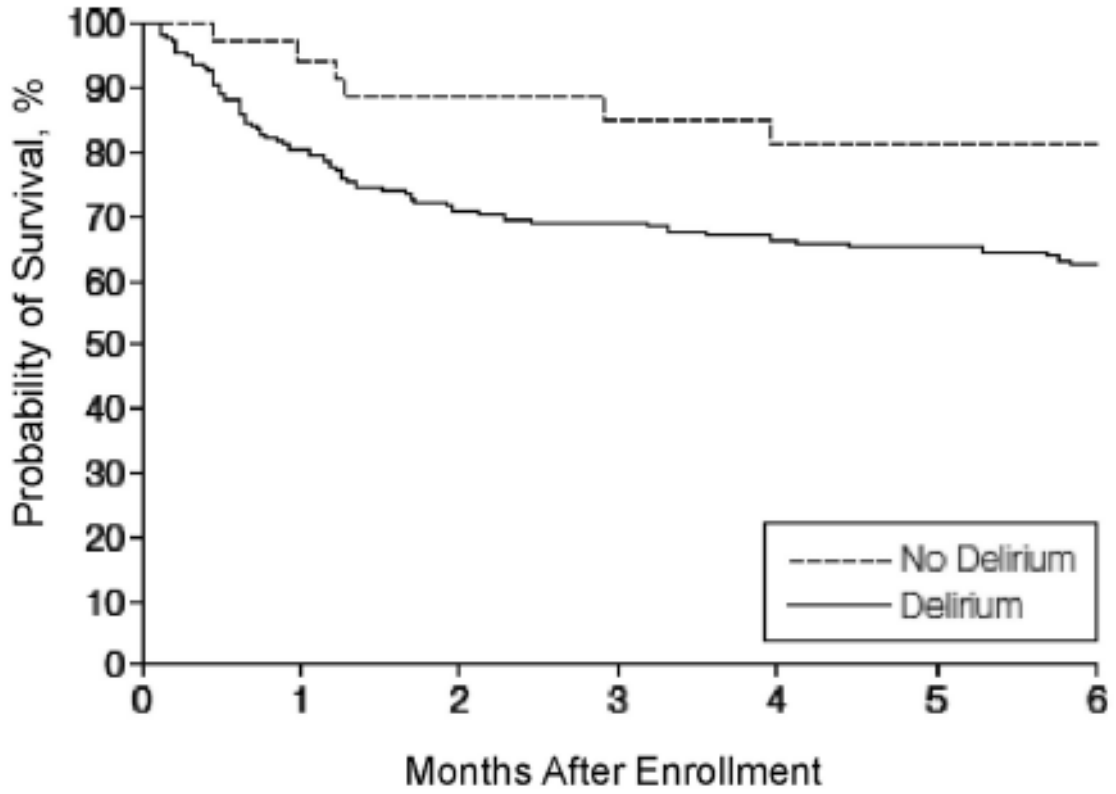
# Výskyt

- 10-30 % pacientů během hospitalizace
- 16-83 % na PRIM (KARIM FNO – 20-25%)
- Závislost na věku
- Typicky po operaci – tím častěji, čím je chirurgické trauma rozsáhlejší
- ↑ mortalita během hospit. i po propuštění
- ↑ pravděpod. dlouhodob. kognitiv. deficitu až 10x
- ↑ morbidita (respirační, hojení, dekubity)
- ↑ riziko ztráty soběstačnosti
- Vícenáklady až + 40 % (USA – 1,5-20 mld USD/rok)

Am Psych Assoc. Practice guidelines for treatment of delirium. Am J Psych 1999

Franco K. Psychosomatics 2001

Polderman KH. The delirious pt in the ICU. Yearbook ICEM 07




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| No Delirium | 41 | 34 | 28 | 25 | 22 | 21 | 19 |
| Delirium | 183 | 138 | 116 | 111 | 104 | 98 | 88 |

**Figure 1.** Delirium is independently associated with 6-month mortality. Multivariable Cox proportional hazards analysis demonstrated that patients who experience delirium in the intensive care unit were three times more likely to die at 6 months (hazard ratio, 3.2; 95% confidence interval, 1.4 to 7.7; $p = .008$) after adjustment for age, Charlson Comorbidity Index, modified Blessed Dementia Rating Scale score, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score, sepsis, acute respiratory distress syndrome, and time-varying covariates for coma and use of sedative and analgesic medications. Reprinted with permission from Ely et al (21).

# Výskyt pooperačního deliria

- Delirantní epizoda - 30-40 % pac. > 65 let

- Elektivní chirurgie - 11,4 % (Litaker 2001)
- Cévní chirurgie - 36 % (Schneider 2002)
- Chirurgie jater - 17 % (Yoschimura 2004)
- Čelistní chirurgie - 26 % (Yamagata 2005)
- Hrudní chirurgie - 5 % (Vildizeli 2005)

# Typy deliria

- Hyperaktivní (2 %, KARIM FNO 49%)
  - neklid, podrážděnost, nesoustředěnost
  - nespolupráce, halucinace, hlasitá a rychlá řeč
  - zrychlená motorika
  - častější u mladších pac.
- Hypoaktivní (43 %, KARIM FNO 20%)
  - spavost, netečnost, nepozornost
  - zpomalená motorika
  - omezená komunikace s okolím
  - obtížně dg – zejm. na PIM
- Smíšené (55 %, KARIM FNO 31%)
  - nejčastěji – cca ½ případů

Liptzin B et al. Br J Psych 1992
Peterson JF et al. J Am Geriatr Soc 2006

# Synonyma a příbuzné jednotky

- Septická encefalopatie - SAE
- Encefalopatie kriticky nemocných
- ICU psychóza
- ICU syndrome, ICU encephalopathy
- Acute confusional state
- Acute brain failure
- Postoperative cognitive disorder - POCD
- Post-traumatic stress disorder - PTSD

Polderman KH et al. The delirious pt in the ICU. Yearbook ICEM 07
Polito A et al. Encephalopathy in sepsis. Yearbook ICEM 08
Venkatesh B. In: Oh´s Intensive Care Manual, 6th ed, 2009

# Delirium v IM

- Dříve – fatalistický pohled
  - delirium je neoddělitelnou součástí řady kritických stavů
- Od 2. pol. 90. let
  - delirium je potenciálně preventabilní

Polderman KH et al. The delirious pt in the ICU, Yearbook ICEM 07

# Příčiny a rizikové faktory

- SIRS
- Vysoký věk
- Demence
- Vysoká míra kritičnosti stavu
- Nadměrné používání sedativ, opioidů
- Kouření
- Senzorická deprivace
- Spánková deprivace
- Retence moči, stolice
- Omezování, kurtování
- Dehydratace
- Podvýživa, hladovění

Am Psych Assoc. Practice guidelines for treatment of delirium. Am J Psych 1999

Hála M et al. Anest intenziv Med 2006

# Delirium jako NÚ A-S

Benzodiazepiny jsou ve vztahu ke vzniku deliria rizikovější než jiné sedativní látky

Opioidy – rozporná data. Zřejmě: přiměřené dávkování tiší bolest a snižuje d., nadměrné dávkování zvyšuje riziko deliria

McGrane S et al. Sedation in ICU. Minerva Anest 2012

# Delirium na ICU – 4 základní rizikové faktory

- Předcházející demence
- Hypertenze
- **Alkoholismus**
- Závažnost přidruženého onemocnění

ACCCM/SCCM Guidelines for Management PAD in ICU. CCM 2013

# Delirium jako důsledek odnětí alkoholu a návykových látek

- Obvykle **hyperaktivní forma** deliria
- Příznaky syndromu z odnětí
- Typicky se vyskytují po odnětí opioidů, BDZ, **alkoholu**
- Ale také po dexmedetomidinu (po 7 dnech od vysaz.)
- Sy z odnětí může být v IM přehlédnut

