Review Article

Potential of ketamine use in sialendoscopy—a narrative review

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Background and Objective: Sialendoscopy is a procedure that is commonly used nowadays to both diagnose and treat salivary gland stones. Ketamine is a well-studied anesthetic that is known to induce hyper-salivation. We aim to review the current evidence surrounding possible synergistic usage of ketamine in sialendoscopy procedures as a sialagogue, anesthetic and analgesic agent.

Methods: A literature search was completed on PubMed, Embase, and CINAHL online databases using keywords "ketamine" and "sialendoscopy".

Key Content and Findings: The literature search did not reveal any studies that directly studied the possibility of using ketamine in sialendoscopy procedures. However, many articles were found on the diverse uses and the hyper-salivation side effect of ketamine as well as on the need for agents to increase success of identifying the orifice of salivary ducts during sialendoscopy procedures.

Conclusions: Ketamine is a promising anesthetic agent to use in sialendoscopy procedures over other agents given its analgesic and sialorrhea properties. Additionally, ketamine has a well-documented broad safety profile that makes it a favorable anesthetic for short procedures that would be beneficial in short procedures such as sialendoscopy. Future studies evaluating the safety and efficacy of ketamine in sialendoscopy procedures are needed to provide evidence that ketamine reduces need for opioid analgesics and increases procedural success due to hyper-salivation side effect.

Keywords: Opioid-free analgesic; sialorrhea; ketamine; sialendoscopy

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Introduction

Background

Ketamine was first introduced as a human anesthetic in the 1960s by Corssen and Domino, and is now one of the most widely used anesthetic agent to this day (1). Ketamine is a noncompetitive antagonist at the N-methyl-D-aspartate (NMDA) receptor. The widely available form used today for anesthesia is a racemic mixture of two isomers, R (–) and S (+). The S (+) form binds more strongly to NMDA receptors and is largely the driving isomer for the anesthetic effects of ketamine, while the R (–) form has been shown to elicit a sustained antidepressant effect (2).

Ketamine is often favored as an anesthetic option because it has a relatively stable effect on systemic vascular resistance. It also does not cause significant respiratory depression and preserves upper airway reflexes during anesthesia (1). Additionally, ketamine has been found to induce sialorrhea, or hypersalivation. While this raised some concerns about potentially increased risk of laryngospasms, these concerns have yet to be validated by scientific evidence (3). It is not entirely clear whether this side effect is dose dependent, as current literature demonstrates conflicting evidence (4,5). Nevertheless, the

Table 1 The search strategy summary

Items	Specification
Date of search	August 1, 2022–August 29, 2022
Databases and other sources searched	PubMed, Embase, CINAHL
Search terms used	Keywords: ketamine, sialendoscopy
Timeframe	No limitations
Inclusion and exclusion criteria	No language or study type restrictions
Selection process	No restrictions

effect of sialorrhea raises the possibility of synergistic use of ketamine in sialendoscopy.

Sialendoscopy, a minimally invasive technique for salivary gland surgery, was first proposed by Katz in 1991 (6). With subsequent improvement in equipment and techniques, sialendoscopy is increasingly used to diagnose and treat salivary gland stones, known as sialoliths. Sialoliths can form in major (i.e., parotid, submandibular or sublingual) or minor salivary glands. The cause of salivary gland stones is not fully understood, though saliva composition, duct anatomy, foreign bodies are thought to contribute to their formation (7). Most commonly, these stones are formed in the submandibular gland because the saliva there has a higher concentration of calcium and has a more alkaline pH than other salivary glands (8,9). Additionally, the route of the submandibular gland ducts is the most tortuous—running from the angle of the mandible to the base of the tongue—which predisposes this gland to relative stasis and therefore increased risk of stone formation.

Rationale and knowledge gap

Oral and maxillofacial surgeons (OMSs) frequently employ sialendoscopy to treat salivary gland pathologies in patients who fail conservative therapies (i.e., hydration, sialagogue usage, gland massage). These procedures can be done either in the clinic under IV sedation or in the operating room under general anesthesia (10). In the following, we examine the current evidence regarding the usage of ketamine in sialendoscopy. To our knowledge, there are no currently published studies to this end.

Objective

We aim to evaluate the evidence around the hyper-salivatory and perioperative analgesic effects of ketamine, and how they might be synergistically applied for sialoendoscopy. We present this article in accordance with the Narrative Review reporting checklist (available at https://joma.amegroups.com/article/view/10.21037/joma-22-28/rc).

Methods

A literature search was completed on PubMed, Embase, and CINAHL online databases using keywords "ketamine" and "sialendoscopy" in August 2022 (*Table 1*). Our inclusion criteria were studies of any type that provided evidence for the use of ketamine over other anesthetic agents in sialendoscopy procedures. No language or date limitations were set. While no articles that directly studied the use of ketamine in sialendoscopy were found, we did identify a number of studies regarding the diverse uses of ketamine in various clinical settings, as well as a number of studies that leveraged sialagogues in sialendoscopy. These findings further promote the synergistic potential of ketamine use in sialendoscopy.

