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Advances in the Application of Intranasal Dexmedetomidine in Perioperative Anesthesia Management

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Abstract: *Dexmedetomidine is a highly selective α2-adrenergic receptor agonist with favorable sedative, analgesic-sparing and anxiolytic effects. Owing to its relatively mild influence on respiratory function, dexmedetomidine has attracted increasing attention in perioperative management. Intranasal administration, as an emerging route of drug delivery, offers several advantages, including non-invasiveness, high patient compliance and ease of use, thereby further expanding the clinical application of dexmedetomidine in anesthesia practice. Current evidence suggests that intranasal dexmedetomidine is no longer limited to conventional preoperative sedation, but also shows potential value in perioperative emotional and sleep regulation, prevention of emergence agitation, and protection of postoperative brain function. This review summarizes recent advances in the application of intranasal dexmedetomidine in clinical anesthesia, aiming to provide a reference for its rational use in perioperative management.*

Keywords: *dexmedetomidine; intranasal administration; perioperative management; sleep disorders; neurocognitive disorders*

1. Introduction

With the continuous evolution of perioperative management concepts, the goals of anesthesia are no longer limited to ensuring the smooth completion of surgery and maintaining stable intraoperative vital signs. Various perioperative adverse events, such as preoperative anxiety, emergence agitation, postoperative sleep disturbance, and neurocognitive impairment, can affect patient comfort and postoperative recovery to varying degrees, prolong hospital stay, and increase the difficulty of perioperative management [1,2].

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist with favorable sedative, analgesic, and anxiolytic effects [3]. Compared with conventional sedative agents, dexmedetomidine has a relatively mild effect on respiratory function and has been widely used in perioperative management. In the past, dexmedetomidine was mainly administered intravenously. With the development of precision and comfort-oriented perioperative care, intranasal administration has gradually attracted attention. Through the rich vascular network of the nasal mucosa, intranasal administration can achieve rapid drug absorption; it is also easy to perform and associated with high patient compliance, offering certain advantages especially in children and elderly patients [4].

In recent years, intranasal dexmedetomidine has been used not only for conventional preoperative sedation, but has also shown promising application prospects in optimizing anesthetic preparation, improving perioperative psychological and physiological status, and preventing and treating complications. Based on this, this review summarizes recent advances in the application of intranasal dexmedetomidine in clinical anesthesia, with the aim of providing a reference for its rational use in perioperative management.

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2. Pharmacological Basis and Advantages of Intranasal Dexmedetomidine

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist, and its pharmacological effects are mainly mediated through activation of central and peripheral α2-adrenergic receptors [5]. In the central nervous system, dexmedetomidine activates α2 receptors in the locus coeruleus, inhibits norepinephrine release, and activates endogenous sleep-promoting pathways, thereby producing dose-dependent sedative, anxiolytic, and analgesic effects. This effect resembles physiological sleep and is not accompanied by obvious respiratory depression [6]. Peripherally, dexmedetomidine inhibits sympathetic tone and produces cardiovascular effects, including reductions in heart rate, blood pressure, and myocardial contractility, which helps maintain perioperative hemodynamic stability [7]. These unique pharmacological properties allow it to act synergistically with various anesthetic and sedative agents. For example, when combined with opioids, it can enhance analgesic effects and reduce opioid consumption; when combined with propofol or inhalational anesthetics, it can reduce the dose of sedative-hypnotic agents, thereby lowering the risk of related adverse effects [8].

The nasal mucosa has a rich blood supply and relatively thin epithelium. After intranasal administration, dexmedetomidine can rapidly pass through the mucosa and enter the systemic circulation, thereby avoiding the discomfort caused by venipuncture and, to some extent, reducing hepatic first-pass elimination [9,10]. Previous studies have suggested that intranasal dexmedetomidine is generally absorbed relatively rapidly, but its absorption rate and bioavailability may be affected by the administration method, device, formulation, and local nasal conditions. Earlier studies were mostly based on nasal drops or atomized spraying, and reported a bioavailability of approximately 40% in healthy adults, with marked interindividual variability [11]. Some recent studies have reported that the relative bioavailability of nasal spray formulations is further increased, reaching approximately 80% [10]. In addition, pharmacokinetics differ among different populations. In children, especially infants and young children, drug clearance is related to body weight and age. In elderly patients, decreased hepatic and renal function may slow drug clearance and prolong the duration of action, making individualized dosing and the risk of drug accumulation particularly important.