ACCCM/SCCM Guidelines for Management PAD in ICU. CCM 2013

# Delirium jako důsledek odnětí alkoholu

- Závislost na alkoholu – u 15-20 % hospitalizovaných
- U 8-31% z nich se vyvine syndrom z odnětí, zejm. u chirurgických a traumatologických
- Projeví se neurologickou a autonomní dysfunkcí
- Symptomy mohou být život ohrožující, vč. generalizovaných křečí, deliria tremens

ACCCM/SCCM Guidelines for Management PAD in ICU. CCM 2013

# Syndrom z odnětí alkoholu

- Následky – prodloužení UPV, prodl. hospitalizace, persistentní delirium
- Závislost na alkoholu bývá v IM podceňována (nikoli však na KARIM FN Ostrava)
- Pacienti zapírají, příbuzní nevědí nebo zapírají též
- Dif dg příčin deliria u těchto pac. bývá obtížná
- Řešení – symptomatická léčba + psychofarmaka

ACCCM/SCCM Guidelines for Management PAD in ICU. CCM 2013

# ICU encefalopatie

- Vyvíjí se 5-7 dní po přijetí na PIM
- Projevy: agitace, neklid, delirium
- Příčiny – multifaktoriální:
  - Dlouhodobá UPV
  - Spánková deprivace
  - Zkreslené vnímání reality
  - Chybění rytmu den – noc
  - Imobilizace
  - Hlučné a monotónní prostředí
  - Sedativa
  - Základní onemocnění ovlivňující CNS

Venkatesh B. In: Oh´s Intensive Care Manual, 6th ed, 2009

# Diagnostika

- Confusion Assessment Method (CAM)
- Confusion Assessment Method for ICU (CAM-ICU)
- Intensive Care Delirium Screening Checklist (ICDSC)

Inouye SK et al., Ann Intern Med 1990
Ely EW et al. JAMA 2001
Bergeron N et al. Intens Care Med 2001

# CAM-ICU

- 2 stupně klinického vyšetření:
  - A - posouzení míry sedace či agitovanosti
  - B - posouzení kvalitativní poruchy vědomí

# A - Míra sedace

## RASS – Richmond Agitation and Sedation Scale

| skóre | stav pacienta | popis |
|---|---|---|
| +4 | agresivní | nebezpečný pro ošetřující personál, ohrožuje okolí |
| +3 | velmi agitovaný | tahá za katetry, kanyly, riziko sebepoškození |
| +2 | agitovaný | časté bezúčelné pohyby, ev. interferuje s ventilátorem |
| +1 | neklidný | úzkostný, pohyby nejsou energické |
| 0 | bdělý a klidný | |
| -1 | ospalý | pospává, otevře oči na oslovení, kontakt > 10 s |
| -2 | lehká sedace | otevře oči na oslovení, kontakt < 10 s |
| -3 | střední sedace | pohyby nebo otevření očí na oslovení, není kontakt |
| -4 | hluboká sedace | bez reakce na oslovení, po fyzické stimulaci otevření očí nebo pohyb |
| -5 | neprobudný | bez reakce na oslovení nebo fyzickou stimulaci |

Pacienti se skóre -4 a –5 se dále nevyšetřují, u ostatních pacientů – druhý krok

# B - Posouzení deliria

- Položka 1 – náhlý nástup nebo proměnlivost příznaků nebo kontinuální sedace a
- Položka 2 – nepozornost a
- Položka 3 – zmatenost, inkoherentní (dezorganizované) myšlení nebo
- Položka 4 – změněná úroveň vědomí (vigility)

# Faktory vedoucí k nerozpoznání D

- Hypoaktivní delirium (často zaměňováno za depresi nebo demenci)
- Věk ≥ 80 let
- Problémy s viděním
- Předcházející kognitivní porucha

Peterson JF et al. J Am Geriatr Soc 2006

# Rizika deliria

- Zvýšení morbidity
- Samovolná extubace
- Vytržení katétrů, drénů
- Poškození měkkých tkání
- Pády z lůžka

Venkatesh B. In: Oh´s Intensive Care Manual, 6th ed, 2009

# Léčebná opatření

- Nejsou prospekt. studie potvrzující zlepšení výsledků léčby na základě časné a agresivní léčby D, obecně se to však předpokládá.
- Prevence deliria zlepšuje výsledky léčby.
- 2 skupiny možností
  - nefarmakologická opatření
  - léky

Polderman KH. The delirious patient in the ICU. Yearbook ICEM 07

# Nefarmakologická opatření

- Klinické parametry – zajištění homeostázy
  - STK > 90 torr
  - SaO2 > 90 %
  - léčba zákl. onemoc., metabol. rozvratu, infekce…
- Pacient – mj. koncept bazální stimulace
  - Prevence senzorické deprivace (naslouchadla, brýle…)
  - Častá přátelská komunikace s pacientem (i reorientace)
  - Umožnění poslechu denních zpráv
  - Časná a opakovaná mobilizace
- Prostředí – mj. koncept bazální stimulace
  - Rytmus spánku a bdění (světlo, farmaka)
  - Eliminace hluku, zejm. v noci
  - Přítomnost blízkých, známých předmětů
  - Stabilní ošetřovatelský personál

# Zúčastněné neurotransmitery

- Acetylcholin (jeho deficit progreduje s věkem)
- Dopamin
- Serotonin
- Noradrenalin
  a další

# Farmakologická léčba deliria I

- Zhodnocení stávající medikace
- Vysazení některých léků (zejm. anticholinergních) – BDZ, metoklopramid, H2-blokátory, protazin, KS
- Kontrola bolestí, zejm. klidových (NSA)
- Psychofarmaka
  - benzodiazepiny – u d. z odnětí (sedativa, alkohol)

# Farmakologická léčba deliria II

- Neuroleptika – antagonisté $D_2$ receptorů v CNS (potlač. bludů, halucinací, agitovanosti, agresivity)
  - haloperidol (úr. C) 2-5 mg i.v. á 6 hod. nebo 5-10 mg kontin/hod., ev. s úvod. 10 mg bolusem, 1-2 mg p.o. á 2-4 hod.
  - risperidon 0,5-1-4 mg p.o. za den
  - olanzapin 2,5-5 mg p.o. za den
  - tiapridal 100-200 mg á 6-8 hod. i.v. nebo kontin. 20-60mg/hod.
  - levopromazin 25-50 mg i.v. v období noci frakcionovaně
  - melperon 25 mg 1-3x denně p.o.
- Antidepresiva
  - venlafaxin 75 mg denně p.o.
  - citalopram 20 mg á 12 hod.
  - escitalopram 10 mg denně p.o.
  - sertralin 50 mg denně p.o., až případně do 200 mg denně
  - trazodon 75-150 mg denně večer
  - alprazolam 0,25-0,5 mg až 4x denně p.o.

# Farmakologická léčba deliria III

- Další:
  - Dexmedetomidin
  - Opioidy – fentanyl, morfin
  - Fysostigmin 0,15-2 mg i.v., event. 3 mg/hod. kontin.
  - Další inhibitory ACHE – donepezil, galantamin, rivastigmin – účinné v léčbě demence
  - Koxiby
  - Statiny

Dallas P at al. Antipsychotics in the treatment of delirium. J Clin Psychiatr 2007
Grace JB et al. Expert Opin Pharmacother 2006
Moretti R et al. Am J Alzheimers Dis Other Demen 2004
Hála M et al. Anest intenziv Med 2006
Morandi A et al. Chest 2011

# Farmakol. léčba deliria - NÚ

- Dechový útlum (vyšší dávky, kombinace léků)
- Kardiovaskulární (hypotenze, arytmie)
- Ovlivnění peristaltiky (paralytický ileus)
- Extrapyramidový sy
- Vzácně neuroleptický maligní sy

# Alfa-2 agonisté

- Alfa-2 receptor – „nejdůležitější presynaptický receptor v lidském těle“

Gregoretti et al, Current Drug Targets 2009

- Alfa-2 agonismus (zejm. α-2a) - účinek:
  - sympatikolytický
  - hypnotický
  - sedativní
  - analgetický
  - neuroprotektivní

Panzer et al. Crit Care Clinics 2009

Hossain MD et al. Eur J Pharmacol 2004

# Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

## The MENDS Randomized Controlled Trial


Pratik P. Pandharipande, MD, MSCI

Brenda T. Pun, RN, MSN, ACNP

Daniel L. Herr, MD

Mervyn Maze, MB, ChB

Timothy D. Girard, MD, MSCI

Russell R. Miller, MD, MPH

Ayumi K. Shintani, MPH, PhD

Jennifer L. Thompson, MPH

James C. Jackson, PsyD

Stephen A. Deppen, MA, MS

Renee A. Stiles, PhD

Robert S. Dittus, MD, MPH

Gordon R. Bernard, MD

E. Wesley Ely, MD, MPH



**Context** Lorazepam is currently recommended for sustained sedation of mechanically ventilated intensive care unit (ICU) patients, but this and other benzodiazepine drugs may contribute to acute brain dysfunction, ie, delirium and coma, associated with prolonged hospital stays, costs, and increased mortality. Dexmedetomidine induces sedation via different central nervous system receptors than the benzodiazepine drugs and may lower the risk of acute brain dysfunction.

