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# Dexmedetomidine –A novel sedative in ICU

Dr. Paranjpe Jyotsna S, [1] Dr. Gaikwad Shilpa A [2]

[1] *Associate Professor in Anaesthesiology, BVUMC & Hospital, Sangli, Maharashtra, India*
[2] *Assistant Professor in Anaesthesiology, BVUMC & Hospital, Sangli, Maharashtra, India*

**Abstract:** A new alpha-2 receptor agonist Dexmedetomidine appears to mimic many of the actions of mythical 'ideal' sedative/analgesic agent which has been shown to be safe during weaning from mechanical ventilation. Its value as a post-operative sedative and analgesic is becoming more accepted and evident in critically ill patients.

Besides sedation, DEX can be used for treatment of delirium, shivering, drug withdrawal in ICU. It has been extensively used in the perioperative period for attenuation of stress response, pain relief, as an adjuvant to general & regional anaesthesia. It has a strong synergistic effect with other sedatives, opioids and local anesthetics. Other claimed advantages include minimal respiratory depression with cardioprotection, neuroprotection and renoprotection, thus making it useful at various situations including offsite procedures.

Throughout a broad range of plasma concentration, DEX has minimal effects on the respiratory system, predictable & easily treatable side effects like bradycardia & hypotension, favourable pharmacodynamic / pharmacokinetic profile. DEX has evolved as a panacea for various applications / procedures with multiple promising delivery routes for all patients at all age groups. Availability of an antidote (Atipamezole) with similar elimination half life is taking the drug into new frontiers.

Intravenous infusion of DEX is commonly initiated with a 1 μg /kg loading dose, administered over 10 minutes, followed by a maintenance infusion of 0.2–1.0 μg /kg/hour.

A new role as a sole agent for procedural sedation is fast emerging mainly due to its noncumulative nature. Recent multicentric RCTs have demonstrated that DEX is a better alternative for long term sedation since it is found to reduce incidences of delirium and coma in critically ill patients. Their findings suggest that DEX may possess anti-inflammatory effect in sepsis patients during sedation.

A caution should be exercised when administering DEX to patients with advanced heart block or ventricular dysfunction. Volume status should also be assessed when initiating DEX. Since it is extensively metabolized in liver, dose needs reduction in hepatic dysfunction. A rapid bolus of DEX should be avoided given its potential for both hypotensive and hypertensive effects.

**Abbreviations:** DEX- Dexmedetomidine, FDA- Food and Drug Administration

**Key words:** $\alpha_2$-adrenoceptor agonists, analgesic, conscious sedation, critically ill, Dexmedetomidine, hypotensive, ICU sedoanalgesia, postoperative medication

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**Introduction:** Characteristics of an ideal sedative include dose dependent cooperative sedation, minimal depression of ventilation, hemodynamic stability, wide therapeutic window, effective analgesia, minimal and easily treatable side effects, favourable pharmacodynamic / pharmacokinetic profile with reduced risk of delirium and agitation. [1,2] After untiring efforts & a relentless quest to discover a single agent that can achieve these goals for all patients at all age groups, Dexmedetomidine has evolved as a panacea for various applications / procedures with multiple promising delivery routes. [3-7]

**History:** The use of $\alpha_2$-adrenoceptor agonists in human medicine is not new. The first $\alpha_2$-adrenoceptor agonist was synthesized in the early 1960s to be used as a nasal decongestant. Early application of the new substance, now known as clonidine, showed unexpected side effects, with sedation for 24 hours and symptoms of severe cardiovascular depression.[4] Subsequent testing led to the introduction of An imidazoline derivative Clonidine hydrochloride as an antihypertensive drug in 1966.[8] Veterinarians employed xylazine and detomidine to induce analgesia and sedation in animals since 1970.[8,9] DEX a 2nd generation $\alpha_2$ adrenergic receptor specific, pharmacologically active D- isomer of medetomidine was first synthesized in late 1980's. Phase 1 studies were completed in early 1990's, while clinical trials began in late 1990's. DEX was approved by the Food and Drug Administration at the end of 1999 initially as an ICU sedative.[10] By 2000 it became alpha -2 agonist of choice, due to its greater alpha- 2: alpha- 1 affinity (approximately1620:1 for meditomedine vs 220:1 for clonidine and 160:1 for xylazine). [11, 12] This increased selectivity results in more predictable and effective sedation and analgesia and fewer side effects. [13] In late 2008, the FDA approved the use of dexmedetomidine for nonintubated patients requiring sedation prior to and/or during surgical and other procedures. [14]

