Use of dexmedetomidine in the adult intensive care unit

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Abstract

Sedation and analgesia, which are universally used in intensive care units (ICUs), provide patients with comfort and safety. The current trends aim at light sedation; the objective is to ensure the minimal sedation level for improving patients’ autonomy and enabling the professional staff to assess the patients’ neurological status and cognitive functions. Reports in the literature have indicated that a sedative or an entire sedation procedure can affect cognitive processes, the duration of mechanical ventilation and treatment outcomes in critically ill patients. At present, special attention is given to post-sedation delirium. Although sedatives differ in their uptake points, which can influence the quality of sedation, their common characteristic is substantial impairment of cognitive functions, memory and respiration. Alpha 2-adrenergic receptor agonists, which comprise a novel group of agents, are used frequently for sedation. One of these medications is dexmedetomidine, which is designed to sedate adult ICU patients who exhibit a score ≥ –3 according to the Richmond Agitation-Sedation Scale. Recent studies comparing the use of dexmedetomidine and the other sedative agents that are most commonly administered in ICUs demonstrated that the former largely fulfils the expectations of intensivists.

Key words: critical care, adults; critical care, sedation; alpha-2 agonists, dexmedetomidine

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Sedation is one of the basic therapeutic procedures performed in intensive care units (ICUs). During sedation in ICU hospitalization, 42% of patients receive sedatives; in mechanically ventilated patients, this percentage increases to 85% [1]. The aim of sedating mechanically ventilated patients is to depress consciousness as well as to ensure tolerance of the endotracheal or tracheostomy tube and acceptance of a particular ventilatory mode that is necessary for ventilation therapy or lung ventilation [2].

In 2012, a new term of goal-directed mechanical ventilation (GDMV) was introduced [3, 4]. The main goal of GDMV is to maintain spontaneous activity of the respiratory centre [5, 6] by providing suitable levels of sedation and analgesia and acceptance of ventilation procedures by patients; therefore, the procedure of sedation or sedoanalgesia is applied [2, 7]. Moreover, GDMV involves the use of recruitment procedures, repeated daily measurements of PEEP and biomechanical indices, changes in the patient’s body position (including the prone position) and aggressive physiotherapy (massage, positional drainage, and muscle electrostimulation). The addition of analgesics to sedatives is a crucial element of sedation to which the procedure-related pain (associated
with forced positioning of various body parts) can be avoided [2, 8, 9]. The effects of agents on the central nervous system (CNS) and the activity of respiratory muscles must be limited to a desirable and optimal measurable level, hence the term sedoanalgesia. Using sedoanalgesia, depression of consciousness and pain reactions can be modulated, simultaneously planning the completion of mechanical ventilation based on scales and protocols of sedation and systems of devices [2, 4, 10].

At the turn of the second decade of the 21st century, modern sedation faces the challenges that were described above. This modern sedation is also termed “cooperative sedation” i.e., light sedation that is adjusted to specific elements of ICU treatment [11]. However, reports from various intensive care centres have indicated that the lack of any single medication or recognised sequence of agents fulfilling the above expectations and widespread polypragmasy is ineffective.

In their study, Frank and colleagues [12] emphasised that 47% of mechanically ventilated patients reported sleep disorders during their ICU stay and that 43% of these patients reported persistent sleep disorders long after discharge from the hospital.

Recent literature reports have focused much attention on post-sedation delirium, which is a relevant element of complications resulting from sleep disorders during ICU treatment and the sedation itself. Delirium, which likely develops while decreasing the level of sedation or after its completion, has characteristics of the delirious syndrome. The preserved autopsychic orientation is a confusing symptom, which encompasses severe allopsychic disorders, i.e., auditory, visual, tactile hallucinations accompanied by anxiety and sleep disorders. Amnesia regarding this period is a beneficial solution for patients, considering the treatment strategy; however, the occurrence of delirium is relevant and directly increases the mortality rates of ICU patients [7, 13–15]. This problem might be solved by providing periodic interruptions in sedation to reduce adverse side effects and shortening the time of mechanical ventilation and the length of ICU stay. However, the large, randomised, controlled trial of SLEAP investigators did not demonstrate the expected benefits of such a strategy [16]. Therefore, the search for suitable measurement tools to maintain the appropriate depth of sedation is ongoing. Unfortunately, none of the widely accepted scales of sedation assessment used in sedation management protocols prevents too deep or too shallow sedation [2, 11]. Likewise, attempts to prevent inadequate sedation have failed [17, 18]. Wider use of entropy is promising, in which the combination of an EEG signal with electromyography shows good correlation with the clinical state of patients, depth of sedation and pain reactions [19].