**Objective** To determine whether dexmedetomidine reduces the duration of delirium and coma in mechanically ventilated ICU patients while providing adequate sedation as compared with lorazepam.

**Design, Setting, Patients, and Intervention** Double-blind, randomized controlled trial of 106 adult mechanically ventilated medical and surgical ICU patients at 2 tertiary care centers between August 2004 and April 2006. Patients were sedated with dexmedetomidine or lorazepam for as many as 120 hours. Study drugs were titrated to achieve the desired level of sedation, measured using the Richmond Agitation-Sedation Scale (RASS). Patients were monitored twice daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU).

**Main Outcome Measures** Days alive without delirium or coma and percentage of days spent within 1 RASS point of the sedation goal.

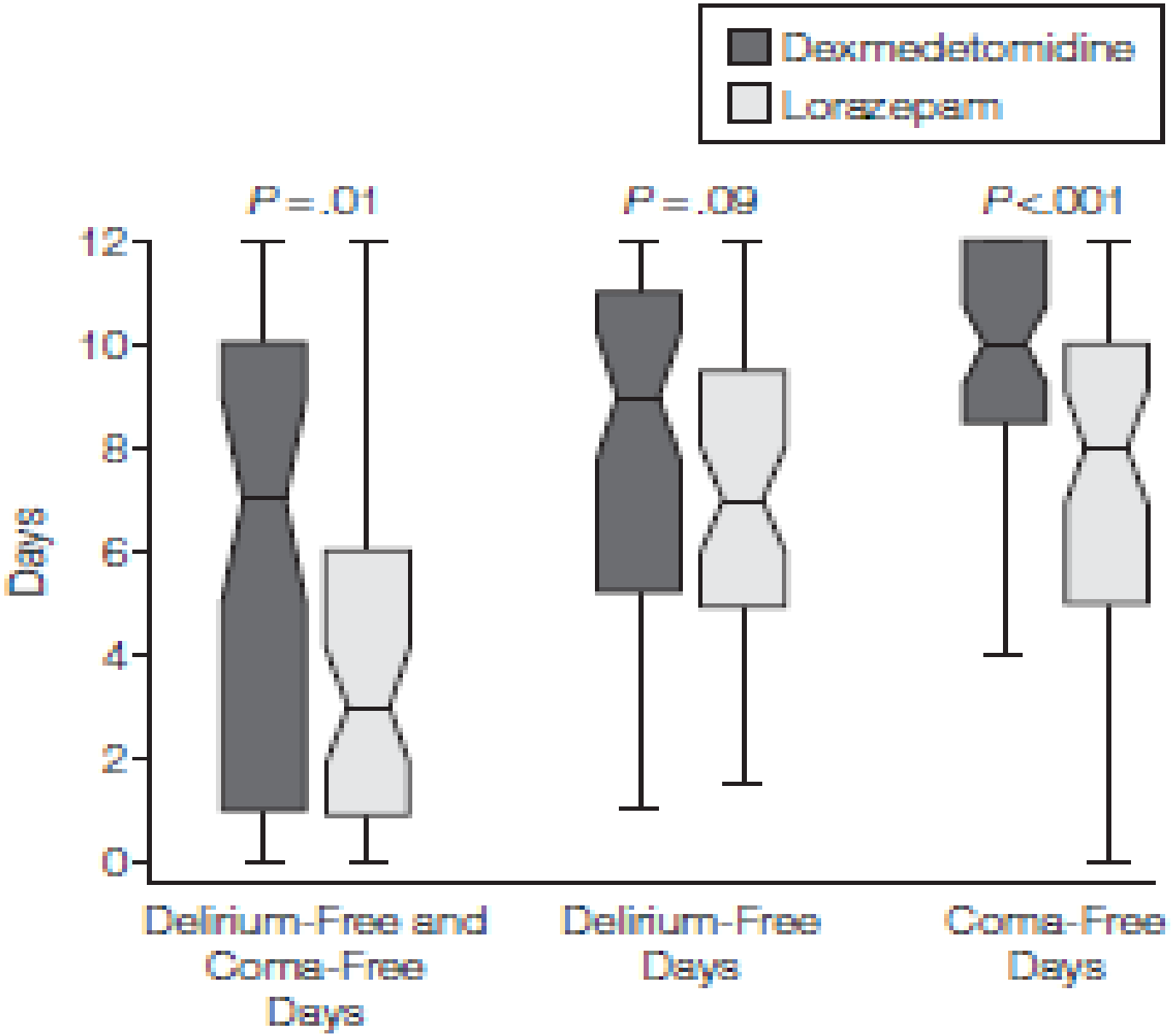
# Farmakoth deliria - dexmedetomidin

- Pandharipande et al, JAMA 2007 – srovnání dex a lorazepamu na výskyt deliria u UPV
  - Sedace dexmedetomidinem
    - 0,15-1,5 μg/kg/hod, max. 120 hod.
  - Sedace lorazepamem
    - 1-10 mg/kg/hod., max. 120 hod.

Závěr – sedace dexmedetominidem u pac.na UPV v prostředí ICU – signifikantně více dní bez deliria nebo komatu při srovnatelných nákladech na léčbu.

**Byl to první RCT, který ukázal, že akutní mozková dysfunkce může být omezena výběrem sedativa.**

**Figure 2.** Delirium-Free and Coma-Free Days During Study



# Dexmedetomidine and the Reduction of Postoperative Delirium after Cardiac Surgery

José R. Maldonado, M.D., Ashley Wysong, M.S.
Pieter J.A. van der Starre, M.D., Thaddeus Block, M.D.
Craig Miller, M.D., Bruce A. Reitz, M.D.

**Background:** *Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances.* **Objective:** *The authors investigated the effects of postoperative sedation on the development of delirium in patients undergoing cardiac-valve procedures.* **Methods:** *Patients underwent elective cardiac surgery with a standardized intraoperative anesthesia protocol, followed by random assignment to one of three postoperative sedation protocols: dexmedetomidine, propofol, or midazolam.* **Results:** *The incidence of delirium for patients receiving dexmedetomidine was 3%, for those receiving propofol was 50%, and for patients receiving midazolam, 50%. Patients who developed postoperative delirium experienced significantly longer intensive-care stays and longer total hospitalization.* **Conclusion:** *The findings of this open-label, randomized clinical investigation suggest that postoperative sedation with dexmedetomidine was associated with significantly lower rates of postoperative delirium and lower care costs.*

(Psychosomatics 2009; 50:206–217)

# Farmakoth deliria - dexmedetomidin

- Maldonado, Psychosomatics 2009 – delirium po KCH operacích:
  - Sedace dexmedetomidinem **3 %** pacientů
    - Úv. 0,4 μg/kg následována 0,2-0,7 μg/kg/h, max. 24 h
  - Sedace propofolem **50 %** pacientů
    - 25-50 μg/kg/min
  - Sedace midazolamem **50 %** pacientů
    - 0,5-2 mg/hod.

