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Experienced Use of Dexmedetomidine in the Intensive Care Unit: A Report of a Structured Consensus

Yoğun Bakım Biriminde Deksmedetomidin Kullanımı Deneyimi: Yapılandırılmış Bir Konsensüs Raporu

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Abstract / Öz

Objective: Management of pain, agitation and delirium (PAD) remains to be a true challenge in critically ill patients. The pharmacological proprieties of dexmedetomidine (DEX) make it an ideal candidate drug for light and cooperative sedation, but many practical questions remain unanswered. This structured consensus from 17 intensivists well experienced on PAD management and DEX use provides indications for the appropriate use of DEX in clinical practice.

Methods: A modified RAND/UCLA appropriateness method was used. In four predefined patient populations, the clinical scenarios do not properly cope by the current recommended pharmacological strategies (except DEX), and the possible advantages of DEX use were identified and voted for agreement, after reviewing literature data.

Results: Three scenarios in medical patients, five scenarios in patients with acute respiratory failure undergoing non-invasive ventilation, three scenarios in patients with cardiac surgery in the early postoperative period and three scenarios in patients with

Amaç: Ağrı, ajitasyon ve deliryum (AAD) yönetimi kritik hastalarda halen sorun oluşturmaktadır. Deksmedetomidinin (DEX) farmakolojik özellikleri bu ilacı hafif ve kooperatif bir sedasyon için ideal bir aday yapmakta, ancak uygulama ile ilgili birçok soru cevapsız kalmaktadır. AAD yönetimi ve DEX kullanımında deneyimli 17 yoğun bakım uzmanından alınan bu yapılandırılmış konsensüs, DEX'in klinik uygulamada doğru kullanımı için endikasyonlar sağlamaktadır.

Yöntemler: Modifiye RAND/UCLA uygunluk yöntemi kullanıldı. Önceden tanımlanan dört hasta popülasyonunda klinik senaryolar, önerilen güncel farmakolojik stratejilerle tamamıyla örtüşmemektedir (DEX hariç). Literatür verileri tarandıktan sonra, DEX kullanımının olası avantajları belirlendi ve uzlaşma için oylandı.

Bulgular: Tıbbi hastalarla 3 senaryo, non-invaziv ventilasyon uygulanan akut solunum yetmezliği hastalarıyla 5 senaryo, erken postoperatif dönemde kardiyak cerrahi hastalarıyla 3 senaryo ve aşikar deliryum hastalarıyla 3 senaryo mevcut AAD stratejileriyle

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overt delirium were identified as challenging with the current PAD strategies. In these scenarios, the use of DEX was voted as potentially useful by most of the panellists owing to its specific pharmacological characteristics, such as conservation of cognitive function, lack of effects on the respiratory drive, low induction of delirium and analgesia effects.

Conclusion: DEX might be considered as a first-line sedative in different scenarios even though conclusive data on its benefits are still lacking.

Keywords: Sedation, delirium, analgesia, intensive care, critically ill patients

zor olarak belirlendi. Bu senaryolarda DEX kullanımı panelistler tarafından, kognitif fonksiyonun korunması, solunum dürtüsündeki etkilerin eksikliği, düşük deliryum indüksiyonu ve analjezi etkileri gibi spesifik farmakolojik özelliklerinden dolayı potansiyel olarak faydalı olarak oylandı.

Sonuç: Faydaları konusunda kesin veriler halen olmamasına rağmen DEX, farklı senaryolarda ilk basamak sedatif olarak düşünülebilir.

Anahtar Kelimeler: Sedasyon, deliryum, analjezi, yoğun bakım, kritik hastalar

Introduction

Invasive procedures, such as tracheal intubation and mechanical ventilation, anxiety and difficulties in communication commonly cause pain, agitation and delirium (PAD) in critically ill patients admitted to the intensive care unit (ICU) (1). The management of PAD remains to be a true challenge despite significant recent scientific advances, particularly in specific populations and settings with elderly, children and patients with shock, brain injury or substance abuse (2) In recent years, several studies showed that deep sedation, even for short periods, compared to light sedation is closely associated to prolonged mechanical ventilation and ICU stay, increased incidence of delirium and high risk of mortality (3-5). Moreover, sedation protocol based mainly on the use of benzodiazepines appears to be related to a higher risk of bad clinical outcome compared to strategies based on propofol (6-10). In fact, the recent evidence-based guidelines strongly support the use of a light sedation strategy and suggest the use of drugs (i.e., propofol and dexmedetomidine (DEX)) that may reduce delirium occurrence (6, 11, 12). Moreover, for the optimisation of the level and quality of sedation, different strategies have been proposed as daily interruption (4), nursing-implemented sedation scale (13, 14) and delirium control to avoid hypnotic drugs (13).

