Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE Open Access

Role of preemptive chlorpheniramine maleate in reducing postoperative agitation after functional endoscopic sinus surgeries (FESS)

Tamer Nabil Abdelrahman* and Amr Ahmed Kasem

Abstract

Background: Agitation with general anesthesia for ear, nose, and throat (ENT) surgeries was so frequent reaching up to 55.4%. Chlorpheniramine maleate a first-generation antihistaminic that antagonizes histamine H1-receptor. It is specifically a potent inverse agonist of the histamine H1 receptor. It is mainly used as an anti-allergic but has some anti-depressant and anti-anxiety actions, with unknown mechanism as well.
The aim is to identify the role of preemptive chlorpheniramine maleate on alleviating or reducing the severity of postoperative agitation following FESS procedures.

Subjects and methods: A total of 90 adult patients undergoing FESS procedure for chronic sinusitis with bilateral postoperative nasal packing. Patients were randomly assigned into two equal groups. The first group (A) 45 patients received chlorpheniramine maleate 5 mg diluted in 9 ml isotonic saline IV 30 min preinduction of general anesthesia while the second group (B) received 10 ml isotonic saline IV as control.

Statistical analysis: It was done using the Statistical Package for Social Sciences (SPSS/version 21) software using arithmetic mean, standard deviation, chi square test, Fisher exact test and *t* test. The level of significance was 0.05.

Results: The degree of agitation measured by (RASS) and the number of patients needed midazolam and its total dose given to reduce severity of agitation postoperatively was remarkably less in group (A) than group (B).

Conclusion: Preoperative single dose of chlorpheniramine maleate is an effective medication that may be used to prevent or reduce the severity of emergence agitation with minimal cardio-respiratory depression.

Keywords: Chlorpheniramine maleate, FESS, Postoperative agitation, Midazolam

Introduction

Emergence agitation is a postanesthetic incident that occurs in the early phase of recovery from general anesthesia, and is characterized by hyperactivity, confusion, disorientation, and possible violent behavior (Vlajkovic and Sindjelic 2007). The incidence of postoperative agitation is not uncommon with a higher incidence in the pediatric age group than in adults with incidence among adults reached up to 21.3%. The incidence of postoperative agitation with general anesthesia for ear, nose, and throat (ENT) surgeries was so frequent reaching up to 55.4% (Yu et al. 2010). Emergence agitation albeit brief but it can have hazardous consequences to both patients and recovery staff such as unplanned removal of endotracheal tubes, nasal packs, or catheters that may be complicated by desaturation, hemorrhage with danger of aspiration, and even falling out of the bed with resulting injuries. Furthermore, it necessitates the usage of additional drugs, resources, and may cause medical staff injuries (Pieters et al. 2010). Many variables were found to be significantly

* Correspondence: tamernabil610@gmail.com
Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain-Shams University, Cairo, Egypt

associated with emergence agitation such as younger age, recent smoking, sevoflurane anesthesia, postoperative pain, presence of a tracheal tube, and presence of a urinary catheter (Kim et al. 2015). In addition, patients undergoing nasal surgery suffer frequently from postoperative sense of suffocation due to intranasal packing both factors were attributed to induce agitation during emergence (Kim et al. 2015; Kim et al. 2013; Rim et al. 2016).

Many assessment tools had been designed and proposed to evaluate the degree of agitation/sedation that can be used in the postanesthesia care unit (PACU). The Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) were suggested by the Society of Critical Care Medicine to be the most valid and reliable agitation/sedation assessment tools due to their psychometric validity in critically ill patients (Barr et al. 2013).

Several pharmacological agents had been used to mitigate postoperative agitation, including opioids (fentanyl, remifentanil), propofol, benzodiazepines (midazolam), α_2-aderenoreceptor agonists (clonidine, dexmedetomidine), and N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine, magnesium sulfate) (Kim et al. 2013; Chen et al. 2013; Dahmani et al. 2010). It was found that a single bolus dose of midazolam, as a premedication, is not effective in preventing postoperative emergence agitation due to its short half-life. However, when 0.03 mg/kg midazolam was given as bolus dose at the end of surgery showed an effective response in preventing such agitation without delaying the emergence time in children having strabismus surgery with sevoflurane anesthesia (Cho et al. 2014).