Currently many countries have granted approval for prolonged use of dexmedetomidine at varying doses (0.1–2.5 μg/kg/hour) and durations up to 30 days. [15]

**Characteristics of alpha-2 adrenoceptors**: alpha-2 adrenoceptors are found in both the central and peripheral nervous system and serve to produce inhibitory functions. [16]

The classification of alpha2-receptors based on anatomical location is complicated since these receptors are found in presynaptic, postsynaptic and extrasynaptic locations. [17] Alpha2-adrenoceptors are divided into three subtypes; each subtype is responsible uniquely for some of the actions of alpha2-receptors. The subtype A, the predominant subtype in CNS, is responsible for the sedative, analgesic and sympatholytic effect; the subtype B, found mainly in the peripheral vasculature, is responsible for the short-term hypertensive response, and the subtype C, found in the CNS, is responsible for the anxiolytic effect. [8] All subtypes are G protein-coupled receptors (GPCR). [8, 17-19]

Presynaptic alpha-2 receptors inhibit the release of noradrenaline by sympathetic postganglionic fibers & adrenaline released by the adrenal medulla, terminating the propagation of pain signals or neuronal cell firing. [4, 8, 20] They serve for an important

negative feedback control of noradrenaline. Activation of postsynaptic $\alpha_2$- adrenoceptors is responsible for peripheral actions of the drug. [17, 18, 20]

**Clinical actions:**

**Central-**

**a.** Sedation, hypnosis, anxiolysis
**b.** Analgesia
**c.** Bradycardia and hypotension

**Peripheral- [4, 8, 17, 18, 20, 22]**

**a.** Decreased GI secretions, inclusive of saliva and decreased GI motility
**b.** Constriction of vascular and other smooth muscles
**c.** Inhibition of rennin-angiotensin (RA) system and decreased release of rennin
**d.** Increased Glomerular Filtration Rate (GFR), Increased excretion of Na, water and thus diuresis
**e.** Decreased intra-ocular pressure
**f.** Decreased insulin release from the pancreas [4]
**g.** Decreased platelet aggregation
**h.** Decreased shivering threshold (by 2°C). [8, 22]

**'Novel' Mechanism of Analgesia and Sedation of DEX** - It induces sedation resembling physiological sleep maintaining reusability without causing respiratory depression. It produces analgesia by central, spinal & peripheral mechanisms. Net result is neither the nerve / terminal are allowed to get stimulated, nor it can transmit / propagate the signal forwards. [4, 8, 20]

The pre-synaptic type of $\alpha_2$- receptors regulates the release of nor-adrenaline and adenosine tri phosphate (ATP), through negative feedback mechanism. [4] In CNS, the specific sites are, Locus Coeruleus of upper brain stem & substantia gelatinosa in spinal cord. [20]

DEX is totally devoid of any direct effects on myocardium. After administering it rapidly or with a relatively large dose (>1000 μg/kg), there is initial transient increase in blood pressure. This is attributable to peripheral vasoconstriction due to stimulation of α-2B adrenoreceptors in peripheral vascular smooth muscles. [8] This rise is neither very marked nor long lasting, but is usually associated with significant bradycardia. [19] This direct effect on the peripheral vascular smooth muscle usually lasts for up to 10 minutes. [4, 11] and can be attenuated by a slow infusion over 10 or more minutes. [4, 11]