In addition to optimising the sedation protocol, researchers attempt to find new medications or sequences that could meet the assumptions of light sedation and the needs of ICU patients.

The retrospective evaluation of sedation conducted by Wunsch and co-workers [20] in 174 American ICUs in more than 109,000 mechanically ventilated patients over an 8-year period (2001–2007) demonstrated a distinct increased consumption of sedatives. The majority of patients received propofol (82.2%); midazolam was administered to only 31.1% of patients and dexmedetomidine was administered to 4% of patients. The latter was most commonly used in cardiac surgery patients (11.7%). The frequent use of propofol and midazolam is associated with relative safety of both agents, although in almost each case these agents must be supplemented with other preparations that affect the clinical picture, the incidence of complications and the procedure costs [2, 9, 20]. The use of infusions with ultra-short-acting opioids (remifentanil) does not change the situation, particularly in cases where sedation use exceeds 4 days [21].

Sedatives vary in their uptake points, which can affect the quality of sedation. The majority of intravenous sedatives and hypnotics act by amplifying the release of the inhibitory neurotransmitter, γ-aminobutyric acid, and by inhibiting the neuronal network activity (barbiturates, propofol, and benzodiazepines). The common characteristics of these agents include their quick hypnotic effect, substantial impairment of cognitive functions and memory as well as suppression of respiration.

The novel agents that are increasingly popular in sedation include alpha-2 adrenergic receptor agonists. Alpha-adrenergic receptors and their distribution in individual CNS structures are essential for proper functioning of the brain; they play an important role in maintaining homeostasis. Although they occur in the entire brain, their individual subtypes are characteristic of particular regions: 2A — for the cerebral cortex, locus coeruleus and hippocampus; 2B — for the nucleus of optic thalamus; 2C — for the cerebral cortex, corpus striatum and hippocampus [22]. All play a significant role in the regulation of dopamine and noradrenaline release; because of their wide distribution, they act on numerous, important, physiological processes.

Among the drugs that stimulate alpha-2 receptors, derivatives of imidazoline are most commonly used, including clonidine, the most popular agent of this group in Europe, and dexmedetomidine, the right-handed isomer of medetomidine, for which selectivity for alpha-2 adrenergic receptors is eight-fold higher than that of clonidine [23, 24]. Unlike classic sedatives that induce some “dimness” of consciousness, alpha-2 adrenergic receptor agonists reduce the sympathetic activity and the extent of agitation, thereby causing a state resembling the non-REM phase of
physiological sleep without impairing cognitive functions [25]. Because of their different uptake point and mechanism of action, they cause a completely different quality of sedation that is induced by inhibition of noradrenergic activity of neuronal network via activation of alpha-2 receptors at the locus coeruleus. The decrease of noradrenaline concentration is responsible for basic side effects of dexmedetomidine, i.e., decreased arterial pressure, bradycardia, and decreased cardiac output in several cases. Alpha-2 receptor agonists exert their anti-nociceptive action at the spinal and supraspinal levels [26, 27]. The major sites of analgesic action are the posterior horns of the spinal cord where the modulation of pain impulses is mediated by the noradrenergic bulbar/spinal pathway. Moreover, the mechanisms inhibiting pain transmission in the peripheral sensory nerves are implicated [26, 28].

