Sedatives in Dental Implant Surgery

Subjects: Dentistry, Oral Surgery & Medicine

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Implant surgery is a lengthy dental procedure, and sedation is often used to reduce discomfort. The effectiveness of sedation has traditionally been evaluated in terms of patient and surgeon satisfaction, but the most important goal is not to induce a deep sleep in the patient, but rather to ensure that the surgery is performed safely and as planned. Additionally, adequate pain control is a necessary requirement for patient and surgeon satisfaction. Most patients undergoing implant surgery are middle-aged or older, and a relatively large number of them have cardiovascular disease. Infiltration anesthesia using articaine or lidocaine in combination with adrenaline is widely used, but its use in patients with cardiovascular disease is limited because of adrenaline's effects on the cardiovascular system. The use of long-acting local anesthetics and the potential efficacy of ultrasound-guided jaw nerve block have been investigated to enhance analgesia without resorting to adrenaline. Midazolam and propofol are usually used for sedation, but dexmedetomidine, which causes less respiratory depression, and the ultrashort-acting benzodiazepine remimazolam are emerging as potential alternatives. Monitoring of anesthetic depth using electroencephalography is effective in maintaining a constant level of sedation. In addition, sedation promotes the stabilization of heart rate and blood pressure, reducing the risks associated with adrenaline and allowing for safer management.

Keywords: conscious sedation ; nerve block ; local anesthetic

1. Introduction

Compared with other dental treatments, implant surgery is invasive and takes a longer time, resulting in stressful situations that people hope to avoid. This is partly why sedation is popular for implant surgery, and another reason is that sedation stabilizes vital signs even if the level is minimal [1]. Since implant surgery requires a higher dose of local anesthetics, including catecholamines, having stable vital signs contributes to safety in implant surgery. Propofol and midazolam are the two main anesthetics used [2]. Dexmedetomidine directly acts on the alpha 2 adrenaline receptor, contributing to the control of changes in vital signs brought about by implant surgery. Remimazolam, the newest ultrashort benzodiazepine sedative, is expected to be useful for sedation in implant surgery. The following paragraphs discuss the characteristics of each sedative and the factors affecting its efficacy.

2. Propofol

Propofol (2, 6-diisopropylphenol) is highly lipophilic, crosses the blood–brain barrier rapidly [3], and is a short-acting agent with a rapid metabolism, thus enabling rapid recovery from sedation, regardless of sedation depth or length [4]. However, the pharmacokinetic parameters of propofol vary depending on patient factors such as sex [5], obesity [6], cardiac output (CO) [7], and hepatic blood flow [8].

With respect to sex, the plasma concentration of propofol decreases more rapidly in females than in males [9], and females tend to recover faster from propofol anesthesia than males [10]. This may because of sex-dependent differences in the formation of liver cytochrome P450s (CYPs), the main metabolic enzymes for propofol [11][12], and UDP-glucuronosyltransferases (UGTs), the main enzymes that catalyze the glucuronidation of propofol [5][13]. To maintain the same level of sedation with propofol between males and females, higher doses are required in females because they metabolize propofol faster than males do [14].

Intravenous sedation in obese patients is relatively difficult to perform compared with that in non-obese patients because airway obstruction easily occurs in obese patients. As the relationship between obesity and sleep apnea is well documented [15], obese patients have a higher risk of respiratory depression during sedation. In addition, the induction time for the same target concentration of propofol is significantly shorter in obese patients [16], suggesting that a lower concentration of propofol is sufficient to sedate and/or that the pharmacokinetics in obese patients differ from those in non-obese patients.

Age has been shown to affect the efficacy of propofol. When the same dose of propofol is administered during induction of general anesthesia and its effect is examined by EEG changes, it has been shown that the depth of anesthesia is deeper in older patients and that a smaller dose of propofol is sufficient to maintain the depth of anesthesia in elderly patients [17][18].

Although propofol is largely metabolized by the liver [8] and kidneys [19], the size and capacity of both organs in obese patients are equal to those in nonobese patients. This indicates that the rate of propofol metabolism is lower in obese patients, especially when the propofol dose is determined based on the amount per body weight. In addition, obesity may cause fatty degeneration of the liver and/or glomerular injury of the kidneys, possibly leading to a reduction in propofol elimination [20]. Thus, the difficulty in performing sedation increases with increasing body mass index.