  Závěr – sedace dexmedetomidinem – signifikantně méně pooperačních delirií, nižší léčebné náklady (zkrácení doby hospitalizace)

**Critical Care**

CRITICAL CARE

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# Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial

*Critical Care* 2010, **14**:R38 doi:10.1186/cc8916

Pratik P Pandharipande (pratik.pandharipande@Vanderbilt.Edu)
Robert D Sanders (robert.sanders@imperial.ac.uk)
Timothy D Girard (timothy.girard@Vanderbilt.Edu)
Stuart McGrane (Stuart.mcgrane@Vanderbilt.Edu)
Jennifer L Thompson (jennifer.l.thompson@Vanderbilt.Edu)
Ayumi K Shintani (ayumi.shintani@Vanderbilt.Edu)
Daniel L Herr (Daniel.L.Herr@medstar.net)
Mervyn Maze (mazem@anesthesia.ucsf.edu)
E Wesley Ely (wes.ely@Vanderbilt.Edu)
The MENDS Investigators (not@valid.com)

# Farmakoth deliria - dexmedetomidin

- Pandharipande et al, CC 2010-11 – srovnání dex a lorazepamu na celkové výsledky léčby u septických pacientů
  - Sedace dexmedetomidinem
    - 0,15-1,5 μg/kg/hod, max. 120 hod.
  - Sedace lorazepamem
    - 1-10 mg/kg/hod., max. 120 hod.

  Závěr – sedace dexmedetominidem u septických pac. – signifikantně více dní bez mozkové dysfunkce a UPV, menší úmrtnost

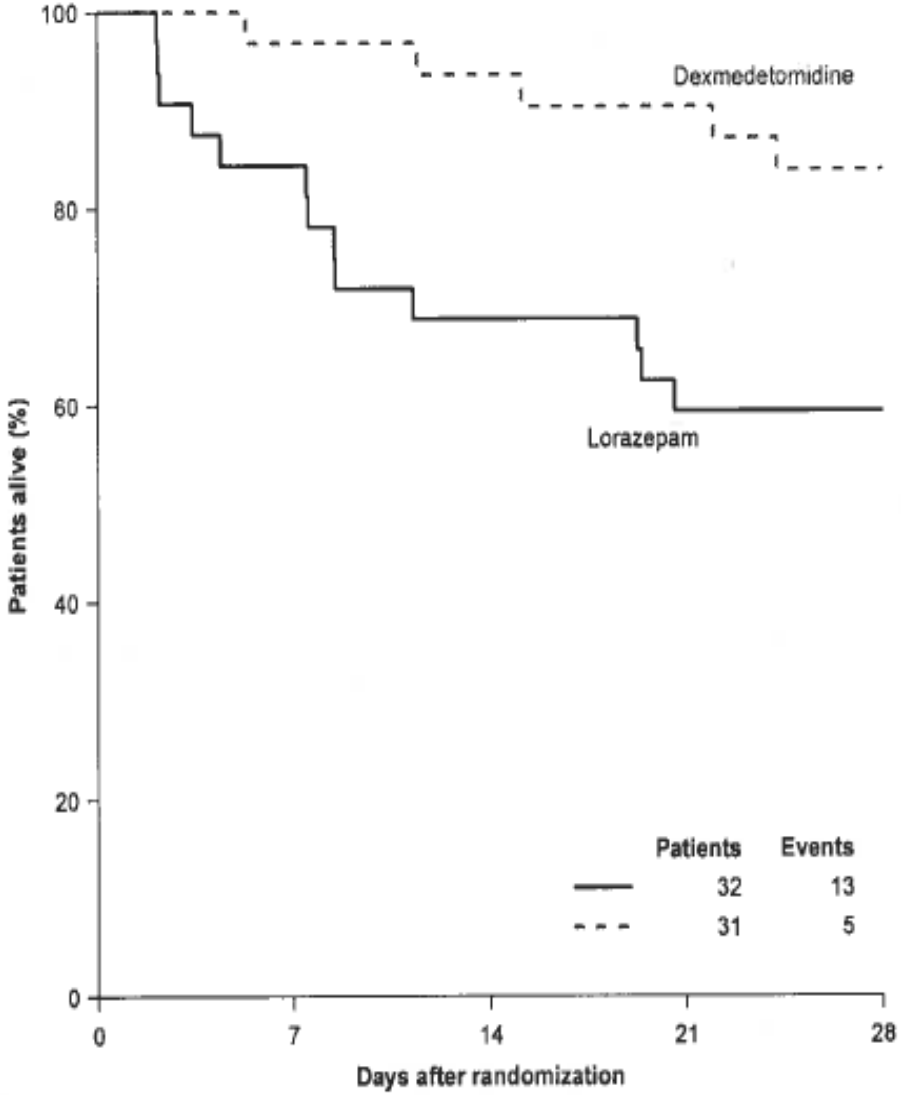


**Figure 3. Kaplan-Meier curve showing probability of survival during the first 28 days according to treatment group, among patients with sepsis.** Dexmedetomidine decreased the probability of dying within 28 days by 70%; this beneficial effect was not seen in patients who were not septic (*P* value for interaction = 0.11 implying an interaction between sepsis and the treatment groups).

**Available online** http://ccforum.com/content/13/3/R75

Research

Open Access

# Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial

Michael C Reade, Kim O'Sullivan, Samantha Bates, Donna Goldsmith, William RSTJ Ainslie and Rinaldo Bellomo

Department of Intensive Care Medicine, Austin Hospital and the University of Melbourne, 145 Studley Road, Heidelberg, Victoria, 3084, Australia

Corresponding author: Michael C Reade, Michael.READE@austin.org.au

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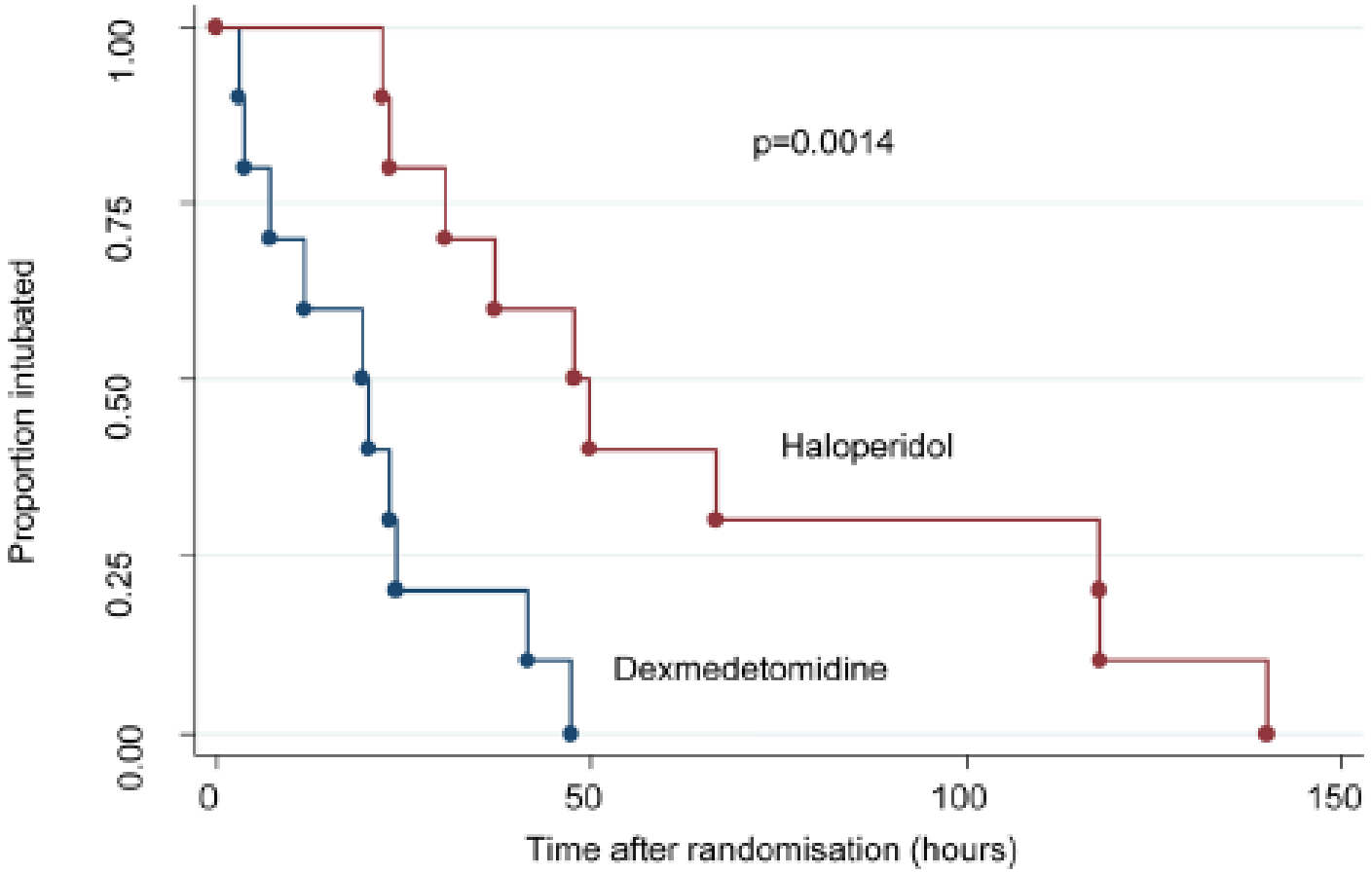
# Farmakoth deliria - dexmedetomidin