Dexmedetomidine is designed for the sedation of ICU adult patients not deeper than -3 according to the Richmond Agitation-Sedation Scale (RASS). Recent studies comparing dexmedetomidine sedation and the most common ICU sedation strategies demonstrated that the former fulfills the majority of expectations of intensivists relative to its place of action in the central nervous system. The SEDCOM study comparing the efficacy and safety of prolonged sedation with dexmedetomidine and midazolam showed that considerably shorter times were required to complete tracheal intubation in the case of dexmedetomidine (3.7 days vs. 5.6 days, \( P = 0.01 \)) with comparable ICU treatment duration (5.9 days vs. 7.6 days; \( P = 0.24 \)). Moreover, amount of time required to achieve the level of sedation enabling ventilation therapy consistent with the protocol were comparable for both agents. Otherwise, delirium was more frequently observed with midazolam (76.6% vs. 54%, respectively; \( P < 0.001 \)). However, dexmedetomidine induced an adverse impact on the cardiovascular system, i.e., bradycardia, which developed in 18.9% of sedated patients [29]. Bradycardia is the most commonly reported adverse effect of dexmedetomidine. The same mechanism that causes bradycardia can have a therapeutic potential in several clinical situations. The Brazilian study published most recently described a series of cases of supraventricular tachyarrhythmias in children and adolescents, in whom the use of dexmedetomidine was the most effective therapeutic management [30].

According to the MENDS study, the use of lorazepam resulted in a significantly higher risk of too deep sedation compared to dexmedetomidine (33% vs. 15%) [31]. The results published by Jakob and colleagues [32] are important. The authors evaluated the usefulness of dexmedetomidine versus midazolam (MIDEX) and propofol (PRODEX). Forty-four European centres participated in the MIDEX trial, and 31 centres participated in the PRODEX trial. Dexmedetomidine was not found to be superior for providing light and moderate sedation (0 to -3 according to RASS). The time of mechanical ventilation was significantly shorter with dexmedetomidine compared to midazolam (123 h vs. 164 h; \( P = 0.03 \)). However, there were no differences in the mechanical ventilation times between dexmedetomidine and propofol (97 h vs. 118 h; \( P = 0.24 \)). Patients sedated with dexmedetomidine were more reactive and cooperative than those sedated with midazolam and propofol, which was observed by the nursing personnel assessing the severity of pain according to VAS during sedation interruptions. The MIDEX trial revealed a significantly higher incidence of bradycardia (\( P < 0.001 \)) and hypotonia (\( P = 0.007 \)) in patients receiving dexmedetomidine, whereas the PRODEX trial demonstrated that the incidence of bradycardia and hypotonia was comparable in the study groups. Agitation, anxiety, and delirium were more common in patients receiving propofol than dexmedetomidine (\( P = 0.008 \)), whereas the incidence of adverse effects was comparable between the groups receiving midazolam or dexmedetomidine. The duration of the ICU stay and hospitalisation as well as mortality rates were comparable in the study groups.

Moreover, alpha-2 agonists, primarily clonidine and dexmedetomidine, are useful for sedation to facilitate mechanical ventilation in alcoholics, particularly in cases of long-term ventilation. American and Italian authors described a series of cases in which dexmedetomidine was effectively used in ICU patients with alcohol withdrawal syndrome, which amplifies noradrenergic neurotransmission and induces anxiety, excitation, hypertension, tachycardia, and muscle tremor [33, 34]. Furthermore, several recent studies disclosed beneficial effects of dexmedetomidine during oscillatory ventilation, for which neuromuscular blocks with all of their consequences have been strongly advocated until recently [35].

The beneficial therapeutic effects of dexmedetomidine on the nervous system can result from its systemic and local action. In the traumatic brain injury model, the local neuroprotective action of dexmedetomidine in the hippocampus region was demonstrated. This effect is substantially stronger compared to the use of moderate hypothermia [36]. The clinical value of dexmedetomidine results primarily from its sympatholytic, sedative and analgesic properties. The agent in question is superior to benzodiazepines with regard to the reduction of agitation in neurological patients who do not require endotracheal intubation [37]. Moreover, dexmedetomidine is more effective in controlling seizures in patients with chronic renal disease and uremic encephalopathy [38]. Rutkowska and co-workers [39], who compared dexmedetomidine and midazolam for sedation of patients with end-stage renal failure, demonstrated that it took twice as long to achieve sedation in the dexmedetomidine group than in the midazolam group (21.0 min
vs. 10.3 min). Notably, during administration of the saturation dose of dexmedetomidine, sedation developed more smoothly. The time from the cessation of drug infusion to the restoration of consciousness (corresponding to score 2 according to the Ramsay scale) was significantly longer when midazolam was used. This phenomenon is attributable to the shorter half-life of dexmedetomidine in patients with renal failure, which can be explained by the reduced binding of dexmedetomidine with plasma proteins and thus a greater availability to the hepatic enzymes responsible for the agent’s metabolism [40].