Compared with intravenous, intramuscular, or oral administration, the most direct advantages of intranasal administration are that it is non-invasive, painless, and easy to perform. For children and patients with difficult venous access, intranasal administration is often more acceptable and is associated with higher patient compliance [12]. In addition, intranasal administration does not require intravenous access and is easy to perform. Under certain conditions, it can be completed by nurses and even implemented in some non-operating room settings, thereby expanding its application prospects in preoperative sedation and procedural sedation. However, intranasal administration is not without limitations. Although its bioavailability is relatively high, it does not reach 100%, and there is considerable interindividual variability [10]. The onset time and depth of sedation with intranasal administration are also less precise and controllable than those with intravenous administration. In addition, increased nasal secretions, mucosal inflammation, inadequate spraying, or poor patient cooperation may affect the actual delivery and absorption of the drug [13].

Overall, intranasal dexmedetomidine combines the pharmacological characteristics of the drug itself with the advantages of the administration route, providing a basis for its further application in psychological modulation, sleep improvement, emergence management, and postoperative brain function protection.

3. Application of Intranasal Dexmedetomidine in Clinical Anesthesia

3.1. Application in Perioperative Psychological and Emotional Regulation

Perioperative anxiety and emotional fluctuations are relatively common in clinical practice, especially in children and patients who are sensitive to surgery. These problems not only affect patients' subjective experience and cooperation, but may also increase the difficulty of perioperative management. Dexmedetomidine activates central α2 receptors and inhibits norepinephrine release, while also exerting anxiolytic effects, providing a theoretical basis for its application in perioperative psychological intervention.

In children, the evidence for intranasal dexmedetomidine in regulating preoperative anxiety is relatively sufficient. The study by Yao et al. showed that, in children undergoing tonsillectomy and/or adenoidectomy, intranasal dexmedetomidine at 1 μg/kg combined with parental presence reduced

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preoperative anxiety scores more significantly than either intervention alone, and improved compliance during anesthesia induction and parental satisfaction [14]. Subsequently, several studies further showed that higher doses could achieve better sedative effects, as reflected by smoother parental separation and better mask acceptance, without increasing the incidence of adverse reactions [15,16]. The study by Jin et al. suggested that the nasal spray formulation of dexmedetomidine could further improve children's compliance and acceptance while maintaining sedative efficacy [12].

It should be noted that perioperative psychological stress is not always limited to preoperative anxiety and tension. Existing studies have confirmed that dexmedetomidine may play a positive role in postoperative acute stress disorder (ASD) or post-traumatic stress disorder (PTSD). In a randomized controlled study involving patients undergoing emergency trauma surgery, Yu et al. found that continuous perioperative use of dexmedetomidine could reduce the incidence of PTSD [17]. In patients undergoing cesarean section, several studies have shown that dexmedetomidine can reduce stress indicators such as cortisol and norepinephrine, help stabilize hemodynamics, and contribute to the improvement of maternal perioperative emotional status [18,19].

Overall, the role of dexmedetomidine in perioperative psychological and emotional regulation has gradually expanded from simple sedation to a comprehensive intervention involving "anti-stress and emotional regulation." In comparison, direct evidence for intranasal administration in this field remains relatively limited and is currently mainly focused on preoperative anxiety intervention. However, based on its pharmacological mechanism consistent with intravenous administration and the existing evidence of anti-stress effects, intranasal dexmedetomidine may still have certain application potential in populations under high-stress conditions, and further studies are needed to clarify its clinical value.

