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Effect of intravenous clonidine on postoperative agitation and recovery time after tonsillectomy

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Abstract: Tonsillectomy is routinely performed in most hospitals, both in adult and pediatric patients. A main objective of anesthesia care for these procedures is swift and comfortable recovery, permitting rapid discharge from the Post Anesthesia Care Unit (PACU). In preventing agitation, overall experience as well as rebleeding risk and the length of stay (LOS) in the PACU stand to improve. Clonidine is known for having an anxiolytic, sedative and analgesic effect, as well as for reducing postoperative vomiting in children. At our department, anesthesia consists of propofol/sufentanil/sevoflurane anesthesia, and paracetamol/diclofenac analgesia. Some anesthetists routinely give additional clonidine 1 mcg·kg^{-1} to children for tonsillectomy, others never do. This retrospective study evaluates the effect of intravenous clonidine on agitation and recovery time following tonsillectomy in different age groups. Out of all consecutive tonsillectomy cases between 1/2016 and 11/2018, a convenience sample of 473 patients was selected and included in this retrospective analysis. Of 473 included patients, 383 did not receive clonidine perioperatively and 90 did. Agitation was defined as a Ramsay Sedation Scale score of 1. In pediatric patients (<18 years), clonidine produced a relative risk reduction of agitation of 35.7% (p=0.235). We found a reduction in LOS in both pediatric and adult patients, of 5 and 11 minutes respectively (p=0.242 and p=0.262). Clonidine seems to reduce agitation and LOS in the PACU when administered perioperatively in patients undergoing tonsillectomy. A sample size calculation shows 463 patients are required in each group to achieve power of 95%. Because of the retrospective nature of our study, with its inherent risk of confounding factors, our findings should be confirmed in prospective studies.

Keywords: Clonidine; emergence delirium; tonsillectomy; anesthesia; recovery room.

Introduction

1. Tonsillectomy

Tonsillectomy is a routine procedure in most hospitals, both in adult and pediatric patients. It is one of the most commonly performed surgical procedures in the pediatric age group worldwide (1). Although it is often planned in an outpatient setting, it is not without risks. A review by Brigger et al. found that 8.9% of pediatric patients experienced complications within the first 24 hours after surgery, including bleeding, respiratory distress, vomiting, poor pain control and need for admittance for overnight observation. The complication rate was found to be even higher (12.3%) when the study data of children aged three and younger were used as a subgroup for separate analysis (2).

Adequate anesthesia of tonsillectomy patients should focus on maintaining the airway, optimizing analgesia, fast and uneventful recovery and prevention of postoperative hemorrhage (1). Due to the robust vascular supply of the tonsils, the latter is the most serious complication. It can occur within 24 hours (primary hemorrhage) or up to 28 days after surgery (secondary hemorrhage) (3-5). Research by Ravi and Howell states that post-tonsillectomy hemorrhage occurs in 3.5%, causing an overall return to the operating room in 0.9%. Bleeding is associated with hypovolemia, an increased risk of aspiration and a potentially difficult intubation (3).

Factors contributing to bleeding are varied. Hemorrhaging is seen more frequently in adults than in children (3, 5, 6). Within the pediatric group, age is also a risk factor, with children over the age of six being more at risk for secondary hemorrhage (4, 6). Inexperience of the surgeon (less than five years of experience) is significantly associated with primary hemorrhage. No significant difference was

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found in sex, starting time of the surgery or monthly average air temperature when looking at pediatric cases (4). In adults, male patients and smokers seem to be more at risk (6). Studies disagree on the influence of the indication for surgery. Some claim that recurrent tonsillitis is associated with higher risk than obstructive symptoms (3, 5, 6), and others find no such correlation (4). Authors also disagree on the influence of the surgical technique used. Xu et al. found a significant increase in primary hemorrhage when comparing coblation - or 'controlled ablation', in which the patient's tonsils are removed by destroying the surrounding tissues that attach them to the pharynx – to monopolar electrical tonsillectomy (4). Other authors observed more bleeding with the use of diathermy, less with blunt dissection (1, 3). A 2017 review by Francis et al. concluded that bleeding was similarly low in most common techniques (5).