Alpha 2-adrenoceptors do not have an active role in the respiratory centre, therefore, DEX throughout a broad range of plasma concentration, has minimal effects on the respiratory system. [23, 24-30] The respiratory effects of DEX include minimal depression of minute volume with no clinically relevant changes in response to PaCO2 and PaO2 even at plasma levels of up to 8 ng/ml. [28]

It is postulated that long-term administration of Clonidine or DEX can increase the number of adrenergic receptors and also induces a supersensitive state. Therefore, sudden discontinuation of either agent may predispose to hypertensive reaction. However; Venn et al

[24] in a prospective observational trial of 12 medical intensive care patients in whom infusions of DEX were allowed for up to 7 days did not find any hypertensive reaction. Other observers also found no significant hemodynamic effects upon withdrawal of medication.[25] Although DEX has no significant effect on adrenocorticotropic hormone (ACTH) secretion at therapeutic doses, cortisol's response to ACTH may be reduced after prolonged use or high doses of dexmedetomidine.[4]

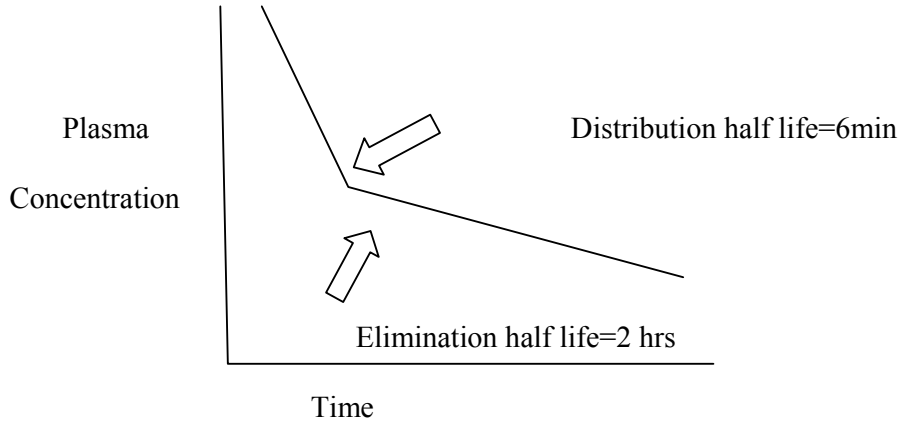
It is observed that DEX does not alter the sweating threshold; there is a dose dependent decrease in the vasoconstriction and shivering thresholds. [21, 22]

**Selective antagonism**: α2-Adrenoceptor agonists do not affect the synthesis, storage, or metabolism of neurotransmitters and do not block the receptors, thus providing the possibility of reversing the hemodynamic effects with vasoactive drugs or the $\alpha_2$-agonist effects with a specific $\alpha_2$-adrenoceptor antagonist.[26] Yohimbine, Atipamezole are known alpha-2 antagonists. Although not orally active, [27] Atipamezole (Antisedan) is found to be an effective antagonist for reversing psychomotor impairment and vigilance in a dose dependent manner following DEX sedation.[8, 26] Changes in saliva secretion, blood pressure, heart rate and plasma catecholamines were similarly biphasic (i.e., they decreased after DEX followed by dose-dependent restoration after atipamezole).[27, 28] A dose ratio of 40:1 to 100:1 for atipamezole: dexmedetomidine was found sufficient for this purpose.[29]

**Pharmacokinetics/Pharmacodynamics**: DEX undergoes almost complete biotransformation into all inactive metabolites in the liver, with <1% excretion of unchanged molecules in the urine or feces. [8, 31] It is necessary to decrease the typical dose in patients with hepatic failure, since there is significant ↑ $t_{1/2}$ in hepatic failure (7.5 hr). The elimination half-life in healthy patients is approximately 2 hours. [4, 8, 11]