Systemic clearance of propofol decreased by up to 42% in the anhepatic phase in patients revived after reperfusion of the liver during living donor liver transplantation [8]. However, total body clearance was not significantly reduced in patients with liver cirrhosis compared with that in control patients [21][22], suggesting that patients with liver cirrhosis may be able to eliminate propofol via an extrahepatic mechanism. As one-third of the total body clearance of propofol is reportedly shared by the kidneys [23], they are relatively important for the extrahepatic elimination of propofol. In contrast, propofol has been reported to ameliorate liver dysfunction in animal experiments [24], suggesting that propofol may be favorable for sedation in patients with reduced liver function.

Liver blood flow, but not CO, is a predictive indicator of propofol clearance in critically ill patients [25]. Although liver blood flow changes in response to food intake [26], no relationship was observed between liver blood flow and CO in experiments using normal dogs that ate meals and exercised on a treadmill [27]. This indicates that liver blood flow affects the metabolism of propofol to some extent, independently of CO. Consequently, propofol can be eliminated in patients with deteriorated liver and normal kidney functions. Moreover, if the liver blood flow can be easily measured, it may enable a more accurate prediction of the rate of propofol metabolism.

As described above, the kidney is another organ responsible for propofol elimination. However, in an experiment involving the induction of general anesthesia in patients with end-stage kidney disease, the effect site concentration of propofol at the time of loss of consciousness was lower, but the difference was not statistically significant [28]. Therefore, a similar or lower dose of propofol is recommended for the induction of general anesthesia in patients with end-stage kidney disease [28]. This is partly because most propofol is metabolized in the liver and the metabolites do not have pharmacological effects. In contrast, another study recommended a higher dose of propofol for the same purpose [29], suggesting that propofol can be safely used in patients with kidney dysfunction. However, increased CO was shown to eliminate plasma propofol in pigs; thus, the lungs and muscles may also contribute to propofol elimination [7]. Therefore, propofol can be safely used in patients with decreased renal function; however, its elimination in patients with reduced liver and kidney function remains unclear. CO is considered to affect the metabolism of rather than renal function.

3. Midazolam

Although midazolam is a relatively short-acting benzodiazepine, its metabolism and elimination times are longer than those of propofol. The effects of midazolam can be reversed by flumazenil [30], and both respiratory and circulatory depression have been reported to be lower than with propofol [31]. Furthermore, midazolam exhibits a stronger amnesic effect than propofol and dexmedetomidine in healthy individuals [32]. Thus, although midazolam is not a new anesthetic, it still has some advantages and is useful for sedation during dental treatments without requiring a syringe pump.

Obese patients have a higher volume of distribution after midazolam administration than healthy subjects, which suggests the possibility of lower blood midazolam levels after administration and slower recovery [33][34]. The clearance and volume of distribution were similar between elderly and adolescent patients; however, pharmacodynamic data showed significant differences between the two groups, indicating that a lower dose is sufficient to achieve sedation in elderly patients [35][36].

Patients with liver cirrhosis showed a distribution and protein binding comparable to those in healthy controls. However, the elimination time is significantly delayed in patients with cirrhosis; therefore, a lower dose of midazolam is recommended for such patients [37]. In patients with chronic kidney disease, most parameters, such as the free fraction, volume of distribution, and clearance, were higher than those in healthy volunteers [38]. Although the elimination half-life of midazolam was almost identical when the parameters were corrected for protein binding, a lower dose of midazolam was proposed for patients with chronic kidney disease. If additional sedative administration is required, propofol should be recommended.

Midazolam is metabolized by CYP3A4 into several metabolites, including the active metabolite alpha-hydroxymidazolam [39][40]. Drug interactions can reduce or increase CYP3A4 activity; however, their effects on CYP3A4 vary depending on the medicine, rather than the category of medicines. For example, the area under the curve (AUC) of midazolam is 2.6–8 times that noted after itraconazole, and the AUC after changing itraconazole to rifampicin was only 2.3% of that during itraconazole treatment [41]. In a group of macrolides, pretreatment with clarithromycin increased the AUC of oral midazolam; however, no such effect was observed for azithromycin [42]. Calcium channel blockers are very popular for controlling blood pressure, and both diltiazem and verapamil increase the AUC of oral midazolam 3–4-fold compared with placebos [43]. As described above, midazolam is very sensitive to CYP3A4 and can be used as a probe to determine whether the investigated drug is an inhibitor or inducer of CYP3A4 [40].