3.2. Perioperative Sleep Regulation and Improvement of Recovery Quality

Perioperative sleep disturbance is relatively common in clinical practice, especially in elderly patients, and mainly manifests as difficulty falling asleep, sleep fragmentation, and reduced rapid eye movement (REM) sleep. It not only affects patients' recovery experience, but may also be closely associated with adverse outcomes such as aggravated postoperative pain, enhanced inflammatory responses, and neurocognitive dysfunction [20]. Compared with traditional sedative agents, dexmedetomidine has less interference with sleep architecture and may even promote the recovery of REM sleep to some extent [21].

In recent years, intranasal dexmedetomidine has attracted increasing attention for improving perioperative sleep. Zheng Zhi et al. showed in patients undergoing laparoscopic hysterectomy that administration of dexmedetomidine nasal spray (50–75 μg) on the night before surgery and the night after surgery significantly reduced Athens Insomnia Scale (AIS) scores and improved sleep quality, accompanied by decreases in anxiety scores and stress-related indicators [22]. Similarly, Fan et al. found that dexmedetomidine nasal spray (50 μg) prolonged postoperative total sleep time (TST) and increased the proportions of deep sleep and REM sleep in patients undergoing laparoscopic gynecological surgery [23]. This effect appears to be more pronounced in elderly patients or those with sleep disorders. Wu et al. showed that preoperative intranasal dexmedetomidine (2 μg/kg) in patients with chronic insomnia significantly improved postoperative sleep quality without increasing the incidence of adverse reactions [24].

Overall, intranasal dexmedetomidine shows relatively consistent effects in improving perioperative sleep quality, especially in elderly patients and those with sleep disorders. However, current studies still differ in evaluation methods, dosing regimens, and timing of administration, and most are single-center studies. The optimal administration regimen has not yet been standardized, and its impact on long-term recovery outcomes still requires further investigation.

3.3. Prevention and Management of Emergence Agitation and Recovery-Period Behavioral Abnormalities

Emergence agitation (EA) or emergence delirium (ED) is one of the common adverse reactions after general anesthesia. It has a relatively high incidence in children receiving inhalational anesthesia and is manifested as abnormal behaviors such as crying, disorientation, and non-cooperation [25]. In severe cases, it not only affects the quality of postoperative recovery, but may also increase the risk of airway complications and accidental injury. Dexmedetomidine has sedative, analgesic, and sympatholytic effects, and can reduce the central excitatory response associated with inhalational anesthetics, giving it certain advantages in the prevention of emergence agitation [26].

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In recent years, intranasal administration, as a non-invasive route of administration, has been increasingly used in pediatric patients. He et al. studied 90 children undergoing dental surgery under sevoflurane anesthesia. The results showed that preoperative intranasal dexmedetomidine at either 1 μg/kg or 2 μg/kg significantly reduced the incidence of emergence agitation in children, and 2 μg/kg was more effective in preventing severe agitation and improving mask acceptance [27]. Jangra et al. compared intranasal dexmedetomidine (2 μg/kg) with oral melatonin in children undergoing ophthalmic surgery. The results showed that the incidence of emergence agitation was lower and the sedative effect was more favorable in the intranasal dexmedetomidine group [28]. Notably, the preventive effect of dexmedetomidine shows a certain dose-dependent pattern within a specific range. Lei et al. administered intranasal dexmedetomidine at 0.5, 1.0, 1.5, or 2.0 μg/kg, or an equivalent volume of normal saline, to children undergoing ambulatory surgery. The results showed that the incidence of emergence agitation gradually decreased as the dose increased, and that the optimal dose was relatively higher in younger children. However, higher doses may prolong emergence time [29]. Further meta-analyses also support these findings. Hu et al. included 20 randomized controlled trials and found that intranasal dexmedetomidine at 1–2 μg/kg significantly reduced the incidence of emergence agitation, with 1 μg/kg achieving a relatively favorable balance between efficacy and safety [30].