DEX exhibits linear kinetics when infused in the recommended dose range. The steady-state volume of distribution is 118 L, and the distribution phase is rapid, with a half-life of distribution of approximately 6 minutes. [4, 8, 11]

**The Pharmacokinetics of DEX**




DEX shows good bioavailability (>70%) when administered by IM, buccal, enteral, intranasal routes. [6, 32-35]

The average protein binding of DEX is 94%, with negligible protein binding displacement by fentanyl, ketorolac, theophylline, digoxin, and lidocaine, all drugs commonly used during anesthesia and in the ICU. [8] There have been no significant sex- or age-based differences in the pharmocokinetic profile, even in elderly and paediatric patients, and pharmacokinetics of the active DEX molecule do not change in patients with renal failure. [4]

**Comparison with other sedatives**:

Clinical effects- [10, 36-41]

| | Benzodiazepines | Propofol | Opioids | α-2 agonists |
|---|---|---|---|---|
| Sedation | Yes | Yes | Yes | Yes |
| Anxiolysis | Yes | | | Yes |
| Analgesia | | | Yes | Yes |
| Arousability | | | | Yes |
| Amnesia | Yes | Minimal | | |
| Control on Delirium | | | | Yes |

**Edge over other sedatives-**

**1. Arousability:** The majority of patients receiving DEX as a primary therapy experienced clinically effective sedation yet were still easily arousable, a unique feature not observed with other clinically available sedatives. [2, 42]

**2.Amnesia:**Unlike benzodiazepines, DEX lacks amnesia.[8,43] However, a study in the ICU patients receiving either DEX or propofol infusions suggests that at an equivalent depth of sedation measured by median BIS values an incidence of recall was low.[38]

**3. Control on delirium:** It is known that sedation induced by drugs acting on the GABA system, such as midazolam or propofol, produce a clouding of consciousness. [8, 26] DEX does not affect thought process. Many researchers have demonstrated the superiority of dexmedetomidine with regard to the treatment or prevalence of delirium. [36, 65]

**4. Analgesia:** Unlike opioids, DEX in clinical doses exhibits good analgesia without causing respiratory depression or constipation.

**5**. **Anxiolysis:** In ICU settings getting calm, cooperative patient is always desirable. Similar to benzodiazepines, DEX produces anxiolysis by central action.

**6. Long term use:** Dexmedetomidine offers the major advantage of a reduction in the incidence of delirium and coma during long-term sedation in the intensive care unit setting. Adverse effects such as bradycardia that occur during short-term sedation with DEX are unavoidable. Interestingly, a secondary beneficial effect associated with the use of DEX is a reduction in the incidence of infection; this appears to be because the use of DEX reduces intensive care unit stay and/or duration of mechanical ventilation. Rebound and/or withdrawal effects after discontinuation at the end of prolonged sedation do not seem to be a concern. DEX seems to be better alternative to benzodiazepines or propofol for long term (upto 30 day) sedation in adults. Due to its noncumulative nature, prolonged DEX infusion has not been reported to have any serious adverse effects. [65] DEX has potential as a main drug for both long- and short-term sedation, and the findings of further studies are awaited with interest.

**7. Sepsis & septic shock:** Critically ill patients in sepsis and septic shock suffer a high degree of stress because of pain and anxiety and organ specific responses to sepsis. An important objective in the management of these patients is to achieve an adequate level of sedation and analgesia. There were interesting outcomes in the study by Pandharipande et al suggesting that DEX may prevent inflammatory effects in sepsis patients during sedation. [65-67]

**8. Effects on withdrawal of drug:** Review of literature suggests that rebound hypertension and tachycardia does not occur following abrupt discontinuation of DEX infusion. [24, 25, 36]

**9. Other claimed advantages:** Minimal respiratory depression with cardioprotection, neuroprotection [23] and renoprotection.