According to a study [44], moderate-to-severe disinhibition was observed in 19.5% of patients undergoing bronchoscopy under midazolam sedation. The study also found that depression, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), and high-dose midazolam administration were associated with disinhibition. However, it has been reported that EBUS-TBNA can be performed under conscious sedation with midazolam, with no complications and high patient satisfaction, using adequate surface anesthesia [45]. To avoid de-suppression during sedation, it is crucial to manage pain by providing sufficient local anesthesia.

4. Dexmedetomidine

Dexmedetomidine is an agonist of alpha 2 adrenergic receptors in the locus coeruleus and inhibits the activity of noradrenergic neurons in the central nervous system [46], which allows it to control fear and excitement and induce sedation with minimal respiratory depression. It is primarily used for intubated sedation in the ICU [47] and less commonly used for outpatient sedation because of its long elimination half-life [48]. However, combining dexmedetomidine with midazolam has also been studied to mitigate the disadvantages of dexmedetomidine [49]. Studies have also shown that dexmedetomidine can be used to provide sedation for implant surgery, resulting in lower pain levels and lower plasma levels of inflammatory cytokines than midazolam [50]. In a randomized controlled trial (RCT) comparing dexmedetomidine with midazolam, dexmedetomidine caused less anxiety at the same level of sedation [51]. Another RCT compared a combination of midazolam and dexmedetomidine to a combination of midazolam and propofol in terms of their effectiveness in preventing unexpected patient movements during dental surgery [52]. Therefore, dexmedetomidine is considered to provide stable and superior sedation during implant surgery. However, the long half-life of dexmedetomidine remains a concern for its use in sedation for dental treatment, as recovery time was not evaluated in these studies.

Owing to its “remarkably wide safety margins” [53], dexmedetomidine can be used in most dental patients. However, obesity can affect the effectiveness of sedatives, and although obesity itself does not affect the clearance of dexmedetomidine, obese patients tend to have higher plasma concentrations of the drug, suggesting that lean body mass should be used as a scaler for obese individuals [54]. Dexmedetomidine is metabolized in the liver through both glucuronidation and the cytochrome P450 system, and its clearance depends on hepatic blood flow, which can be impaired in patients with severe hepatic failure [55]. However, dexmedetomidine has also been suggested to exert a protective effect on the liver during hepatectomy [56]. Taken together, dexmedetomidine may safely provide stable sedation for implant surgery, although its long recovery time may be a concern for some patients and dentists.

5. Remimazolam

Remimazolam is a novel, ultra-short-acting intravenous benzodiazepine anesthetic [57]. According to a meta-analysis as a sedative for endoscopic procedures [58], remimazolam induces deeper sedation than midazolam but is slightly inferior to propofol. Additionally, it is safer to use than midazolam and propofol because of its minimal effects on respiratory and circulatory depression [58]. In a clinical study of patients with hepatic or renal impairment [59], the peak concentration after bolus intravenous injection of remimazolam was not affected by hepatic or renal impairment, the clearance of patients with severe hepatic impairment was reduced by 38.1%, and recovery was somewhat slower than in healthy subjects. In patients with renal impairment, plasma clearance was similar to that observed in healthy subjects. Remimazolam is metabolized by carboxylesterases 1A (CES-1A) in the hepatic metabolism, unlike other benzodiazepines, which are metabolized by the cytochrome p450 enzyme. Although CES-1A is known to be inhibited by alcohol, alcohol has reported to have no effect on remimazolam metabolism [60].

Furthermore, the effect of remimazolam can be reversed by flumazenil [61], a specific benzodiazepine receptor antagonist. A randomized controlled trial comparing the use of remimazolam with midazolam for sedation during oral surgery found that remimazolam resulted in a higher success rate and earlier recovery [62]. Despite limited published research on the

use of remimazolam for sedation during implant surgery, it is expected to be a suitable sedative in clinical dental settings [63].

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