Chlorpheniramine maleate is a first-generation antihistaminic that antagonizes histamine H1-receptor. It is specifically a potent inverse agonist of the histamine H1 receptor (Simons 2004). It is mainly used as an antiallergic but has some anti-depressant and anti-anxiety actions, with unknown mechanism as well (Simons 2004; Gruetter et al. 1992). The elimination half-life of chlorpheniramine ranges between 13.9 and 43.4 h in adults following a single dose in clinical studies (Yasuda et al. 1995). The use of chlorpheniramine maleate perioperatively was proved to affect the hemodynamics within 20% of basal levels, so it is safe to use in the view of hemodynamic changes (Hahm et al. 2006).

Aim of the work

The aim of the study is to identify the role of preoperative chlorpheniramine maleate on alleviating or reducing the severity of postoperative agitation following FESS procedures.

Patients and methods

This is a prospective, randomized, double-blind study carried out at Ain-Shams University Hospitals, Cairo, Egypt from January 2019 to May 2019. Randomization was done with the help of a computer-generated list of numbers. This study was approved by the Research Ethics Committee at the Faculty of Medicine, Ain Shams University Hospital, Cairo, Egypt (FAMSU R 01/2019). A written informed consent was obtained from all patients before the study. A total of 90 adult patients undergoing (FESS) procedure for chronic sinusitis with bilateral postoperative nasal packing. Patients were randomly assigned into two equal groups, 45 patients each by a computer-generated lists. The first groups of patients were assigned to the chlorpheniramine maleate group (A) and the second group patients were assigned to the placebo group (B). Group assignment, preparation, and administration of drugs were performed by a junior anesthetist who is neither involved nor interested by any means in the study. Blind grouping was kept to all including the patients themselves, until the completion of study.

Inclusion and exclusion criteria

The inclusion criteria of these patients included adult patients (age 21-50 years), class I-II according to American Society of Anesthesiologists (ASA) physical status subjected to FESS without septoplasty.

Exclusion criteria included patients below 21 years old or over 50 years old, patients with ASA physical status class III-IV, morbid obesity with body mass index (BMI) > 30 kg m^{-2} at initial hospital visit, history of neuropsychiatric ailment or chronic use of antipsychotic or sedative or drugs, severe cardiovascular disease, any coagulopathies, pregnancy, history of recent, or chronic use of antihistaminic drugs, history of relevant drug allergy, any possibility of anticipated difficult intubation.

Preoperative anesthetic assessment

All patients were subjected to a thorough medical history, physical examination together with thorough airway assessment by Mallampati classification (Mallampati et al. 1985), laboratory investigations (fasting blood sugar, kidney, liver function tests, serum electrolytes, coagulation profile, and electrocardiogram) preoperatively. They were also counseled about the anesthetic management and potential complications of both surgery and anesthesia, and the explanations of numerical pain analog scale (NAS) from 0-10. All these data was documented.

Anesthetic protocol

All patients were admitted to the operating room (OR) induction area where patients' identification were confirmed and 18-gage intravenous cannulae were inserted to all participants. The participants of group (A) received 5 mg chlorpheniramine maleate "Pirafene, Memphis

pharm. Co." diluted in 9 ml isotonic saline intravenous (IV) prior to induction of general anesthesia by 30 min while participants in group (B) received 10 ml isotonic saline (placebo) IV as control.

General anesthesia started for all patients with intravenous lignocaine 1.0 mg/kg, propofol 2.0 mg/kg, then atracurium 0.5 mg/kg, fentanyl 2 μg/kg then they were intubated orally which was fixed after confirmation of its place by auscultation then oral packing with wet gauze under vision using a laryngoscope. Anesthesia was maintained by mixture of oxygen (O_2) and air along with 2% sevoflurane then atracurium 0.1 mg/kg was given for maintenance of muscle relaxation. All patients received ranitidine 50 mg slowly IV, ondansetron 4 mg, and ketorolac tromethamine 30 mg diluted in 8 cc normal saline slowly IV over 5 min (Ketolac, Amiriya for Pharm. Ind.) immediately after intubation to control postoperative pain, nausea, and vomiting. All patients were monitored by standard monitors including, the pulse oximeter, non-invasive blood pressure, end-tidal carbon dioxide, and electrocardiogram. Hypotension if needed was done by intravenous infusion of nitroglycerine at a rate of 0.5 to 10 μg/kg/min titrated to target mean arterial blood pressure (Mbp) lesser than baseline preoperative values by 30% (i.e., 50-65 mmHg). At the end of the procedure, Mbp was restored to baseline preoperative value by stoppage of nitroglycerine infusion and administration of crystalloids (500 ml).