**10. Antidote:** Linear pharmacokinetics and similar elimination half-lives of DEX & antidote Atipamezole (app. 2 hrs) are a clear advantage considering the possible clinical applications. [27, 28]

**Adverse effects** : [39-41]

| | Benzodiazepines | Propofol | Opioids | α-2 agonists |
|---|---|---|---|---|
| Prolonged weaning | Yes | | Yes | |
| Respiratory depression | Yes | Yes | Yes | |
| Delirium | Yes | Yes | Yes | |
| Hypotension | Yes | Yes | Yes | Yes |
| Tachycardia | | | Morphine | |
| Bradycardia | | | Fentanyl | Yes |
| Constipation | | | Yes | |

**Prevention & treatment of adverse events after DEX:** Literature review suggests that patients in the dexmedetomidine-treated group have a higher incidence of sinus bradycardia (heart rate <60 beats per minute) than those in benzodiazepine -treated group. [36, 65]
When DEX is infused with doses more than 1.5 μg /kg, bradycardia and hypotension have been reported in almost 40% healthy surgical patients; [17, 27] usually, these temporary effects are predictable and can be successfully treated with atropine or ephedrine and volume infusions. [2, 8, 48] However, sympatholytic or bradycardic actions of $\alpha_2$-adrenoceptor agonists may be deleterious in hypovolemic patients or patients with fixed stroke volume. Overdose may cause first-degree or second-degree atrioventricular block, atrial fibrillation. Severe bradycardia leading to cardiac arrest has been reported in the literature, but the case reports have multiple confounding factors that might have contributed to the cardiac arrest. [11]

Most of the adverse events associated with DEX use occur during or briefly after loading of the drug. Multiple studies have demonstrated that by omitting or reducing the loading dose, adverse effects can be reduced. [4, 11, 21, 26, 31] Although avoiding the loading dose may prevent erratic hemodynamic effects, it may potentially prolong the onset of action and time to steady state for DEX. [11]

Hyperglycemia occurs more frequently among dexmedetomidine-treated patients. [24, 36]

The teratogenic effects of DEX have not been adequately studied at this time, but the drug does cross the placenta and should be used during pregnancy only if the benefits justify the risk to the fetus. [4, 8]

**Dosage and administration:** Intravenous infusion of DEX is commonly initiated with a 1 μg /kg loading dose, administered over 10 minutes, followed by a maintenance infusion of 0.2–1.0 μg /kg/hour. There may be great individual variability in the hemodynamic effects (especially on heart rate and blood pressure), as well as the sedative effects of this drug. For this reason, the dose must be carefully adjusted to achieve the desired clinical effect. [2, 11, 34, 35]

Limiting its usefulness is the caution that the drug cannot be bolused due to concerns about peripheral alpha-2 receptor stimulation with resulting hypotension, [2, 24] combined with its high cost relative to generic medications like propofol, fentanyl and midazolam which can achieve similar clinical effects.[4]

## Indications:

**Intensive care unit sedation-** 'pharmacological' sleep with DEX resembles normal physiological sleep. This is relevant because deprivation correlates with the development of ICU psychosis. [38] DEX is useful in preventing emergence delirium and agitation. [2, 3]