Apart from bleeding, patients undergoing tonsillectomy, especially young people, are more likely to suffer from agitation in the Post Anesthesia Care Unit (PACU) (7, 8). A lot of investigations that look into emergence agitation (EA) focus on surgery in the ear, nose, and throat (ENT) area (7, 9). This may be due to the investigators' suspicion that this population is at increased risk for agitation. Data compiled by Voepel-Lewis et al. demonstrates that ENT surgery is indeed associated with a higher risk of emergence agitation. There is no solid evidence to determine why this is the case, but a "sense of suffocation" has been suggested as a contributing factor (7).

2. Emergence agitation

Emergence agitation refers to a common (10-80% in pediatric patients) (10) condition, characterized by psychomotor agitation, excessive motor activity, and perceptual disturbances in the early post-anesthetic period. It can both be caused by pain, as well as be mistaken for it. It is associated with pre-existing anxiety and physiological factors such as hypoxemia, hypercapnia, sepsis, residual medication effects, electrolyte imbalance and hypoglycemia (10, 11).

Forty-two percent of pediatric anesthetists consider EA to be a troublesome clinical situation and 45% use medication to prevent it (10). Although they are usually short-lived and resolve spontaneously, EA events put patients at risk of self-injury or can lead to injury to the attending staff. They can provoke bleeding at the surgical site, accidental removal of drains or intravenous catheters, respiratory depression, and delayed discharge. They require additional attention, which puts a strain on nursing staff, and can increase medical costs. They also lower patient and parent satisfaction (10-13). In adults, emergence agitation is strongly associated with postoperative delirium, which can lead to prolonged hospital stay and an increase in morbidity and mortality (12, 14).

A precise pathophysiological explanation for the phenomenon of EA has not yet been found. Several factors are thought to promote EA in children undergoing surgery, such as high levels of anxiety, the new environment, separation from parents or caregivers, and encounters with the unfamiliar faces of nursing and medical staff (12).

An important factor in EA is the anesthetic technique. The widespread use of newer volatile anesthetics such as sevoflurane and desflurane, as opposed to older agents such as halothane, or total intravenous anesthetics (TIVA) is linked to a higher incidence of EA (10, 15). Sevoflurane and desflurane are successfully used for anesthesia in both adults and children, but they are both low-solubility inhalational anesthetics, with a short washout time. This is a contributing factor to an early arousal post procedure, which can promote EA through disinhibition-excitement (10, 12). In addition, sevoflurane induces sharp slow waves in the electroencephalogram (EEG), which are also seen in epilepsy. This stimulation of the central nervous system might contribute independently to EA in patients receiving sevoflurane (7, 10, 12).

As a way to measure sedation and agitation, multiple sedation scores exist, a lot of which were originally intended for use in the Intensive Care Unit (ICU). One of these is the Ramsay Sedation Score (table 1), which originated in 1974. It is still one of the most commonly used scores today to monitor the level of sedation in ICU and shows a good correlation with objective methods such as the Bispectral Index (BIS) (16, 17). It has been adopted to score agitation and alertness in postoperative patients at the PACU.

Table 1

Ramsay sedation score [16]

Ramsay sedation score
Awake 1. Patient is anxious, agitated or restless 2. Patient is cooperative, orientated or tranquil 3. Patient responds to command only
Asleep levels depend on the patient's response to a light glabellar tap 4. Brisk response 5. Sluggish response 6. No response

To treat or prevent EA in children, several modes of action have been suggested. A number of non-pharmacological interventions has been tried, including age-appropriate educational materials, paternal presence at induction or emergence, and distraction. The evidence supporting these techniques is not conclusive. Parental presence at emergence has no proven effect on EA (10), while parental presence at induction yields conflicting results (10). Trials have also been conducted using pharmacological interventions such as dexmedetomidine, fentanyl, ketamine, clonidine and benzodiazepines, most prominently midazolam, but a gold standard has yet to be set (10, 18).

3. Clonidine

Clonidine is well known for its antihypertensive effect. Additionally, it has an anxiolytic, sedative and analgesic effect. This multitude of separate, often beneficial effects has led to an increase in popularity with anesthesiologists worldwide (9, 11, 19, 20).