DEX is an agonist of α_2-adrenergic receptors that acts on the 'locus coeruleus', exerting sedative, analgesia and anti-shivering effects without interference on the central and peripheral respiratory drive. Its proprieties, combined with an excellent safety profile at the appropriate doses (15), make DEX ideal for light and cooperative sedation in critically ill patients (16). Although several clinical experiences have reported the possible advantages provided by DEX in different settings, scientific data are still weak, and many questions remained unanswered regarding its use in daily practice. Who is the patient/scenario that benefits the most? What is the correct dose approach in different patients?

The present study reports the results of a structured consensus of 17 intensivists well experienced on PAD management and DEX use aimed to identify and analyse the unsolved questions and to provide practical indications for the appropriate use of DEX in clinical practice.

Methods

A modified RAND/UCLA appropriateness method was used (17). RAND/UCLA is a structured process for integrating evidence from the scientific literature with experts' clinical judgement to produce explicit criteria to determine the appropriateness of specific procedures when high-quality and definitive evidence (usually from large randomised controlled trials) are missing.

Two moderators (GM and LT) selected 15 panellists based on their experience in the use of DEX for management of sedation and delirium in critically ill patients. All panellists were intensivists with >10 years of clinical experience from medical, surgical, mixed and cardiac surgery ICUs of tertiary hospitals in Italy.

In the first structured meeting led by the two moderators at which all panellists were present, the panellists were instructed on the RAND/UCLA method, particularly on the definition of clinical scenarios and rating procedures. After an initial discussion on the main difficulties in PAD management and the clinical experience on the use of DEX, in accordance with the evidence-based guidelines that recommend a different approach to PAD in specific populations and settings, the panellists defined the clinical scenarios into four different subgroups of critically ill patients: (1) medical patients, (2) patients with acute respiratory failure candidates to non-invasive ventilation (NIV), (3) patients with cardiac surgery in the early postoperative period and (4) patients with overt delirium. Then, for each patient subgroup, the panellists were asked to identify clinical scenarios that do not properly cope by using the current recommended pharmacological and non-pharmacological PAD strategies (except DEX), and the possible advantages allowed by the use of DEX in those scenarios. Moreover, the group identified specific clinical scenarios where the use of DEX is not recommended or is inappropriate.

Two or three panellists were assigned the task of reviewing literature data, particularly evidence-based documents and the new clinical trials, and presenting their findings at a second structured meeting held 3 months later for each clinical scenario. During this meeting, literature data were reviewed and discussed by the entire group, and if any controversies occurred, the list of clinical scenarios was better redefined to

Table 1. Clinical scenarios do not properly cope by the current pain, agitation and delirium strategies (without considering dexmedetomidine) identified by the panellists and subdivided into four subgroups of critically ill patients. The ballot for each scenario is also reported

	Appropriate	Inappropriate	Uncertain
Medical patients			
Weaning from sedation in patients with prolonged mechanical ventilation (>72 h)	17	0	0
Underlying degenerative cerebral diseases	15	1	1
Weaning from sedation in patients with substance abuse	13	0	4
Patients undergoing NIV			
Dose-dependent respiratory drive depression induced by current sedatives	16	1	0
Airway control in sedated patients undergoing NIV	14	1	2
Risk of oversedation and difficulties in obtaining a light sedation level	16	1	0
Sleep disturbances	14	1	2
Intolerance to NIV in patients with agitation/delirium	17	0	0
Patients with post-cardiac surgery			
Dose-dependent respiratory drive depression induced by current sedatives	15	1	0
Propofol and benzodiazepines show no analgesia properties	14	0	2
Gastrointestinal paralysis due to opioids	13	0	3
Patients with delirium			
Risk of oversedation and difficulties in obtaining a light sedation level	17	0	0
Use of benzodiazepines may increase the incidence of delirium	17	0	0
Practical use of antipsychotics and anxiolytics for agitation and delirium	16	0	1

NIV: non invasive ventilation

avoid uncertainness in the rating procedures. All the literature material was readily available at any time for all the panellists. Each member of the panel completed the first round of rating within 6 weeks after the meeting using a specific rating sheet. The panellists rated each clinical scenario as 'appropriate', 'inappropriate' or 'uncertain' on a scale of 1 to 9 points, with 1=completely inappropriate and 9=fully appropriate (9). The ratings were analysed by the moderators to identify the scenarios with disagreement (as discussed below). In a third meeting, summaries of the group's overall ratings of the scenarios with disagreements were presented, and the scenarios were adequately discussed. Then, the panellists individually rerated the scenarios, and their rating sheets were collected by the moderators. With regard to the potential benefits of DEX use, which were not clearly specified, the panellists were invited to focus on the expected effects of DEX on the length of mechanical ventilation, ICU stay and occurrence of delirium and not to consider the cost in making their judgements.