Overall, intranasal dexmedetomidine has relatively consistent evidence supporting its role in preventing emergence agitation and has considerable clinical application value in pediatric patients. However, current studies are still mainly concentrated in children, and evidence in adult patients remains relatively limited. At the same time, differences remain among studies in agitation assessment criteria and administration regimens, and the optimal dose and timing of administration require further clarification.

3.4. Application in Postoperative Brain Function Protection

Perioperative neurocognitive disorders (PND) are common postoperative complications, with a relatively high incidence in elderly patients and high-risk surgical populations. They not only affect the quality of patient recovery, but are also closely associated with adverse outcomes such as prolonged hospital stay, limited long-term cognitive recovery, and increased mortality risk [2].

Existing studies have reported that the occurrence of PND is associated with multiple factors, including enhanced neuroinflammatory responses, oxidative stress, neurotransmitter imbalance, and disruption of the sleep-wake rhythm [31]. As a highly selective α2-adrenergic receptor agonist, dexmedetomidine can inhibit sympathetic excitation, reduce catecholamine release, and attenuate the impact of perioperative stress responses on the central nervous system [32]. At the same time, dexmedetomidine also has certain anti-inflammatory and antioxidant effects. It can inhibit the release of pro-inflammatory cytokines, reduce microglial activation, and alleviate oxidative stress injury, thereby exerting neuroprotective effects through multiple mechanisms [33].

In recent years, studies on intranasal dexmedetomidine in neuroprotection have gradually increased. Chen et al. conducted a randomized, triple-blind, placebo-controlled trial involving 348 elderly patients undergoing major noncardiac surgery and administered intranasal dexmedetomidine using a weight-based regimen. The results showed that the incidence of postoperative delirium was significantly lower in the dexmedetomidine group than in the control group (18.4% vs. 32.8%), and sleep quality on the night before surgery was also significantly improved [34]. Similarly, Fang et al. found in elderly patients with sleep disorders undergoing cardiac surgery that intranasal dexmedetomidine (0.3 μg/kg) combined with conventional treatment further reduced the incidence of postoperative delirium [35]. The study by He et al. showed that, in patients undergoing general anesthesia, perioperative intranasal dexmedetomidine (1.5 μg/kg) not only improved sleep quality, but also alleviated postoperative cognitive impairment to a certain extent, suggesting that the neuroprotective effect of dexmedetomidine may not be limited to short-term delirium prevention, but may also influence longer-term cognitive recovery [36].

Overall, intranasal dexmedetomidine has shown certain potential in reducing the incidence of postoperative delirium and improving some cognitive function indicators, especially in elderly and high-risk populations. However, current studies are still mainly medium-sample clinical trials with relatively short follow-up periods, and evidence regarding its effects on long-term neurocognitive outcomes remains insufficient. Further high-quality studies are needed for validation.

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4. Dose and Timing of Intranasal Dexmedetomidine Administration

At present, no unified standard has been established for the dose and timing of intranasal dexmedetomidine administration, and they are usually adjusted according to patient age, body weight, and perioperative management goals.

In adult patients, commonly used doses are mostly 1 μg/kg or fixed doses of 50–100 μg. The dose range in pediatric patients is relatively wide. For preoperative sedation, although 1 μg/kg is commonly used, some studies suggest that its sedative depth and mask acceptance may be insufficient; therefore, 1.5–2 μg/kg is often used clinically to achieve more satisfactory sedative effects [37].

Regarding administration timing, current use is still mainly based on a single preoperative dose, primarily to relieve preoperative anxiety and improve the anesthesia induction process. Multiple studies have shown that administration 30–60 min before surgery may be the optimal dosing window. This time window allows sufficient time for drug absorption and onset of action, thereby achieving the expected anxiolytic and sedative effects [38]. On this basis, some studies have also attempted to extend the timing of administration to before and after the perioperative period, such as application on the night before surgery or in the early postoperative period, to improve sleep and reduce stress responses. Reports of additional intranasal dosing during or after surgery are relatively limited. If longer-lasting or more precisely controlled sedation is required, intravenous administration is usually preferred in clinical practice.