Its unique sedative action and lack of respiratory depression has been shown to be safe during weaning from mechanical ventilation. [49] DEX need not be discontinued and the ongoing sedation can be maintained following tracheal extubation [25, 40] or for some nonintubated patients. [11]
In a Phase IV study, DEX was found safe in dosages up to 1.4 μg /kg/hour for greater than 24 h and did not produce rebound tachycardia or hypertension when abruptly discontinued. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) randomized trial reported an earlier return to a delirium-free cognitive state and more ventilator-free days with DEX when used for 24 to 120 h. The above studies indicate that it can be used long-term (>24 h) in critically ill patients. [2, 3]
In a multicentric trial done in five countries (US, Australia, Brazil, Argentina, and New Zealand) the safety and efficacy of DEX was compared with that of midazolam in critically ill, mechanically ventilated patients. The protocol involved DEX administration at varying doses (0.1–2.5 μg/kg/hour) for up to 30 days. They concluded that comparable sedation levels, dexmedetomidine-treated patients spent less time on the ventilator, experienced less delirium, coma and developed less tachycardia and hypertension. Prolonged dexmedetomidine infusion has not been reported to have any serious adverse effects. The most notable adverse effect of dexmedetomidine was bradycardia. [36] DEX appears to provide several advantages for prolonged ICU sedation compared with the GABA agonist midazolam [36] administration results with equal or even longer sedation compared to high doses (0.06 mg/kg) of midazolam. It leads to depressive effects on hemodynamic parameters at the dose of 1 μg/kg. [37]

DEX has a strong synergistic effect with other sedatives and opioids, with a 50 to 70% reduction in propofol, midazolam and opioid requirements having been observed. [2, 5, 38]

Stress is considered to be a major risk factor in myocardial ischaemia after surgery. The reduction in heart rate can theoretically reduce myocardial oxygen demand, and hence subsequent ischaemia and infarction. [40, 41] This is of major importance in critically ill patients, especially during periods of stress e.g. endotracheal suctioning, physiotherapy, and mobilization. Although no study has been conducted on DEX on the incidence of ischemia, two other $\alpha_2$ adrenoceptor agonists; mivazerol and clonidine have been shown to reduce ischaemia. [40]
DEX appears to be most suitable for use in hemodynamically stable patients refractory to other sedatives. Furthermore, $\alpha_2$-agonists may offer an alternative in patients developing tolerance to opioids or in those forms of pain with poor response to opioid analgesics, like sympathetically maintained neuropathic pain. [57]
Fairbanks et al [58] tested the interaction of intrathecally administered Morphine-clonidine combinations in mice made acutely or chronically tolerant to Morphine. Morphine tolerance has been attributed to a reduction of opioid-adrenergic antinociceptive synergy at the spinal level. They concluded that spinally administered adrenergic/opioid synergistic combinations may be effective therapeutic strategies to manage pain in patients apparently tolerant to the analgesic effects of Morphine.
**Ceiling effect** -A retrospective analysis of different doses of DEX for ICU sedation by Jones et al [52] suggested that doses greater than 0.7 μg /kg/hr did not enhance sedation but the incidence of side effects. This is further endorsed by the meta-analysis by Tan [52] where it was observed that incidence of bradycardia requiring intervention increased in studies that used both a loading dose and maintenance doses of dexmedetomidine in excess of 0.7 μg /kg/hr.

Jaakola [43] found that a single IV dose used for human tourniquet pain resulted in analgesia with a ceiling effect at the dose of 0.5 μg/kg.

## Nonsedative Use of DEX in the ICU:

**Delirium -** Delirium in the critically ill patient is associated with significant increases in morbidity and mortality. It has been postulated that sedatives that work through GABA receptor interaction may play a role in the pathophysiology of delirium in the ICU. The "maximizing efficacy of targeted sedation and reducing neurological dysfunction" trial was recently published.[11] The literature showed that cardiac surgical patients who were randomized to receive DEX at sternal closure were less likely to develop delirium than patients sedated with propofol or benzodiazepines (8% vs 50%).[11]

**Shivering** - Postoperative shivering is caused by disarray in thermoregulation and could result in significant increases in myocardial oxygen consumption. An alpha-2 receptor agonist such as DEX is thought to potentially reduce postanesthetic shivering by inhibiting central thermoregulation control and vasoconstriction. [11, 21, 22] Shukla et al [53] in their study on post-spinal anaesthesia shivering concluded that Clonidine offered better thermodynamics than tramadol, (both 0.5 μg /kg) with fewer side effects. Various studies on animal models &

on humans confirm that alpha-2 agonists like Clonidine exert their anti-shivering effect at hypothalamus by decreasing thermoregulatory threshold for vasoconstriction & shivering. They also reduce spontaneous firing in locus coeruleus- a pro shivering centre in pons. At spinal level they suppress release of neurotransmitters at dorsal horn which modulates cutaneous thermal inputs.