Clonidine is a mixed α_1 and α_2-receptor agonist, with a predominant α_2 action. Its main effect is sympatholytic, reducing norepinephrine release by stimulation of prejunctional α_2-adrenoreceptors, which have an inhibitory effect (19, 21). The sedative effect of clonidine is due to its action on the locus coeruleus in the brainstem, which has a high density of α_2-receptors (9, 22). Upon binding to the receptor, clonidine causes a hyperpolarization of noradrenergic signaling to the ventrolateral preoptic area. This region of the brain is active during sleep and releases inhibitory neurotransmitters such as GABA and galanin, which inhibit the neurons of the ascending arousal system that play a part in alertness and arousal (9, 22).

Clonidine administration has long been successfully used for prophylaxis and treatment of agitation in adult ICU patients and has been proposed as a potential method to prevent postoperative agitation (22, 23). When used as premedication in children, a dose of 4 mcg·kg^{-1} orally or intranasally and 5 mcg·kg^{-1} rectally, clonidine provides adequate sedation (19). Upon comparison to midazolam, a slower onset of sedation was seen with clonidine (38 ± 15 minutes vs 30 ± 13 minutes), but the quality of sedation was better with clonidine, and parental satisfaction was markedly higher (19). A possible reason for the former could be the more pronounced sympatholytic effect and the added analgesic properties of clonidine (19). Midazolam sometimes induces paradoxical agitation and hallucinations, both of which can be resolved by the administration of clonidine (19).

The main side-effects of clonidine are bradycardia and hypotension, most often seen with higher doses or during continued administration (24, 25). The mechanism responsible for this is stimulation of α_2-adrenergic inhibitory neurons in the medullary vasomotor center, leading to a decrease in sympathetic nervous system activity. This manifests itself as peripheral vasodilation and a decrease in systolic blood pressure, heart rate and cardiac output (19). When used cautiously, this side-effect may be wielded to the benefit of the surgeon. Premedication with oral clonidine has been shown to reduce intraoperative bleeding and can be beneficial in procedures where a bloodless surgical field is preferred, such as neurosurgical, major orthopedic, ear, nasal surgery or tonsillectomy (22, 26).

Some authors suggest that clonidine might delay PACU discharge due to prolonged postoperative sedation (23). This observation is a matter of debate and appears to depend on dosage, with some authors finding no increase in length of stay, (27, 28) while others do (11).

Another concern surrounding perioperative use of clonidine is profound postoperative respiratory depression. This, however, seems to be unfounded. Clonidine decreases oxygen consumption and adrenergic stress response in the postoperative period. Although it mildly potentiates opiate-induced respiratory depression, clonidine on its own account does not induce severe respiratory depression (19, 29).

When administered intravenously, clonidine improves the analgesic effect of anti-inflammatory agents. Combined usage with local anesthetics, opioids and ketamine also has a potent antinociceptive effect (19). In combination with non-steroidal anti-inflammatory drugs (NSAIDs), Reimer et al. found clonidine to be an effective analgesic in children undergoing (adeno)tonsillectomy. Compared to fentanyl, clonidine produced similar low visual analog pain scores (VAS), without a higher incidence of side effects or a difference in the number of morphine or codeine rescue doses administered (19).

The anti-emetic effect of clonidine, though perhaps not as well-known, has been proven in multiple studies (19). Alizadeh et al found that administration of oral clonidine (4 mcg·kg$^{-1)}$ had a beneficial effect on postoperative nausea and vomiting (PONV) in children who underwent appendectomy. In 76.7% of patients who received clonidine, no PONV was seen, compared to

23.3% in the control group (p<0,001). Patients in the clonidine group also needed substantially less rescue antiemetics (10% vs 19.3%, p<0.001) (30). Similar findings were reported by Taheri et al., when looking at adults undergoing outpatient ear surgery. They observed a complete response (no PONV and no need for rescue antiemetic medication, during the first 24 hours after anesthesia) in 33% of the control group, compared to 67% of the clonidine group (p 0.01) (31).

4. Goal of the study

By reviewing the results of 473 patients who underwent a tonsillectomy in a three-year period, the aim of this study was to retrospectively evaluate the incidence of EA in our population, as well as the effect of the intraoperative administration of 1 mcg·kg^{-1} intravenous clonidine on agitation and recovery time in the patients age <18. We also wanted to determine the number of patients needed in each group to reach statistical significance. The use of these results in the sample size calculation thus provides the required information for subsequent research.