Compared to other sedatives, a unique feature of dexmedetomidine is its inability to inhibit the central respiratory drive [41]. The central mechanisms that control respiration have not been established; however, there is evidence that alpha-2 agonists play a significant role in modulating respiratory activity [42, 43].

The survey of the most recent literature reports on dexmedetomidine indicated that sedation of patients with myasthenia gravis (MG) is of great interest. The PubMed database contains only one case report demonstrating the usefulness of dexmedetomidine in this disease. The authors described the repeated use of dexmedetomidine in a female patient in the operating room. The agent was administered for the first time in a pregnant (week 28) patient with symptoms of gestosis undergoing emergency Caesarean section. The urgency required general anaesthesia for which vecuronium was unfortunately used, which resulted in ICU hospitalisation, prolonged neuromuscular blockage and mechanical ventilation. The use of dexmedetomidine enabled the physicians to achieve an extreme extent of sedation with preserved consciousness and good tolerance of the endotracheal tube, thus facilitating the likelihood of early extubation. Another intervention in the same patient was a scheduled thymectomy without striated muscle relaxation. The patient was extubated immediately after surgery. Although the authors admitted that dexmedetomidine is the agent of choice for sedation for patients with MG, additional studies are required [44]. In Poland, dexmedetomidine cannot be used outside ICUs.

The sympatholytic action of dexmedetomidine is essential for patients undergoing cardiac surgery. Decreases in heart rate and arterial pressure and release of endogenous catecholamines favourably affect the cardiac oxygen balance and haemodynamic stability. Moreover, stimulating postsynaptic alpha-2 receptors in the muscular layer of blood vessels enables counterbalancing of the vasodilating effect resulting from a decrease in noradrenaline release [45]. Compared to propofol or midazolam, dexmedetomidine displays an advantage in patients that can easily awaken in response to tactile or verbal stimulation, which enables earlier evaluation of their neurological condition to detect possible neurological complications and to implement early therapeutic management. Another asset is the antiarrhythmic action of dexmedetomidine. A dose of 0.7 (± 0.3) μg kg⁻¹ was observed to be effective in 96% of patients with paroxysmal supraventricular tachycardia treatment, showing substantially higher efficacy compared to adenosine [46].

The meta-analysis published last year concerning the use of dexmedetomidine for sedation after cardiac surgical procedures demonstrated lower rates of delirium, tachycardia and hyperglycaemia and shorter times of mechanical ventilation; however, the incidence of bradycardia was higher. The analysis did not reveal differences in the duration of hospitalisation, ICU stay, doses of opioids and postoperative mortality [47].

Clinical observations demonstrating the lack of efficacious sedation or excessively expressed hypotension after the use of dexmedetomidine in patients after aorto-coronary bypass surgery motivated the Turkish researchers to explore a possible correlation between the clinical effect of the medication and the genetic variability of the adrenergic alpha-2 receptor. Their findings demonstrated that patients with the G allele of the gene encoding the alpha-2 receptor were more resistant to the sedative effects of dexmedetomidine [48].

The incidence of postoperative delirium syndrome is higher in elderly patients after cardiac surgery than after other surgical procedures. Considering the marked impact of delirium on the duration of hospitalisation, treatment costs, long-term cognitive impairment and mortality, the reduction in its occurrence and the shortening of its duration are important aspects of treatment in this group of patients.