**Substance withdrawal** - Patients having a history of alcohol/drug abuse are frequently admitted to the ICU. Furthermore, patients who have been in the ICU on prolonged sedation or analgesia may also develop acute withdrawal symptoms upon discontinuation of these medications. The use of an alpha-2 adrenergic agonist has long been recognized as a potential agent for the treatment of substance withdrawal. Clonidine has been used in alcohol withdrawal. As such, the use of DEX for the management of withdrawal symptoms has been reported; however, these data are mostly limited to case reports.[11] DEX may have special value in alleviating opioid withdrawal symptoms besides helping to control pain.[54]

**Sepsis & Septic shock -** Despite advances in supportive care, the mortality rate in patients with severe sepsis continues to exceed 30%. Sedation is an important part of the therapy of critically ill patients in ICU. In a well conducted double-blind RCT in a priori-determined subgroup analysis of septic vs non-septic patients Pandharipande et al studied the effect of dexmedetomidine versus lorazepam on clinical outcome in the form of risk of delirium & death. Septic patients receiving dexmedetomidine had more days free of brain dysfunction and mechanical ventilation and were less likely to die than those that received a lorazepam-based sedation regimen. Interesingly these results were more pronounced in septic patients than in non-septic patients. [65] Several studies have found that midazolam inhibits human neutrophil function and the activation of mast cells induced by TNF-α *in vitro.* It is noted that DEX infusion decreases cytokine production while midazolam infusion does not affect it in septic patients.[65-67] These findings suggest that one of the mechanisms of anti-inflammatory effects of dexmedetomidine may be modulation of cytokine production by macrophages and monocytes .

**Weaning from mechanical ventilation:** Spontaneous breathing trials (SBT) and intermittent mandatory ventilation (IMV) are common techniques utilized to expedite the ventilator weaning process. These techniques often require the reduction and/or discontinuation of sedatives and analgesics. However, anxiety, fear and agitation are amongst the most common non-pulmonary causes of failure to liberate from mechanical ventilation. [59] Arpino et al used DEX infusion in a group of mechanically ventilated patients who failed previous attempts at weaning and extubation secondary to agitation. After DEX initiation, 65% of the patients were successfully extubated. [60] In a similar study Shehabi et al [59] reported a success rate of 73%. DEX also has a promising role as first-line therapy in ventilated, agitated patients with NIV. [61]

**Perioperative use:** Dexmedetomidine has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses in the perioperative period.[45] It reduces the requirements for volatile anesthetics, sedatives and analgesics, attenuates stress response without causing significant respiratory depression. [8] It has been used for pre-

medication, and as an adjunct to general anesthesia as well as a sole anesthetic agent.[2] It is an almost ideal agent for monitored anaesthesia care (MAC) despite its lack of amnesia and poor controllability because of its slow onset and offset.[8] Alpha-2 adrenergic agonists have both analgesic & sedative properties when used as an adjuvant in regional anaesthesia.[12,45]

**As an end of life medication:** Dexmedetomidine may also offer a new paradigm in the pharmacologic treatment of symptoms of distress (intractable pain, agitation or delirium) at the end of life. Its opiate sparing effects has important implications for the management of acute postoperative pain and chronic pain states, including disorders involving spasticity or myofascial pain, neuropathic pain, sympathetically maintained pain such as complex regional pain syndrome (CRPS) and chronic daily headaches. It is evolving as an adjuvant analgesic, both as intravenous and intrathecal infusion, in cancer pain refractory to multiple treatment modalities. [63, 64]

**Administration and Monitoring :** Dexmedetomidine is supplied in a single 2-mL clear glass vial at a concentration of 100 mcg /mL. It must be diluted to a final concentration of 4 mcg / mL. DEX should be administered using a controlled infusion device in a setting with continuous monitoring capabilities. Frequent assessment with a valid sedation assessment tool should be done and dosing of the drug titrated to maintain a targeted sedation score.