The median of the ratings of all panellists was calculated, and we defined the inappropriate scenario with a median value from 1 to 3 (4-6=uncertain and 7-9=appropriate) for each scenario. 'Disagreement' for each scenario was defined when >5 panellists rated outside the 3-point region (1-3, 4-6 and 7-9) containing the median (14).

Results

The challenging clinical scenarios in PAD management and rationale for the use of DEX are shown in Tables 1 and 2.

In the four predefined subgroups of ICU patients, 17 panellists identified 14 clinical scenarios with difficulties in PAD management. Of the 14 scenarios, three were in medical patients, five in patients with acute respiratory failure candidates to NIV, three in patients with cardiac surgery in the early postoperative period and three in patients with overt delirium (Table 1).

Medical patients

All panellists agreed that in patients with mechanical ventilation lasting >72 h, weaning from sedation may be difficult. Similarly, for the large majority of the panellists, PAD management may be complicated in patients with underlying degenerative cerebral diseases and with substance abuse. Specific DEX pharmacokinetic/pharmacodynamic characteristics may be really helpful for weaning from prolonged sedation, management of patients with underlying cerebral diseases and substance abuse. In fact, DEX does not appear to impair the peripheral and central respiratory drive, facilitates patient interaction with the environment, improves the quality of sleep and may reduce neurovegetative response.

Table 2. The rationale for the use of dexmedetomidine in the clinical scenarios does not properly cope by the current pain, agitation and delirium strategies. The ballot for each rationale is also reported

Clinical scenarios	Rationale for dexmedetomidine use	Appropriate	Inappropriate	Uncertain
Medical patients				
Weaning from sedation in patients with prolonged mechanical ventilation (>72 h)	DEX does not impair respiratory drive	17	0	0
	DEX improves the comfort and interaction with the environment	17	0	0
Underlying degenerative cerebral diseases	DEX reduces the occurrence of delirium and exerts protective effects on cognitive function	17	0	0
Weaning from sedation in patients with substance abuse	DEX reduces neurovegetative response to stress	15	0	2
Patients undergoing NIV				
Dose-dependent respiratory drive depression induced by current sedatives	DEX does not impair respiratory drive	17	0	0
Airway control in sedated patients undergoing NIV	DEX allows better upper airway protection and reduces the occurrence of bronchoconstriction	17	0	0
Risk of oversedation and difficulties in obtaining a light sedation level	DEX pharmacodynamics reduces the risk of oversedation	14	0	3
Sleep disturbances	DEX improves sleep quality, mimicking natural electroencephalography pattern	16	0	1
Intolerance to NIV in patients with agitation/delirium	DEX improves the comfort and interaction with the environment	17	0	0
Patients with post-cardiac surgery				
Dose-dependent respiratory drive depression induced by current sedatives	DEX does not impair respiratory drive	17	0	0
Propofol and benzodiazepines show no analgesia properties	DEX may exert synergic analgesia effects	16	0	0
Gastrointestinal paralysis due to opioid use	DEX may reduce the occurrence of gastrointestinal paralysis due to opioid use	13	0	3
Patients with delirium				
Risk of oversedation and difficulties in obtaining a light sedation level	DEX does not impair respiratory drive	17	0	0
	DEX improves the comfort and interaction with the environment	15	0	2
Use of benzodiazepines may increase the incidence of delirium	DEX reduces the occurrence of delirium and exerts protective effects on cognitive function	17	0	0
Practical use of antipsychotics and anxiolytics for agitation and delirium	DEX in combination with antipsychotics preserves cognitive function and reduces the occurrence of delirium	15	0	2
	DEX allows reduction of other antipsychotics	14	1	2

DEX: dexmedetomidine; NIV: non invasive ventilation

Patients undergoing NIV

There was an excellent agreement that current sedatives exert a dose-dependent respiratory drive depression. Thus, difficulties in maintaining light sedation still has been considered to be problematic in many patients undergoing NIV with high risk of oversedation requiring special attention for the upper airway control. In addition, the intolerance to NIV interfaces in very agitated patients (Richmond Agitation-Sedation Scale (RASS) >3) or patients with delirium, and sleep disturbances during NIV remain unsolved issues for the majority of the panellists. DEX may be a valid option for patients undergoing NIV because, in addition to the maintenance of respiratory drive, it appears to provide a better upper airway control, reducing the occurrence of bronchospasm and the risk of over sedation.