Discussion

Sialorrhea in sialendoscopy

Ketamine has long been known to cause sialorrhea (1). Often, atropine is given intra-operatively in conjunction with ketamine to mitigate this side effect (5). The mechanism of action of sialorrhea is unclear. M1 and M3 are the known major acetylcholine receptors in the salivary gland. A study demonstrated decreased salivation in mice with both M1 and M3 knockouts (11). Clinically, patients with dry mouth syndrome are treated with cholinomimetics such as pilocarpine and carbachol. Ketamine, on the other hand, has been shown to inhibit muscarinic acetylcholine receptors (12). As such, one might expect ketamine to

reduce rather than increase salivary flow. As such, this is an area that is poorly understood and an area that requires further research.

However, the hyper-salivatory effect of ketamine may be helpful in sialendoscopy, particularly for the first part of the procedure. Sialendoscopy involves two distinct phases: salivary duct access and intraductal exploration (13). Access is thought to be the most technique-sensitive and time-consuming portion of the procedure due to the delicate structure and variable location of the salivary gland papilla (14,15). Current techniques include use of guidewire to locate the duct followed by serial dilation that slide over the guidewire, addition of viscous lidocaine infiltration in the duct for hydro-dilatory effects, or even angiocath-guided insertion of the endoscope (16,17). Still, identifying the orifice remains a challenge. The ductal orifice is the narrowest aspect of the duct, measuring as small as 0.1–0.2 mm, for both the submandibular and parotid gland (14,18). In this setting, ketamine could be helpful as a sialagogue. One study demonstrated increased visibility of the submandibular duct from 63% to 95% with the application of oral ascorbic acid (vitamin C) and another with lemon juice (19,20). Even if the duct in question is completely obstructed, there may be some benefit in using sialagogues to better identify the contralateral duct as a reference. Once the duct is accessed, it is explored for pathology. At any point, if hypersalivation needs to be reduced, glycopyrrolate can be given to the patient to minimize secretions.

Perioperative analgesic effects of ketamine

Ketamine has a noticeable analgesic action at small doses (defined as less than 1 mg/kg when administered intravenously) (21,22). Ketamine does so through both analgesic and anti-hyperalgesia properties at the NMDA receptor level (23). Additionally, ketamine has been shown to be more effective if given before noxious stimulus (24). This effect is referred to as "preemptive analgesia", meaning that the memory of pain is reduced, thereby also decreasing the need for post-operative pain medications. As such, ketamine given prior to sialendoscopy procedures may be helpful in supplementing intraoperative local anesthesia and reducing post-operative pain (25-27).

Currently, there are no widely used guidelines within OMS regarding post-sialendoscopy pain control. Studies suggest that this procedure is generally well tolerated by patients and that patients can typically resume daily life immediately post-operatively (28,29). Pain control regimens may consist of mostly over-the-counter analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen. Nevertheless, opioids may also be prescribed by some OMSs for patients who are more sensitive or on a "just-in-case" basis (30). After all, OMSs commonly prescribe short courses of opioids after other office-based procedures, such as third molar extraction and orthognathic surgery (31,32). To this end, ketamine may be particularly helpful in helping mitigate the post-operative pain level and possibly reduce the need for opioids.

Safety of ketamine for OMS

Ketamine is a well-studied drug that has been shown to be able to provide adequate sedation without compromising the airway (1,33). It is a common agent used in procedural sedation in OMS offices and also the emergency department for this reason (34-36). Regarding sialendoscopy specifically, completing the procedure in the office setting and the operating room had no significant differences in clinical outcomes (10,37,38). Furthermore, a recent study found that the mean total time burden of in-office sialendoscopy was 39 versus 278 minutes for the OR, corresponding to an average total procedure charge of $720 versus $13,956 (37). As such, when clinically feasible, in-office IV sedation for sialendoscopy should be considered.

Limitations and future study

While the usage of ketamine in sialendoscopy is promising, there remain limitations that should be considered. Ketamine has other known side effects, such as psychiatric disturbances in mood state and body image, floating sensations, vivid dreams or illusions, and occasional frank delirium during emergence. These side effects can be minimized by the administration of a benzodiazepine (39). There are also patients for whom ketamine use is contraindicated, such as those with renal or hepatic dysfunction (40).

Nevertheless, ketamine remains a promising choice that warrants investigation for safety and efficacy of usage in sialendoscopy. Studies can evaluate the effect of ketamine use on OMSs perceptions of procedural difficulty that are then corroborated with procedural duration. On the patient side, studies can evaluate the effect of ketamine use on post-operative pain levels in sialendoscopy. Further, these studies may elucidate other potential complications specific to sialendoscopy, persistent sialorrhea after

identifying the duct of interest or poor patient experience due to psychiatric side effects of ketamine. Ultimately, it will be helpful to build standardized guidelines across OMS regarding the benefits and drawbacks of employing ketamine in sialendoscopy.

Conclusions

Ketamine's effects of hypersalivation and analgesia, along with its broad safety profile, make it a potentially synergistic anesthetic to use in sialendoscopy. Possible benefits range from shortening procedure times to improving patient pain levels. As such, future studies evaluating the safety and efficacy of ketamine use in sialendoscopy are strongly indicated and can be influential in shaping future standards of practice.

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