- Reade et al, CC 2009 – srovnání dex a haloperidolu u agitovaných intub. pacientů
  - Sedace dexmedetomidinem
    - 0,2-0,7 μg/kg/hod
  - Sedace haloperidolem
    - 0,5-2 mg/hod

  Závěr – sedace dexmedetomidinem – signifikantně časnější extubace (19,9 vs. 24,0 h), dex významně zkrátil dobu hospitalizace na ICU ze 6,5 na 1,5 dne

**Figure 2**




**Graph showing time to extubation.**

Anesthesiology 2009; 111:1075–84
Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

# Prevalence of Delirium with Dexmedetomidine Compared with Morphine Based Therapy after Cardiac Surgery

## A Randomized Controlled Trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study)

Yahya Shehabi, F.J.F.I.C.M.,* Peter Grant, F.R.A.C.S.,† Hugh Wolfenden, F.R.A.C.S.,† Naomi Hammond, M.N.,‡ Frances Bass, B.N.,§ Michelle Campbell, B.N.,§ Jack Chen, Ph.D.‖

***Background:*** **Commonly used sedatives/analgesics can increase the risk of postoperative complications, including delirium. This double-blinded study assessed the neurobehavioral, hemodynamic, and sedative characteristics of dexmedetomidine compared with morphine-based regimen after cardiac surgery at equivalent levels of sedation and analgesia.**

***Methods:*** **A total of 306 patients at least 60 yr old were randomized to receive dexmedetomidine (0.1–0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or morphine (10-70 $\mu g \cdot kg^{-1} \cdot h^{-1}$) with open-label propofol titrated to a target Motor Activity Assessment Scale of 2–4. Primary outcome was the prevalence of delirium measured daily *via* Confusion Assessment Method for intensive care. Secondary outcomes included ventilation time, additional sedation/analgesia, and hemodynamic and adverse effects.**

***Results:*** **Of all sedation assessments, 75.2% of dexmedetomidine and 79.6% ($P = 0.516$) of morphine treatment were in the target range. Delirium incidence was comparable between dexmedetomidine 13 (8.6%) and morphine 22 (15.0%) (relative risk 0.571, 95% confidence interval [CI] 0.256–1.099, $P = 0.088$), however, dexmedetomidine-managed patients spent 3 fewer days (2 [1–7] *versus* 5 [2–12]) in delirium (95% CI 1.09–6.67, $P = 0.0317$). The incidence of delirium was significantly less in a small subgroup requiring intraaortic balloon pump and treated with dexmedetomidine (3 of 20 [15%] *versus* 9 of 25 [36%]) (relative risk 0.416, 95% CI 0.152–0.637, $P = 0.001$). Dexmedetomidine-treated patients were more likely to be extubated earlier (relative risk 1.27, 95% CI 1.01–1.60, $P = 0.040$, log-rank $P = 0.036$), experienced less systolic hypotension (23% *versus* 38.1%, $P = 0.006$), required less norepinephrine ($P < 0.001$), but had more bradycardia (16.45% *versus* 6.12%, $P = 0.006$) than morphine treatment.**

***Conclusion:*** **Dexmedetomidine reduced the duration but not the incidence of delirium after cardiac surgery with effective analgesia/sedation, less hypotension, less vasopressor requirement, and more bradycardia *versus* morphine regimen.**

ANALGESIA and sedation is an important component of the postoperative management of cardiac surgery patients. However, no single agent or combination of agents have shown a clear superiority in improving clinically relevant outcomes such as delirium.[1–3]

Delirium is a very common complication in older people admitted to hospital.[4,5] Given its high incidence, the consequences of delirium place a substantial burden on both patients and healthcare systems as a result of increased morbidity, decline in long-term cognitive function, and higher mortality rates.[6–7]

Although the prevalence of delirium after cardiac surgery can vary from 20–50%,[8–11] predictors of delirium

# Dex vs. morfin a delirium

- Shehabi et al, A-gy 2009 – srovnání dex a morfinu po KCH operacích
  - Analgosedace dexmedetomidinem
    - 0,1-0,7 μg/kg/hod
  - Analgosedace morfinem (+ propofol)
    - 10-70 μg/kg/hod

  Závěr – analgosedace dex – nesignifikantně méně delirií (8,6% vs. 15%), dex významně zkrátil dobu deliria (2 vs. 5 dní) a podpořil časnou extubaci. Pac. s dex měli častěji bradykardii, ale méně často hypotenzi a menší potřebu vazopresorů

# Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients

## A Randomized Trial

Richard R. Riker, MD
Yahya Shehabi, MD
Paula M. Bokesch, MD
Daniel Ceraso, MD
Wayne Wisemandle, MA
Firas Koura, MD
Patrick Whitten, MD
Benjamin D. Margolis, MD
Daniel W. Byrne, MS
E. Wesley Ely, MD, MPH
Marcelo G. Rocha, MD
for the SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group

**Context** γ-Aminobutyric acid receptor agonist medications are the most commonly used sedatives for intensive care unit (ICU) patients, yet preliminary evidence indicates that the $\alpha_2$ agonist dexmedetomidine may have distinct advantages.

**Objective** To compare the efficacy and safety of prolonged sedation with dexmedetomidine vs midazolam for mechanically ventilated patients.

**Design, Setting, and Patients** Prospective, double-blind, randomized trial conducted in 68 centers in 5 countries between March 2005 and August 2007 among 375 medical/surgical ICU patients with expected mechanical ventilation for more than 24 hours. Sedation level and delirium were assessed using the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for the ICU.

**Interventions** Dexmedetomidine (0.2-1.4 μg/kg per hour [n=244]) or midazolam (0.02-0.1 mg/kg per hour [n=122]) titrated to achieve light sedation (RASS scores between −2 and +1) from enrollment until extubation or 30 days.