Patients with post-cardiac surgery

One panellist who had no experience in this setting did not participate in the scenario identification and ballot. Similar to the patients undergoing NIV, the panellists identified problematic dose-dependent respiratory depression of the current sedatives. An issue was also raised on the lack of analgesia

Table 3. Inappropriate use of dexmedetomidine

Clinical scenarios	Appropriate	Inappropriate	Uncertain
DEX should be not used for sedation in patients outside the ICU	7	5	5
DEX should be not used as sole induction agent for tracheal intubation	17	0	0
DEX should be not used for sedation during muscle relaxants use	17	0	0
DEX should be not used in patients requiring deep sedation	14	1	2
DEX should be not used in patients with refractory hemodynamic instability	17	0	0
DEX should be not used in patients with severe neurological diseases (e.g., traumatic brain injury and neurosurgery)	12	0	5
DEX should be not used during pregnancy and breast feeding	17	0	0
DEX should be not used as the sole agent for the treatment of refractory status epilepticus	17	0	0
DEX should be not used for delirium prophylaxis	10	4	3

DEX: dexmedetomidine; ICU: intensive care unit

properties of propofol and midazolam and on the possible negative effects of opioids on gastroenteric motility. The mild analgesia effect of DEX was considered relevant in this population as well as its low impact on gastroenteric atony.

Patients with delirium

In patients with delirium, the panellists highlighted the difficulties in obtaining and maintaining a strategy of light sedation and cooperation, with risk of oversedation. Moreover, all the panellists recognise the appropriate use of antipsychotics in delirious critically ill patients as a true challenge. The panellists indicated that the low risk of oversedation, reduction of delirium time and preservation of cognitive function make DEX a useful option in patients with delirium in combination with other antipsychotics.

Inappropriate use of DEX

The panellists considered the inappropriate use of DEX as an induction agent for tracheal intubation, for the treatment of status epilepticus, for sedation during muscle relaxants use and in patients with refractory hemodynamic instability and requiring deep sedation (Table 3). Only 71% of the experts considered DEX to be inappropriate in patients with traumatic brain injury and after neurosurgery. Similarly, only 59% of the experts did not indicate the use of DEX for delirium prophylaxis in specific populations. A wide difference in opinions also occurred on the European Medical Agency restriction to use DEX only in patients admitted to the ICU, with 60% of the panellists who were uncertain or in disagreement with this restriction.

Discussion

This structured consensus by experts from 17 Italian ICUs showed that PAD management in critically ill patients is still problematic in many circumstances, and that DEX may represent a valuable option due to its peculiar pharmacological characteristics. Moreover, the experts agreed that DEX should be used with caution in specific patients, but it may be considered for use even outside the ICU and for patients with limited data available, for instance in patients with cerebral dysfunction.

Weaning from prolonged sedation may be a challenging task, particularly in patients undergoing invasive mechanical ventilation for acute respiratory failure or cerebral dysfunction (e.g., cerebral stroke or traumatic brain injury). In these settings, deep sedation is usually achieved immediately after ICU admission and maintained for several days to control discomfort and facilitate mechanical ventilation. Moreover, in these patients, daily interruption of deep sedation is impracticable and rarely applied, and deep sedation usually continues until clinical improvement or weaning from the mechanical ventilation (18). Recently, different authors showed that a light sedation strategy with DEX (RASS between –2 and 1) appears to provide good tolerance of the endotracheal tube and to reduce the incidence of agitation, delirium and need of physical restraints (19, 20). In the difficult-to-wean patients, the use of DEX, compared to other agents, might improve patient-ventilator asynchrony and increase the success of weaning from the mechanical ventilation because it does not interfere with the respiratory drive (21-23). However, it is important to underline that the use of DEX did not significantly reduce the duration of mechanical ventilation in medical patients (19, 20, 22, 24).