Methodology

1. Study protocol

The authors applied for institutional ethics committee approval (AZ Maria Middelares, Ghent, Belgium, reference number: B017201940595. Approved on 07/06/2019. Chairman of the committee: Germonpré P. MD). Following approval, a retrospective study was performed. Out of all tonsillectomy cases admitted to the Maria Middelares Hospital between January 2016 and November 2018, a convenience sample of 473 cases was selected. Several surgeons and anesthetists were involved in the procedures.

As per hospital protocol, no premedication was administered to any of the patients. In the case of pediatric patients, parents were allowed to accompany their child into the operation room up until the moment of loss of consciousness. Non-invasive monitoring was used in all cases, including pulse oximetry, capnography, oscillatory blood pressure measurement and electrocardiography. If considered to be of an appropriate age and level of maturity, patients underwent an intravenous catheter insertion and an intravenous induction with propofol was performed. In smaller children, we provided an inhalation induction with sevoflurane (either with or without addition of nitrous oxide), followed by insertion of an intravenous line. After oral intubation, patients were ventilated.

For maintenance of anesthesia, only sevoflurane was used. As determined by institutional protocol, analgesia was given, using weight-dependent doses of sufentanil (1 mcg·kg^{-1}), paracetamol (15 mg·kg^{-1}) and diclofenac (1 mg·kg^{-1}). Some anesthesiologists routinely administered clonidine 1 mcg·kg^{-1}, others never gave clonidine in this indication. All patients were weaned off the ventilator and extubated upon completion of the surgery. After extubation, patients were brought to the PACU, where they were monitored by the nursing staff until considered safe to discharge. In case of pediatric patients, one parent per child was allowed to stay in the recovery room as soon as the patient showed signs of arousal.

All anesthetic data was registered via automated anesthesia records, both in the operating theatre and in PACU. Postoperative sedation assessment was under hospital protocol recorded in all patients using the Ramsay Sedation Score (16) and captured in the electronic patient record. Likewise, the time of arrival at the PACU, as well as the time of reaching the institutional discharge criteria, was recorded in the electronic patient record.

2. Data analysis

All data was manually extracted from the electronic patient and anesthesia records. The data was subsequently imported into Microsoft Excel 16.0 (Microsoft, Redmond, USA) and analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). EA was defined as a Ramsay Sedation Score of 1. In addition, the time between arrival at the PACU and reaching the objective discharge criteria was computed as the number of minutes between the manually registered PACU discharge and admission time. Patients were stratified into two age groups : children (age 1-17) and adults (age ≥18).

In a first analysis, the incidence (95% confidence intervals) of EA and average (SD) time to reach discharge criteria was determined in both age groups. For this overall assessment, the data were analyzed for both the patients that did receive clonidine and the patients that did not receive clonidine in the respective age groups.

For adult patients, only time to reach discharge criteria was used in the further analysis because the incidence of EA was expected to be low, and – most importantly – in adult patients, many anesthetists only administer clonidine in patients with a known history of EA. As such, this was considered a major

confounder that renders any further analysis in the adult age group unreliable.

In the patients age <18, based on the incidence of EA in those who received clonidine (*Ic*) and patients who did not receive clonidine (*Iu*), the relative risk reduction was calculated as follows: (*Iu - Ic.)/Iu*

Normality of continuous variables was tested with Kolmogorov-Smirnov test and the level of significance was set as *P<0.05*. Unpaired two-sided T-tests were used to assess statistical significance of the difference in the time to reach discharge criteria. A Chi squared test was used to assess statistical significance of the difference in EA.

Upon finding promising results, that lacked statistical significance, we used our results for average time to reach discharge criteria to perform a sample size calculation using G*Power 3.1 (32).

Results

No patients were excluded from analysis. Of 473 included patients, 383 did not receive clonidine perioperatively and 90 did. Table 2 shows the number of patients in each of the groups.

Table 2

Number of patients in each group

	Clonidine			
	Clonidine -		Clonidine +	
	Agitation		Agitation	
	No	Yes	No	Yes
Age 1-17	200	41	57	7
Age ≥ 18	136	6	26	0

Table 3

Average (SD) time to reach discharge criteria in children and adults who received clonidine (clonidine +) or did not receive clonidine (clonidine -)

Time to reach discharge criteria (min)		
	Clonidine -	Clonidine +
Age 1-17	40 (25)	35 (21)
Age ≥ 18	64 (46)	53 (46)

The overall incidence of EA in children was 15.7%. The incidence of EA in adults was 3.6%. In the pediatric group, 10.9% of patients who received clonidine were agitated (95%CI 3.2-18.5%), compared to 17% (95% CI 12.2-21.7%) in the control group. No adults who had received clonidine were agitated, compared to 4.2% of those in the control group (95%CI 0.9%-7.5%). In pediatric patients (<18 years), clonidine produced a risk reduction of 35.7% (p=0.235) for EA.