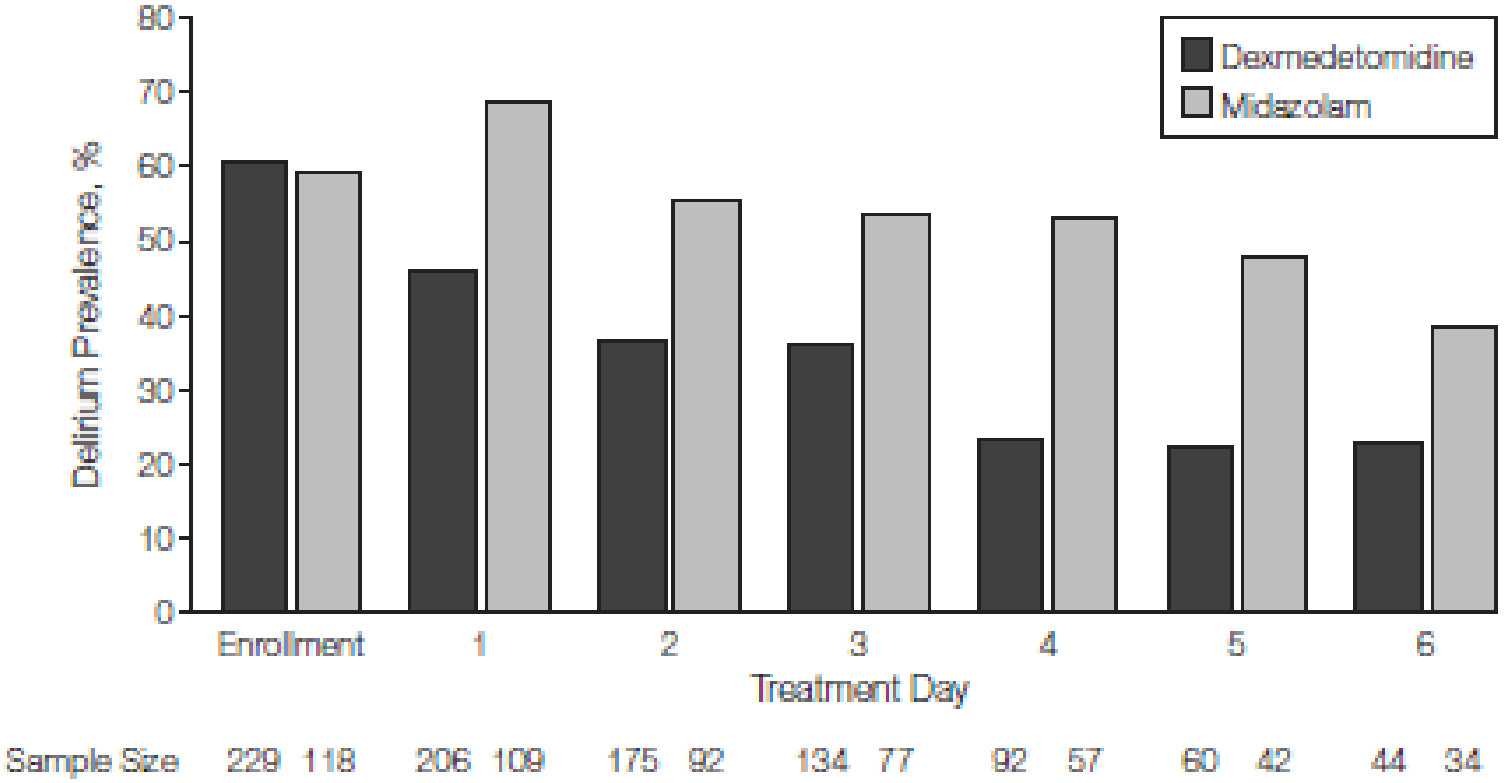
**Main Outcome Measures** Percentage of time within target RASS range. Secondary end points included prevalence and duration of delirium, use of fentanyl and open-label midazolam, and nursing assessments. Additional outcomes included duration of mechanical ventilation, ICU length of stay, and adverse events.

# Dex v.s. midazolam a delirium

- Riker et al, JAMA 2009 – srovnání dex a midazolamu v sedaci kriticky nemocných
  - Sedace dexmedetomidinem
    - 0,8 µg/kg/hod, dále titrace dle RASS
  - Sedace midazolamem
    - 0,06 mg/kg/hod, dále titrace dle RASS

  Závěr – sedace dexmedetomidinem – signifikantně méně delirií (54% vs. 76,6%), dex významně zkrátil dobu hospitalizace na ICU 5,9 vs. 7,6 dne. Pac. s dex měli častěji bradykardii, ale méně často tachykardii a hypertenzi.

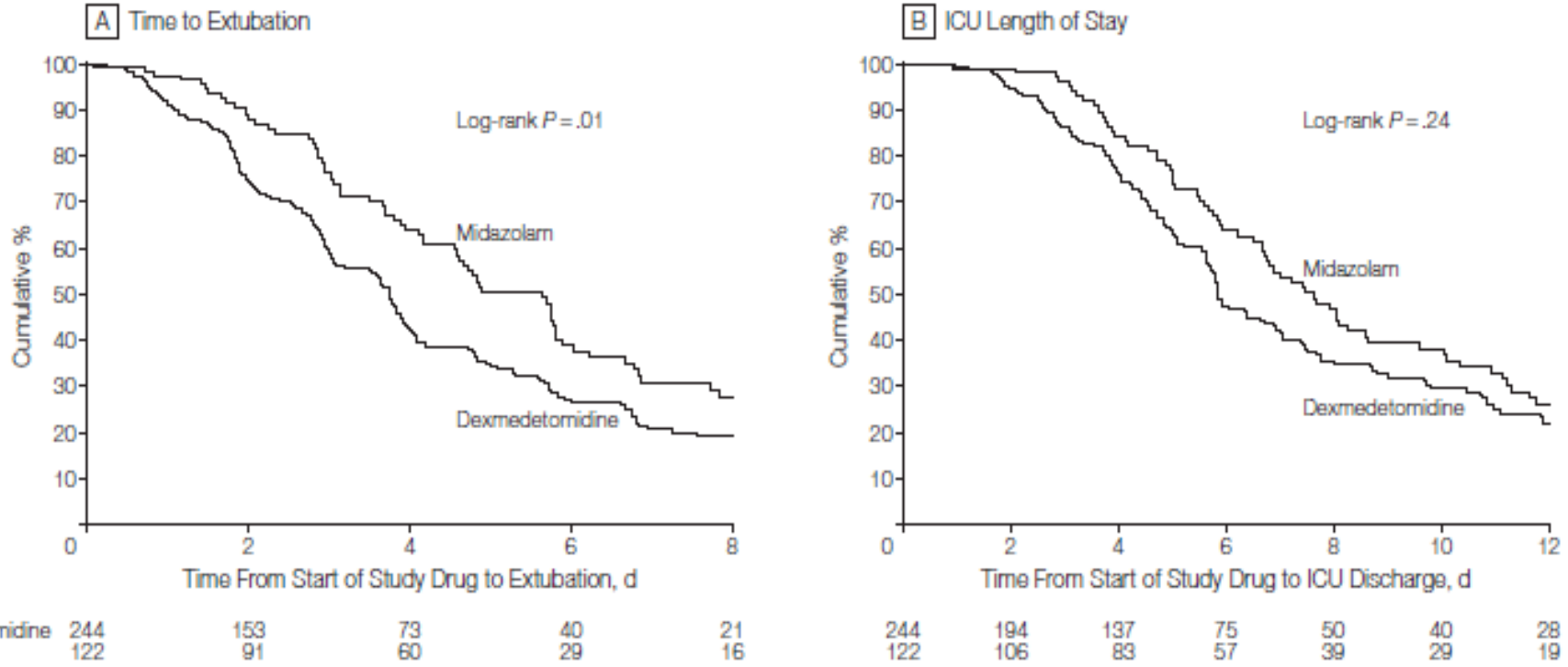
**Figure 2.** Daily Prevalence of Delirium Among Intubated Intensive Care Unit Patients Treated With Dexmedetomidine vs Midazolam




Delirium was diagnosed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[24] At baseline, 60.3% of dexmedetomidine-treated patients and 59.3% of midazolam-treated patients were CAM-ICU–positive ($P = .82$). The effect of dexmedetomidine treatment was significant in the generalized estimating equation[27] analysis, with a 24.9% decrease (95% confidence interval, 16%-34%; $P < .001$) relative to midazolam treatment. Numbers differ from those for primary analysis because patients were extubated, discharged from the intensive care unit, or had missing delirium assessments.


©2009 Amer

**Figure 3.** Time to Extubation and Intensive Care Unit (ICU) Length of Stay Among Patients Treated With Dexmedetomidine vs Midazolam




A, Time to extubation was calculated from the start of study drug to the time of extubation after which no reintubation occurred. Patients not extubated were censored at time of study drug discontinuation. The median time to extubation was 1.9 days shorter for the dexmedetomidine group than for the midazolam group (3.7 days [95% confidence interval {CI}, 3.1-4.0] vs 5.6 days [95% CI, 4.6-5.9]; $P = .01$ by log-rank test). B, Length of ICU stay was calculated from start of study drug to time of order for ICU transfer. Patients without discharge were censored at the time of study drug discontinuation. The median length of ICU stay was similar between the dexmedetomidine and midazolam groups (5.9 days [95% CI, 5.7-7.0] vs 7.6 days [95% CI, 6.7-8.6]; $P = .24$ by log-rank test).