At the end of surgery and after installment of the nasal packs and upon attaining spontaneous breathing, muscle relaxant was antagonized by 50 μg/kg neostigmine and 10 μg/kg atropine, then thorough oral suctioning under vision with removal of the oral pack then awake extubation was done and the patients were transferred to the postanesthesia care unit PACU. Upon arrival to PACU, a pulse oximeter and noninvasive blood pressure (NIBP) monitors were attached to the patient. Discharge criteria from PACU was stable vital signs, pain score less than or equal to 2, no nausea or vomiting, calm and alert patient.

Postoperative analgesic regimen

It started immediately on arrival to the recovery unit where patients received acetaminophen 1 g IV and to be continued every 6 h postoperatively and 5 mg nalbuphine IV would be given if breakthrough pains (i.e., more than + 6 on NAS) until pain score ≤ 4 for the first 12 h postoperative. Nalbuphine consumed taking care not to exceed 5 mg at a time with drug lag of at least 2 h between 2 successive doses of rescue agent.

Patients assessment

All patients were assessed for the following:

1. The preinduction and postextubation mean arterial blood pressure (MbP)
2. The duration of surgery and anesthesia with time needed for extubation
3. Assessment of agitation

Postoperative agitation was assessed immediately after recovery inside OR and continued in the PACU by a blinded observer using the Richmond Agitation Sedation Scale (RASS) every 5 min for continuous 20 min (Sessler et al. 2002). In case of severe agitation with RASS ≥ 3 postoperatively patients were first reassured, if not enough to reduce patients' agitation, so midazolam 1 mg IV was given to reduce agitation with thorough follow-up of patient's respiration. It can be repeated every 5 min till agitation became obtunded (RASS ≤ 2) with continuous monitoring of the patients' respiration and following PACU discharge protocol. The number of patients that needed midazolam and the total dose of midazolam needed to control agitation were also recorded.

4. Assessment of pain

Pain intensity was assessed and recorded as a secondary outcome to our study starting at 30 min postoperative then at 2, 6, and 12 h postoperatively using the numerical analog scale (NAS) where 0 is no pain and 10 is the worst imaginable pain as rated by the patient. A blinded team member assessed pain and patients that exhibited no agitation were also evaluated for pain after 30 min of recovery. Nalbuphine was used as a rescue analgesic to ameliorate pain. The total number of participants needed rescue analgesia and the total dose needed during the first 12 h postoperatively were recorded and compared between both groups. We used nalbuphine after evaluation of agitation and assessment of pain to avoid perplex to the outcome measurement.

5. Assessment of postoperative complications

We compared between both groups regarding the respiratory rate immediately after extubation, the occurrence of desaturation or laryngospasm, postoperative nausea and vomiting, and the need to give antiemetic in the PACU.

The primary end point to this study was the occurrence of severe agitation not responding to reassurance and midazolam and endangering the patient, or the occurrence of severe hypoxemia, bleeding either nasal or oral, or the occurrence of postoperative atypical hypotension.

Results

This is a prospective comparative double-blind study that included a total of 90 consented adult patients

undergoing bilateral FESS procedure for chronic sinusitis with bilateral postoperative nasal packing. Patients were randomly divided equally into two groups, the first 45 patients were assigned to chlorpheniramine maleate group (A) (n = 45) and the other group to placebo group (B) (n = 45); all participants completed the trial (Fig. 1).

The demographic characteristics of the study participants are illustrated in Table 1. There were no statistically significant differences between the two groups regarding patients' age, body mass index (BMI), gender, American Society of Anesthesiology (ASA) physical status, and number of smokers (Table 1).

Comparing both groups' mean arterial blood pressure (MAP), there were no statistical differences either immediately preinduction or postextubation values of MAP (P = 0.111, 0.110 respectively). Comparing the total amount of nitroglycerine used to achieve hypotensive anesthesia and the total volume of fluids used intra-operatively revealed also statistically non-significant results (P = 0.081, 0.215 respectively), while comparing the duration of surgery and anesthesia together with the time needed for extubation in both groups showed non-significant statistical difference (P = 0.103, 0.210, 0.102 respectively) (Table 2).