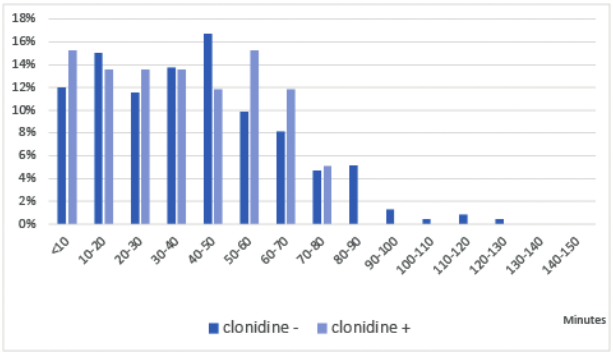

Fig. 1. — Time to reach discharge criteria in patients age <18, in 10 minute intervals (%).

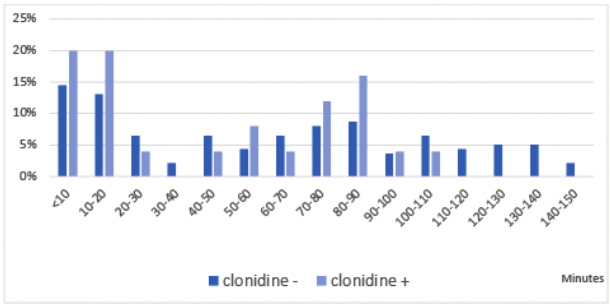

Fig. 2. — Time to reach discharge criteria in patients age ≥18, in 10 minute intervals (%).

The average time to reach discharge criteria in either age group is shown in table 3. Clonidine reduced the time to reach discharge criteria by 12.5% (p=0.242) in children and by 17.1% (p=0.262) in adults. The percentage of patients who have reached discharge criteria per 10 minutes is shown in figures 1 and 2.

For the sample size calculation, we found that in order to detect a difference with an α-error of 0.05 and a power of 0.95, 463 patients will be needed in each group, amounting to a total of 926.

Discussion and Conclusion

In our population, the incidence of EA in adults is significantly lower than in children (3.6% vs. 15.7%). This is consistent with the literature. The incidence of EA after general anesthesia varies widely among different studies in adults (0.25-19%) (14, 33). The incidence of EA in children also varies, but is significantly higher (2-80%) (23, 34).

All of our patients received sevoflurane as a maintenance anesthetic, with or without the addition of nitrous oxide for induction. Sevoflurane and desflurane are associated with more emergence delirium than older agents, such as isoflurane or

halothane (9, 10, 22, 28). Costi et al. examined the effect of different interventions on the occurrence of EA. They failed to detect a difference between sevoflurane and desflurane, but did find more EA with these agents than with halothane and propofol (35). Subsequent studies also showed no difference in incidence or severity of EA (15, 36). A 2015 meta-analysis in pediatric patients found less frequent EA with desflurane use than with sevoflurane (12, 37). Likewise, a randomized controlled trial in adults also found less agitation with desflurane. Possible contributing factors for this may be elevated lactate and glucose concentrations in the parietal cortex due to sevoflurane anesthesia, and the occurrence of clinically silent epileptogenic activity with sevoflurane (7, 10, 12, 36).

Nitrous oxide (N_2O) is commonly used for the induction and maintenance of anesthesia in children, combined with other inhalational anesthetics. There appears to be no association with emergence agitation (12, 33). Some studies have even found an attenuating effect of N_2O on EA in pediatric patients, despite its rapid washout time (12, 38). To reliably determine the association between N_2O use and EA, more research would be needed, although several medical and environmental concerns are considered convincing grounds to discourage its use (39).