During NIV, patient agitation and intolerance to interface are the main reasons for failure, but very few data are available in the literature (25). For instance, the recent systematic review by the Cochrane group (26) on the use of NIV as weaning strategy from invasive mechanical ventilation showed that none of the studies included, but one, reported standardised sedation protocols, and the use of sedation was described only in four trials (27-30). A survey on sedation practice in patients undergoing NIV for acute respiratory failure indicated that <25% of the patients received sedation, usually with benzodiazepine (33%) or opioid alone (29%) (31). Moreover, it should be kept in mind that the majority of sedatives interfere with the respiratory drive and might reduce the control of the upper airways with an increased risk of inhalation and reintubation (32). Although data on the use of DEX during NIV are still insufficient for definitive conclusions (33-35), the panellists support

the use of DEX as a first-line sedative during NIV owing to its pharmacodynamic characteristics that offer significant advantages compared to other sedatives in terms of respiratory drive conservation and protection of the upper airways.

Several recent studies and two meta-analyses indicated that DEX may reduce the time to extubation in patients recovering from cardiac surgery especially those undergoing pump coronary artery bypass grafts (36-40). Propofol and midazolam, which are currently used in the postoperative period in patients with cardiac surgery, do not exert any analgesia effect, and thus opioids should be combined to control postoperative and procedural pain. It is well known that the use of opioids induces impairment of intestinal motility with risk of postoperative ileus (41). In this context, the analgesia proprieties of DEX may be advantageous in decreasing the opioid dose. In fact, it has been shown that the use of DEX allows a satisfactory pain control with lower dose of opioids and appears to be associated with a lower risk of postoperative ileus (42).

Delirium often complicates the patient management and outcome with prolonged ICU and hospital length of stay and increased mortality (43-45). Most of the clinicians recognised that in patients with delirium, the management of symptoms and agitation is often intricate. For instance, the use of benzodiazepines in critically ill patients is related to a high risk of delirium even though the true mechanisms are still uncertain (46-51). Additionally, it should be kept in mind that the withdrawal of benzodiazepines is commonly associated to delirium development (52). The use of haloperidol or other first generation of antipsychotics led to conflicting results. In fact, many studies reported life-threatening collateral effects, such as third degree atrioventricular block, ventricular tachycardia and neuroleptic malignant syndrome, with the use of high doses of haloperidol to control the symptoms of patients with delirium (53, 54). A second generation of atypical neuroleptic drugs was recently introduced with good results even though it still inconclusive (55, 56). The difficulties in managing patients with delirium led the research toward the identification of causative factors and to develop specific strategies for preventing its occurrence. Among these strategies, the introduction of DEX in light sedation protocols was associated with a significant reduction in delirium occurrence and preservation of cognitive functions (6, 15, 19). Although the true mechanisms have not been elucidated, the more physiological sleep pattern provided by DEX with the restoration of the awake-sleep rhythm associated to light and cooperative sedation may justify the difference with other sedatives in the risk of delirium (57, 58). Unfortunately, two recent multicentre randomised trials on patients with surgery (404 patients) and sepsis requiring mechanical ventilation (201 patients) did not show any benefit by using DEX in reducing delirium, cognitive dysfunction, mortality and ventilator free-days (59, 60).

Few promising data on the role of DEX in treating agitated delirium are available. A recent trial showed that DEX may be useful as a rescue drug for treating agitation due to delirium refractory to haloperidol in ICU non-intubated patients (61). Similarly, a multinational, randomised, double-blind study (DahLIA trial), including mechanically ventilated patients in whom extubation was considered inappropriate owing to the severity of agitation and delirium, demonstrating DEX compared to the placebo group provides a significant decrease of mechanical ventilation time and of ICU and hospital length of stay (62).

With regard to inappropriate use, the panellists agreed that DEX should be avoided or used with caution in contexts with limited experience of use, for instance in patients with refractory hemodynamic instability or with severe acute neurological injury. On the contrary, the limitation of use only in ICU patients was considered too restrictive, and the panellists support the use of DEX outside the ICU for light sedation during procedures, such as endoscopy and transcutaneous cardiac procedures, because the lack of effects on the respiratory drive (as discussed above) facilitates spontaneous breathing during the procedures.

Conclusion

Many controversies and uncertainties remain to be elucidated for the appropriate and effective management of PAD in critically ill patients. Avoiding prolonged deep sedation combined with personalised approach and use of non-pharmacological strategies appear to be the keys for further improvement. With this aim, the favourable pharmacological characteristics make DEX a useful option as a first-line sedative particularly in challenging scenarios, such as weaning patients from prolonged sedation or patients undergoing NIV for acute respiratory failure. The promising initial results and the positive clinical experiences support the use of DEX in these situations even though conclusive data on its benefits are lacking, and many practical questions regarding its use still remained unanswered.

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