Comparing the incidence of postoperative complications among both groups' patients like desaturation, laryngospasm, and nausea and vomiting and hence the need for antiemetics in postanesthesia care unit (PACU); there was no statistically relevant difference between both groups (Table 3).

Table 1 The demographic data and clinical characteristics of patients in group (A), and group (B)

Variable	Group A (n = 45)	Group B (n = 45)	P value
Age (years)			
Mean ± S.D.	32.20 ± 8.25	34.93 ± 8.47	0.062
BMI (kg/m^2)			
Mean ± S.D.	29.00 ± 2.94	29.84 ± 2.96	0.089
Gender			
Male/female	32 (71.1%)/13 (28.9)	30 (66.7%)/15 (33.3%)	0.327
ASA physical status			
I / II	30 (66.7%)/15 (33.3)	27 (60.0)/18 (40.0)	0.214
No. of smokers	27 (60%)	33 (73.3%)	0.23

According to RASS, the degree of agitation of both groups of patients immediately after recovery and continued in PACU at 5, 10, 15, and 20 postoperatively was remarkably lower in group (A) than group (B) with a statistically significant differences between both groups (P value = 0.008, 0.029, 0.001, 0.001, 0.001 respectively) (Fig. 2).

Regarding the number of patients needed dormicum and its total dose is given to reduce severity of agitation postoperative was remarkably less in group (A) than group (B) (P value 0.0027, 0.042) (Table 4).

Regarding postopertive pain assessment starting 30 min after recovery and at 2 h postoperatively, the VAS of both groups patients showed statistically significant difference between both groups (P value 0.011, 0.048