Our results suggest that clonidine at 1 mcg·kg^{-1} is associated with less agitation, both in adults and children. Several studies show a positive effect of clonidine on EA, but there is little consensus on the optimal dosage. Kulka et al showed that peroperative clonidine at 2 mcg·kg^{-1} body weight IV has a positive effect on amplitude and prevention of agitation in young children, with no prolongation of LOS in the PACU (28). This absence of prolonged LOS is also found by Bock et al. after use of 3 mcg·kg^{-1} IV, (27). but Ydemann et al. on the other hand, noticed an increased LOS for the same dose (11). Other studies also note a negative effect on LOS in the PACU, related to excessive postoperative sedation (9, 40). In a study by Bergendahl et al. this drowsiness was also demonstrated after rectal clonidine (5 mcg·kg^{-1}) in children undergoing adeno-tonsillectomy. However, the parents of the children in this study mentioned a preference for a sleepy and calm child after the procedure, rather than an alert and agitated child. PACU nurses also prefer a child who sleeps a little longer but can be discharged smoothly afterwards to a child who wakes up fast but is agitated. The underlying reason for this is that an agitated child is more at risk for self-injury and requires more attention, care and medical interventions from the staff (10, 11). An important note in this regard is that pronounced sleepiness caused by clonidine at an adequate dose is not related to serious side effects such as respiratory depression (18, 40).

Using 1 mcg·kg^{-1} body weight, we notice a shortening in length of stay in the PACU. Furthermore, when looking at the patients who spend the longest time in the PACU, we notice they tend to belong to the group who did not receive clonidine. Several explanations are possible. Because of its suppressive effect on the sympathetic nervous system, clonidine is associated with lower blood pressures in the PACU, which may contribute to a lower bleeding risk after tonsillectomy (28). Previous research has also shown that preoperative peroral administration of clonidine at 4 mcg·kg^{-1}, or intraoperative administration of 3 mcg·kg^{-1} IV provides a reduction in PONV, compared to placebo or midazolam (11, 22, 25). This in itself may contribute to a shorter LOS in the PACU, but also to a lower bleeding risk, as avoiding gag reflexes and as such Valsalva maneuvers, will result in less oozing. This effect could be further enhanced by the analgesic and anxiolytic effect of clonidine and the reduction of agitation (1, 20). It is possible that the patients in our control group who spent a longer time in the PACU had higher pain scores upon awakening, and needed more analgetics before they could be discharged. In our study, no separate data was collected regarding PONV or bleeding.

A possible limitation of our study is the use of the Ramsay Sedation Score. This might not be the ideal tool for assessment of agitation. Upon comparing the Ramsay Sedation Scale to the Richmond Agitation Sedation Scale (RASS) in adult ICU patients, Rasheed et al. found weak interrater agreement with use of the Ramsay scale. In comparison, the RASS showed excellent interrater agreement and a consistent agreement with clinical observation and practice among different observers. This suggests that use of the RASS may result in a more reliable assessment of sedation levels (17). Furthermore, although the Ramsay scale is convenient for reliable recording of the patient's mental state in clinical routine, it has limited ranking for agitation status and levels of restlessness; one score only describes agitation (16, 17). While the Ramsay scale has been used both in pediatric ICU and children in PACU, there may be other scoring systems that are better suited to assess sedation and agitation in children, such as the Pediatric Anesthesia Emergence Delirium (PAED) scale (12). As such, we would advocate that in prospective studies, such scales would be more appropriate.

Undergoing (adeno)tonsillectomy is associated with increased incidence of EA (41). In our population, we observed a positive effect of clonidine 1 mcg·kg^{-1} on the incidence of agitation. Notably, although prolonged LOS is one of the most mentioned side effects, we observed the opposite with a faster discharge from the PACU in the clonidine group. The reason for this faster recovery after anesthesia needs to be investigated in further research, but we can speculate that if the patients – be it after some delay – wake up gently, and relatively pain-free, they can leave the PACU faster than patients who wake up very quickly, suffering from pain and agitation, and subsequently must be managed pain-free before they can be discharged.

Our study has a number of limitations. Firstly, the number of patients who received clonidine was relatively low compared to the control group. Furthermore, our results seem promising, but failed to reach statistical significance, most likely due to our small sample size. We will attempt to remedy this by further inclusion of patients. In order to assess the amount needed, we have performed a sample size calculation using time to reach discharge criteria. Given the retrospective nature of our study, we believe this variable best incorporates all possible effects – positive and negative – of clonidine that may affect the quality of postoperative recovery. Finally, because of the limitations of a retrospective study, with its inherent risk of undetected confounders, further prospective studies will be needed to confirm our findings.

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