# Dex v.s. benzodiazepiny a delirium

- Nabízí se otázka, zda k významnému omezení výskytu deliria vede:
  - vyvarování se GABA-agonistů
  - nebo pozitivní vliv α-2 agonistů ?

Hipp DM et al. Neurotherapeutics 2012

# Dex u otrav excitačními drogami a halucinogeny

- Dex svým sympatolytickým účinkem působí proti hyperstimulaci KVS a CNS v souvislosti s intoxikací excitačními drogami a halucinogeny

Wong GT, Irwin MG. Anaesthesia 2013

# Dexmedetomidine: A Review of its Use for the Management of Pain, Agitation, and Delirium in the Intensive Care Unit

Kevin E. Anger*

## CONCLUSIONS

Dexmedetomidine's alpha 2 agonist proprieties lend itself as a potential therapeutic option for the management of pain, agitation, and delirium in the ICU setting. Since its introduction to clinical practice, literature on dexmedetomidine has continued to expand on its use in a variety of indications and critically ill patient populations. The potential improvement in outcomes such as mechanical ventilation and delirium with dexmedetomidine have triggered further research into how we manage our patients pharmacologically and non-pharmacologically in the ICU setting. The mild to moderate sedative properties of dexmedetomidine make it a viable pharmacological option for many critically ill patient populations. Limitations of existing literature on efficacy and safety prevent dexmedetomidine from becoming an all purpose, work horse agent for pain, agitation, and delirium in the ICU. Future research will continue to help define the role of dexmedetomidine in the ICU.

# Dexmedetomidine Reduces the Risk of Delirium, Agitation and Confusion in Critically Ill Patients: A Meta-analysis of Randomized Controlled Trials

Laura Pasin, MD, Giovanni Landoni, MD, Pasquale Nardelli, MD, Alessandro Belletti, MD, Ambra Licia Di Prima, MD, Daiana Taddeo, MD, Francesca Isella, MD, and Alberto Zangrillo, MD

*Objectives:* Delirium frequently is observed in critically ill patients in the intensive care unit (ICU) and is associated strongly with a poor outcome. Dexmedetomidine seems to reduce time to extubation and ICU stay without detrimental effects on mortality. The objective of the authors' study was to evaluate the effect of this drug on delirium, agitation, and confusion in the ICU setting.

*Design:* Meta-analysis of all the randomized clinical trials ever performed on dexmedetomidine versus any comparator in the ICU setting.

*Setting:* Intensive care units.

*Participants:* Critically ill patients.

*Interventions:* None

*Measurements and Main Results:* Pertinent studies were independently searched in BioMedCentral, PubMed, Embase, and the Cochrane Central Register of clinical trials. Primary endpoint was the rate of delirium, including the adverse events, agitation and confusion. The 13 included manuscripts (14 trials) randomized 3,029 patients. Overall analysis showed that the use of dexmedetomidine was associated with significant reductions in the incidence of delirium, agitation and confusion (298/1,565 [19%] in the dexmedetomidine group *v* 337/1,464 [23%] in the control group, RR = 0.68 [0.49 to 0.96], p = 0.03). Results were confirmed in subanalyses performed on patients undergoing noninvasive ventilation (1/53 [2%] in the dexmedetomidine group *v* 7/49 [14%] in the control group, RR=0.18 [0.03 to 1.01], p = 0.05), receiving midazolam as a comparator (268/1,164 [23%] in the dexmedetomidine group *v* 277/1,025 [27%] in the control group, RR = 0.68 [0.47 to 1.00], p = 0.05) and in general ICU setting patients (204/688 [30%] in the dexmedetomidine group *v* 204/560 [36%] in the control group, RR = 0.68 [0.45 to 0.81], p < 0.01).

*Conclusions:* This meta-analysis of randomized controlled studies suggests that dexmedetomidine could help to reduce delirium in critically ill patients.

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*KEY WORDS: dexmedetomidine, delirium, agitation, confusion, intensive care unit*

DELIRIUM IS a commonly observed manifestation in hospitalized patients, with a reported incidence ranging between 11% and 80% in the intensive care unit (ICU) setting.[1] Its pathophysiology is highly heterogenous and not completely understood. One of the primary mechanisms involved seems to be an imbalance in neurotransmitter systems, in particular a reduction of the acetylcholine activity.[2] Other involved neurotransmitter disorders are an excess of serotonin and dopamine, which both affect the cholinergic system.[3] Moreover, the relevantilated patients in the ICU setting suggesting that dexmedetomidine reduces time to extubation and ICU stay. Moreover, the known side effects (increased incidence of bradycardia and a trend toward an increased risk of hypotension) had no effect on overall mortality. The authors, therefore, decided to perform an updated meta-analysis of all the randomized clinical trials (RCTs) ever performed on dexmedetomidine versus any comparator in the ICU setting to evaluate the effect of this drug on delirium, agitation, and confusion.

# Dex snižiuje výskyt deliria, agitace a zmatenosti u kriticky nemocných – metaanalýza RTCs

- 14 RCTs, randomizováno 3.029 pacientů
- Dex signifikantně lepší jak u pacientů na všeobecné ICU, tak u pacientů s neinvazivní ventilací, tak ve srovnání s midazolamem

Pasin L et al. J Cardiothoracic Vasc Anesth 2014

OPEN

# Neurocognitive Dysfunction Risk Alleviation With the Use of Dexmedetomidine in Perioperative Conditions or as ICU Sedation

## *A Meta-Analysis*

*Bo Li, MD, Huixia Wang, MD, Hui Wu, MD, and Chengjie Gao, MD*

**Abstract:** Many studies have reported the beneficial effects of dexmedetomidine on postoperative neurocognitive function but overall evidence is not as clear. We examined this conundrum by meta-analyzing studies that used dexmedetomidine in perioperative conditions or as intensive care unit (ICU) sedation and utilized reliable neurocognitive assessment tests.

The literature search was undertaken across several electronic databases including EBSCO, Embase, Google Scholar, Ovid SP, PubMed, Scopus, and Web of Science.

Literature search was carried out across several electronic databases and relevant studies were selected after following precised inclusion criteria. Meta-analysis of risk differences (RDs) was carried out and subgroup analyses were performed.

Twenty studies were selected from which data of 2612 individuals were used. Initial dexmedetomidine dose was $0.68 \pm 0.27$ and maintenance dose was $0.54 \pm 0.32$ in the trials. Dexmedetomidine treatment was associated with significantly lower risk of postoperative/postanesthesia neurocognitive dysfunction both in comparison with saline-treated controls (RD [95% confidence interval, CI]: −0.17 (−0.30, −0.04); $P = 0.008$) and comparators (−0.16 [−0.28, −0.04];

**Abbreviations**: CAM-ICU = confusion assessment method for intensive care unit, DSST = digital symbol substitution test, MMSE = minimental state examination, RCTs = randomized clinical trials, RD = risk difference.