Overall, intranasal dexmedetomidine administration has a certain degree of flexibility in terms of dose and timing, and individualized selection should be made according to patient characteristics and perioperative goals. Current studies still have problems such as inconsistent dose ranges and substantial differences in evaluation indicators, and the optimal administration strategy requires further clarification through high-quality studies.

5. Safety and Adverse Reactions

Intranasal dexmedetomidine has a relatively high level of safety within the commonly used dose range. Compared with intravenous administration, intranasal administration has a relatively gradual onset of action and has less effect on respiratory function; therefore, it has been increasingly used for perioperative sedation and anxiolysis. Existing studies have shown that intranasal dexmedetomidine is generally well tolerated in both adult and pediatric populations, with a low incidence of serious adverse events [4,39]. At the same time, because intranasal absorption avoids a rapid increase in plasma concentration, its effects on hemodynamics are relatively stable.

The main adverse reactions of dexmedetomidine are related to its α2 receptor agonist effect, with bradycardia and hypotension being the most common, and these reactions show a certain dose-dependent pattern [40]. These reactions are more common in elderly patients, patients with cardiovascular disease, or those concomitantly using β-blockers. Therefore, dose control and close monitoring are needed during clinical application. In addition, some patients may experience excessive sedation or prolonged recovery time, especially at higher doses or in patients with increased individual sensitivity. Local adverse reactions are relatively uncommon. A few patients may experience transient nasal discomfort or dryness, which is generally mild and can resolve spontaneously [41].

Overall, intranasal dexmedetomidine has a favorable safety profile and a predictable spectrum of adverse reactions. Most adverse reactions are mild and dose-related. Its clinical application is generally controllable, but it should still be used cautiously in elderly and high-risk populations according to individual patient conditions.

6. Limitations and Future Research Directions

Although intranasal dexmedetomidine currently has certain application value in perioperative management, the overall evidence still has some limitations. Most existing studies are single-center studies with small sample sizes, and the study populations are mainly concentrated in pediatric patients. The applicability of related conclusions to elderly or high-risk patients requires further validation. In addition, there are considerable differences among studies in administration dose, timing of administration, and evaluation indicators, which affects the comparability of results to some extent. At present, systematic comparative studies on different administration strategies are lacking, and the

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optimal application model remains unclear. In terms of outcome indicators, current evidence mainly focuses on preoperative sedation and anxiolysis. Although some studies have involved outcomes such as emergence responses, sleep quality, and postoperative delirium, the overall evidence remains limited. For longer-term clinical benefits, especially recovery of neurocognitive function, systematic and sufficient research support is still lacking.

Based on the above considerations, larger-sample, multicenter randomized controlled studies are still needed in the future. For elderly patients, high-risk patients, and patients with underlying diseases, higher-quality randomized controlled trials should be conducted to systematically evaluate its safety and efficacy. At the same time, according to different perioperative goals, such as sedation, sleep regulation, and brain function protection, the optimization of dose, timing of administration, and multi-time-point intervention strategies can be further explored. In terms of outcome indicators, in addition to short-term perioperative responses, follow-up assessment of long-term neurocognitive function and overall recovery quality should be strengthened to more comprehensively reflect its clinical value.

7. Conclusion

In summary, intranasal dexmedetomidine, as a non-invasive route of administration, is gradually expanding its application in perioperative management. Existing studies have shown that it can be used not only for conventional preoperative sedation, but also has certain potential in emotional and sleep regulation, prevention and treatment of emergence agitation, and postoperative brain function protection. Compared with intravenous administration, the intranasal route has a relatively gradual onset and less respiratory depression, providing a relatively gentle intervention option for perioperative management. In clinical practice, intranasal administration is more suitable as a supplementary approach to existing sedation strategies, and its specific positioning in different populations and perioperative goals is still being gradually clarified. With the continuous accumulation of evidence-based data and clinical experience, the role of intranasal dexmedetomidine in comprehensive perioperative management is expected to become clearer and to play a more stable role in individualized management.

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