Similar to other patients treated in ICUs, the essential element of prevention and the treatment of delirium is the use of sedation based on the protocol targeted at its defined depth. In the DEXCOM trial that involved 306 patients > 60 years of age who underwent coronary artery vascularisation, the group of patients treated with dexmedetomidine at a dose of 0.1–0.7 μg kg⁻¹ h⁻¹ was compared to the group receiving morphine at a dose of 10–70 μg kg⁻¹ h⁻¹; the double-blind method was applied. In both groups, propofol was titrated to maintain motor activity. The trend observed indicated a lower incidence of postoperative delirium and a significantly shorter duration of delirium in the dexmedetomidine group (P = 0.032). The analysis of the subgroups showed a significantly lower incidence of delirium in patients receiving dexmedetomidine (P = 0.001) and requiring circulatory support with intra-aortal counterpulsation [49]. Maldonado and colleagues [50] demonstrated that the frequency of delirium after cardiac surgery was 3% in patients sedated postoperatively with dexmedetomidine and 50% in groups sedated with propofol or midazolam; notably, a reduced incidence of delirium was associated with lower treatment costs. The meta-analysis published last year invo-
living 33 studies regarding the risk factors of delirium after cardiac surgery revealed that the use of dexmedetomidine sedation is one of two factors (the other one being Fast-track protocols) that significantly reduces the risk of delirium [51].

In ICUs, dexmedetomidine can be useful in unusual clinical situations, which was emphasised by Knapik (unpublished data). One situation was the recovery from deep sedation in two patients previously undergoing extracorporeal membrane oxygenation (ECMO). Another situation was the control of extremely severe delirium and the restoration of normal sleep rhythm and alertness in a female patient with advanced cachexia and alcohol addiction syndrome who was admitted to the ICU after cardiac arrest, which occurred in the hospital and was caused by an extreme electrolyte disorder. Patients undergoing ECMO constitute a challenge with respect to sedation techniques. The demand for sedatives is enormous and substantially exceeds conventional doses [52]. Because the pharmacokinetics of sedatives, as well as that of analgesics and antibiotics, is so widely disturbed, several studies concerning these issues were conducted that addressed dexmedetomidine [53, 54].

Patients undergoing ECMO require deeper sedation because of attempts to achieve spontaneous respiration; particularly in the presence of hypovolaemia in which the cannulae are suctioned, and therefore, the number of rotations of a pump driving the ECMO system rapidly decreases and oxygenation markedly deteriorates. This fact was highlighted in the report regarding a female patient with pandemic influenza treated with ECMO in the ICU of the Silesian Centre for Heart Diseases in Zabrze [55]. However, the most difficult moment was when ECMO support could be discontinued. The sedation that had been previously used for many days or even weeks could be tapered or could be withdrawn. The experiences of the Silesian centre indicated that this moment may prove to be extremely difficult. In two patients under the age of 30 years, the initially intensified adrenergic reaction was observed followed by disorders of normal sleep rhythm and alertness. The addition of dexmedetomidine to the other sedatives used, substantially limited the extent of both problems; consequently, it was possible to significantly shorten the stage of sedation withdrawal.

Dexmedetomidine was noted to be efficacious when it was necessary to alleviate the symptoms of extremely severe delirium. Intensified disorders and poor response to conventional medications as well as many days of insomnia caused a gradual deterioration of the patient’s condition. The simultaneous administration of dexmedetomidine and midazolam for sedation resulted in spectacular improvement. Similar situations were published recently in other reports [56, 57].

An ageing population is a global problem that is particularly visible in Europe. According to forecasts, the elderly (≥ 65 years of age) will constitute 30% of the population in 2050 [58]. These people will need to be hospitalised more often. The elderly are more susceptible to the action of sedatives and frequently develop a paradoxical reaction to sedatives. The incidence of cognitive disorders is significantly higher in this group. Therefore, sedation-related benefits and potential risks should be considered; moreover, individual susceptibility to procedure-associated discomfort must be evaluated, the depth of sedation must be determined and appropriate medications must be chosen. Numerous medications used for sedation tend to depress the activity of major systems, i.e., respiratory and cardiovascular systems, which explains why their use is limited in patients with impaired respiratory and cardiovascular systems. Dexmedetomidine does not induce respiratory depression and can be used as an alternative therapy to midazolam, which is commonly used to sedate elderly patients. Currently, the usefulness of dexmedetomidine in this particular population cannot be determined because of the limited number of studies concerning its use in the elderly and the lack of studies involving elderly patients treated in ICUs.

**CONFLICT OF INTEREST**

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**References:**