In regards of monitoring the depth of sedation, Turkmen et al [55] have reported that Richmond agitation sedation scale levels significantly correlate with a processed electroencephalogram (bispectral index) values during DEX sedation in critically ill patients requiring mechanical ventilation in the intensive care unit.

Bol et al [56] studied the anesthetic profile of DEX on the basis of steady-state plasma concentrations (range, 0.5–19 ng/ml ) using defined stimulus-response, ventilatory, and continuous electroencephalographic (EEG) and cardiovascular effect measures in rats. They concluded that IV dexmedetomidine primarily exerts bradycardic, sympathetic depressant, and sedative/hypnotic actions. Analgesic actions and loss of the corneal reflex are observed only at higher plasma concentrations. The applied EEG measure seems to reflect sedation /hypnosis but seem to have limited value to predict the deeper DEX levels of analgesia and anesthesia.

Patients with hepatic dysfunction may require a lower dose of DEX than healthy subjects to achieve a similar response, given the extensive hepatic metabolism of DEX. A rapid bolus of DEX should be avoided given its potential for both hypotensive and hypertensive effects. Given the hemodynamic effects of DEX, caution should be exercised when administering to patients with advanced heart block or ventricular dysfunction. Volume status should also be assessed when initiating DEX, because hypovolemic patients are most likely to experience the hypotensive/bradycardic effects. The sedative, bradycardic, and hypotensive effects of DEX are most likely additive when administered with other medications. [44] As such, caution should be exercised when coadministering with other sedatives, analgesics, vasodilators, or other negative chronotropic medications. [11]

**Cost effectiveness:** When the cost involved in sedating an average 70 kg man was calculated, the cost for the use of DEX was slightly higher than that of propofol. However, the use of morphine was lower in DEX group compared to propofol. Taken these factors into account, the cost involved in the use of DEX was almost similar to propofol. [40] Dasta et al [50] in their study in mechanically ventilated patients found that continuous sedation with DEX results in

significantly lower total intensive care unit costs compared with midazolam infusion due to decreased intensive care unit stay costs and reduced mechanical ventilation costs.
A retrospective analysis of postoperative management of cardiothoracic surgical patients by Dasta et al [50] in 250 hospitals found significantly lower overall hospital charges for those who received DEX compared to patients who received standard sedation therapy. Their results suggest that the use of DEX in the real world after cardiothoracic surgery may have a potential economic benefit. [11, 25]

**Patients in whom Dexmedetomidine is not recommended [2]**

1. Refractory haemodynamic instability, including:
a. Systolic blood pressure of less than 90 mmHg or a mean BP less than 60 mmHg despite significant vasopressor support, such as vasopressin > 2 units per hour or noradrenaline or adrenaline > 0.2 μg/kg/ min or dobutamine > 10 μg/kg/min.
b. Heart rate less than 55 beats per minute, not induced by beta-blocking agents.
c. High grade atrioventricular block in the absence of pace maker.
2. Microvascular free flap procedures, as α2 agonists may cause direct vasoconstriction and reduction in flap blood flow.
3. Severe liver dysfunction (Child-Pugh class C).
4. Recent acute epilepsy or uncontrolled seizure activity.
5. Neurovascular patients including those with recent intervention for a cerebral aneurysm or arterio-venous malformation, particularly patients within days of aneurysmal or traumatic subarachnoid haemorrhage or those considered at high risk of vasospasm.
6. Pregnancy or breast feeding.

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