## INTRODUCTION

It is well-recognized that intensive care unit (ICU) survivors face a high risk for cognitive impairment that may persist much longer after recovery.[1] Emergence delirium is an acute form of brain dysfunction that can become dangerous and result in serious consequences for the patient including injury, severity in pain, hemorrhage, and self-extubation.[2] Such a form of neurocognitive dysfunction affects up to 80% of mechanically ventilated ICU patients and is a predictor of cognitive impairment in elderly patients without critical illness.[1] The main risk factors for postoperative cognitive impairment and decline include increasing age, low education level, and severity as well as duration of surgery[3]; besides, preoperative benzodiazepines use and surgery type are also identified as risk factors.[2]

# Dex v perioperačním období

- Metaanalýza
- 20 studií, 2612 pacientů
- Použití dex v perioperačním období a při A-S na ICU je spojen s nižším rizikem neurokognitivních dysfunkcí než při použití jiných farmak

Li B et al. Medicine 2015

Hindawi Publishing Corporation
The Scientific World Journal
Volume 2014, Article ID 805013, 12 pages
http://dx.doi.org/10.1155/2014/805013

*Review Article*

# Interpatient Variability in Dexmedetomidine Response: A Survey of the Literature

**Samantha F. Holliday,[1] Sandra L. Kane-Gill,[2] Philip E. Empey,[2] Mitchell S. Buckley,[3] and Pamela L. Smithburger[2]**

[1] *University of Pittsburgh School of Pharmacy, 3501 Terrace Street, Pittsburgh, PA 15261, USA*
[2] *Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, 3501 Terrace Street, Pittsburgh, PA 15261, USA*
[3] *Banner Good Samaritan Medical Center, Department of Pharmacy, 1111 E. McDowell Road, Phoenix, AZ 85006, USA*

Correspondence should be addressed to Pamela L. Smithburger; smithburgerpl@upmc.edu

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Fifty-five thousand patients are cared for in the intensive care unit (ICU) daily with sedation utilized to reduce anxiety and agitation while optimizing comfort. The Society of Critical Care Medicine (SCCM) released updated guidelines for management of pain,

Pediatr Drugs (2014) 16:267–274
DOI 10.1007/s40272-014-0078-0

REVIEW ARTICLE

# The Pharmacologic Management of Delirium in Children and Adolescents

**Susan Beckwitt Turkel · Alan Hanft**

Published online: 5 June 2014
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**Abstract** Delirium is a serious and common problem in severely medically ill patients of all ages. It has been less addressed in children and adolescents. Treatment of delirium is predicated on addressing its underlying cause. The management of its symptoms depends on the off-label use of antipsychotics, while avoiding agents that precipitate or worsen delirium. Olanzapine, quetiapine, and risperidone are presently considered first-line drugs, usually replacing haloperidol. Other agents have shown promise, including

## 1 Introduction

From antiquity to the present, delirium has been recognized as a severe illness with a significant association with lethality. Electroencephalographic abnormalities were first described during World War II [1], and after the war, as delirium was more specifically characterized, it was recognized that a derangement in functional metabolism appears to underlie all instances of delirium, which is reflected at the clinical level by

# Farmakologická léčba deliria u dětí a mladistvých

- První volba
  - Olanzapin, quetiapin, risperidon – vytlačují haldol
- Slibné
  - Melatonin – obnovuje spánkový rytmus
  - Dexmedetomidin – mj. umožňuje snížit dávky benzodiazepinů a opioidů, které zhoršují delirium

Turkel SB, Hanft A. Paediatric Drugs 2014

Curr Opin Anaesthesiol. 2014 Jun;27(3):309-15. doi: 10.1097/ACO.0000000000000076.

# Emergence delirium in children: an update.

Dahmani S[1], Delivet H, Hilly J.

Author information:

• [1]aDepartment of Anesthesiology and Intensive Care, Robert Debré University Hospital bParis Diderot University, Paris VII, Paris Sorbonne Cité cINSERM UMR 676, Robert Debré University Hospital dDepartment of Pain Management, Robert Debré University eParis Descartes University, Paris V, Paris Sorbonne Cité, Paris, France.

## Abstract

### PURPOSE OF REVIEW:

Emergence delirium in children is still considered as a mysterious complication

# Urgentní delirium u dětí

- Vystrašení předškoláci
- Po anestezii sevo- a desfluranem
- Dex je lepší než propofol a opioidy, neboť má analgetický účinek a působí preventivně proti PONV

Dahmani S et al. Curr Opini Anaesthesiol 2014

SpringerLink
FULL-TEXT ARTICLE

Med Monatsschr Pharm. 2014 Apr;37(4):124-31; quiz 133-4.

# [Psychopharmalogical treatment of delirium in the elderly].

[Article in German]

Drach LM.

## Abstract

Delirium is frequent in hospitalized elderly. Treatment of the medical problems causing delirium is paramount. Mostly antipsychotics are used for treatment of psychological and behavioral symptoms in delirium. Increased mortality of elderly and demented patients receiving antipsychotics suggests caution in prescribing antipsychotics for delirium. Standard treatment is low-dose haloperidol. If more sedation is needed, melperone or pipamperone can be used. In delirious Parkinsonian patients or if dementia with Lewy-bodies is suspected quetiapine is better tolerated.

# Farmakol. léčba deliria ve stáří

- Používá se plejáda psychofarmak s riziky NÚ
- V intenzivní péči se ukázal užitečný klonidin a nověji dexmedetomidin
- Pro použití melatoninu zatím není dostatek údajů

Drach LM. Med Monatsschr Pharm 2014

# Léčba syndromu z odnětí alkoholu

- Benzodiazepiny – základ léčby i při nejistotě o účinnosti a bezpečnosti
- Zatím chybí data srovnávající BDZ a dex
- Tím americké doporučení končí

ACCCM/SCCM Guidelines for Management PAD in ICU. CCM 2013

Journal of Critical Care 29 (2014) 298–302

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# Influence of dexmedetomidine therapy on the management of severe alcohol withdrawal syndrome in critically ill patients

Erin N. Frazee, PharmD [a,*], Heather A. Personett, PharmD [a], Jonathan G. Leung, PharmD [a], Sarah Nelson, PharmD [a], Ross A. Dierkhising, MS [b], Philippe R. Bauer, MD, PhD [c]

[a] Hospital Pharmacy Services, Mayo Clinic, Rochester, MN
[b] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN
[c] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN

ARTICLE INFO

*Keywords:*
Alcohol withdrawal delirium
Alcoholic intoxication
Conscious sedation
Critical illness
Dexmedetomidine

ABSTRACT

*Purpose:* Although benzodiazepines are first-line drugs for alcohol withdrawal syndrome (AWS), rapidly escalating doses may offer little additional benefit and increase complications. The purpose of this study was to evaluate dexmedetomidine's impact on benzodiazepine requirements and hemodynamics in AWS.
*Materials and Methods:* This retrospective case series evaluated 33 critically ill adults with a primary diagnosis of AWS from 2006 to 2012 at an academic medical center.
*Results:* Dexmedetomidine began a median (interquartile range) of 11 (2, 32) hours into intensive care unit admission and was titrated to an infusion rate of 0.7 (0.4, 0.7) $\mu g\ kg^{-1}\ h^{-1}$ to achieve the desired depth of sedation. In the 12 hours after dexmedetomidine began, patients experienced a 20-mg reduction in median cumulative benzodiazepine dose used ($P < .001$), a 14-mm Hg lower mean arterial pressure ($P = .03$), and a 17-beats/min reduction in median heart rate ($P < .001$). Four (12%) patients experienced hypotension (systolic blood pressure < 80 mm Hg) during therapy, and there were no cases of bradycardia (heart rate < 40 beats/min).
*Conclusion:* Dexmedetomidine decreased benzodiazepine requirements and improved the overall hemodynamic profile of patients with severe AWS. These results provide promising evidence about the potential benefit of dexmedetomidine for AWS.

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# Dex v léčbě těžkého syndromu z odnětí alkoholu

- Retrospektiva – 7 let, 33 pacientů
- Časné nasazení Dexu snížilo spotřebu benzodiazepinů a zmírnilo hyperreaktivitu sympatiku
- Slibné údaje podporující potenciální přínos dexmedetomidinu u závažného syndromu odnětí alkoholu

Frazee EN et al. J of Critical Care 2014

# Delirium a dex na KARIM FNO

- 1 ORIM, 1 rok (2014) - 74 delirií z 332 pac.
  - hyperaktivních 36 (49%)
  - hypoaktivních 15 (20%)
  - smíšených 23 (31%)
- Muži jsou významně častěji postiženi deliriem
- Exitus je významně častější u pac. s deliriem
- Dex používáme u cca 50% pac. s hyperaktiv. nebo smíšeným deliriem
- 4 µg/ml, 40-100 ml/hod ~ 0,5-1,4 µg/kg/hod