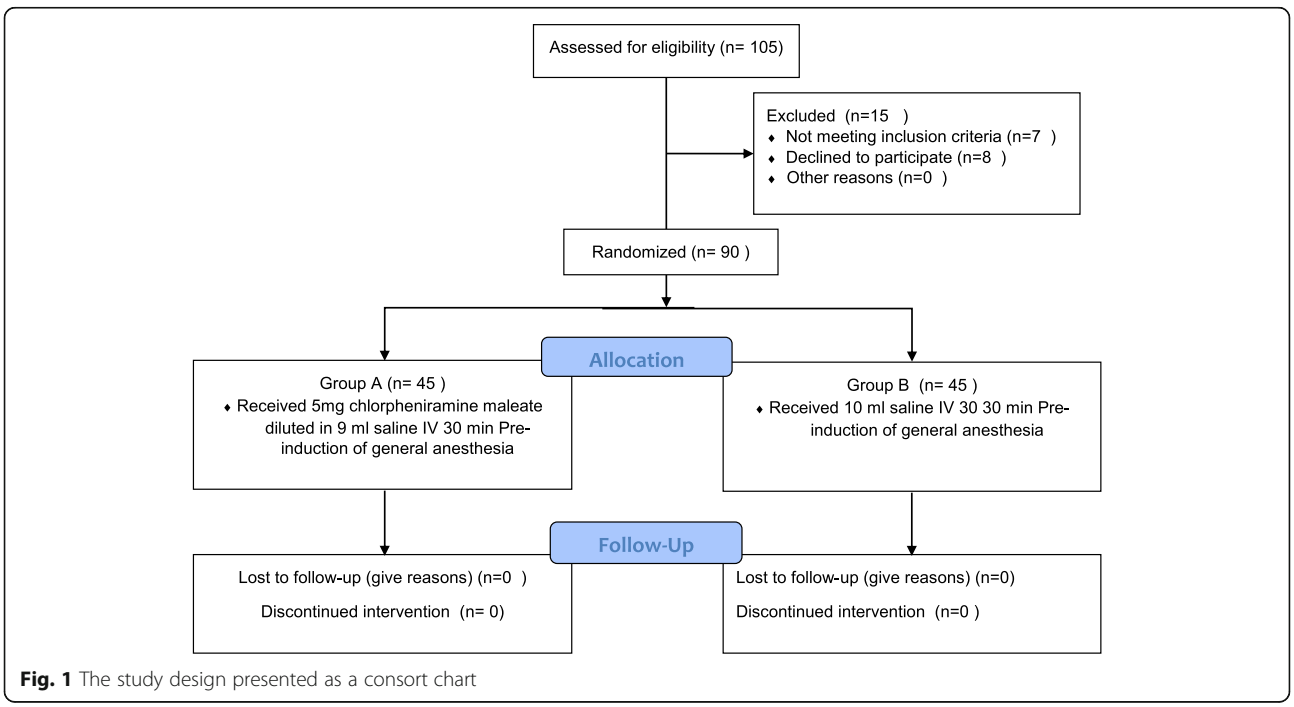

Fig. 1 The study design presented as a consort chart

Table 2 Comparison between the two studied groups regarding pre induction and MAP, total amount of nitoglycerine, total infused volume intra-operative fluid infused

	Group A (n = 45)	Group B (n = 45)	P value
1) Mean arterial pressure (MAP)			
Preinduction (MAP) (mmHg)	80.49 ± 4.73	79.11 ± 5.83	0.111
Postextubation (MAP) (mmHg)	89.51 ± 5.44	88.24 ± 4.20	0.110
2) Total amount of nitroglycerine needed (mg)	5.97 ± 0.78	6.21 ± 0.79	0.081
3) Total infused volume of fluids intra-operative (ml)	519.1 ± 137.31	542.0 ± 136.87	0.215
4) Duration of surgery (min)	61.04 ± 17.77	65.76 ± 17.28	0.103
5) Duration of anesthesia (min)	66.82 ± 14.30	69.91 ± 21.14	0.210
Time for extubation (min)			
Mean ± S.D.	5.49 ± 1.53	5.91 ± 1.59	0.102

respectively) while there was no statistically significant difference between both groups' VAS at 6 and 12 h postoperatively. The number of patients needed rescue analgesia was higher in group B (P value 0.047) (Table 5).

Statistical analysis

The data was collected and entered into the personal computer. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS/version 21) software.

The statistical test was used as follow:

Arithmetic mean, standard deviation, for categorized parameters, chi-square test was used, while Fisher exact test was used if any cells had a number less than 5. While for parametric data to compare between two groups, t test was used. The level of significance was 0.05.

Sample size

The primary outcome of this study was the incidence of postoperative agitation. Using STATA program, setting alpha error at 5% and power at 80%, results from the previous study [18] showed that the incidence of postoperative agitation was lower in the treatment group than in the control group (34% vs 54; P = 0.044), and the incidence of severe postoperative agitation was also lower in the treatment group than in the control group (8% vs 38% respectively; P = 0.001). Based on that result, the needed sample is 45 patients per group after taking into account a 20% drop out rate.

Table 3 comparing both groups regarding postoperative complications

	Group A	Group B	P value
Respiratoy rate/min at extubation	18.22 ± 1.40	18.38 ± 1.53	0.308
Desaturation	2.2%	0%	0.314
Laryngospasm	2.2%	0%	0.314
Postoperative nausea	2.2%	4.4%	0.557
Postoperative vomiting	0%	0%	
Antiemetics in PACU	0%	2.2%	0.314

Discussion

Among various procedures that require general anesthesia, nasal surgeries are followed by a higher incidence of emergence agitation (Kim et al. 2015; Kim et al. 2013). This higher possibility of developing agitation during nasal surgeries is due to sense of suffocation resulting from trickling of blood in the airway, and nasal packing, so it is recommended to do awake extubation; however, awake extubation may intensify emergence agitation (Feldman and Patel 2010). The exact mechanism of postoperative emergence agitation is unknown (Polat et al. 2015).

Based on the pathophysiology of nasal congestion or obstruction, which involves a number of underlying mechanisms including pathological causes and surgical causes, there is a local release of inflammatory mediators including histamine that plays a significant role in such problem (Naclerio et al. 2010).

Our research studied the effect of preemptive administration of chlorpheniramine maleate IV 30 min before induction of anesthesia; we found that it effectively reduced the incidence and severity of postoperative agitation in patients undergoing FESS surgery as shown in our results where the RASS measured at 0, 5, 10, 15, 20 min postoperatively was significantly lower in group (A) than group (B) and hence the number of patients needed midazolam and the dose of midazolam was significantly lower in group (A).

These results could be explained by the fact that chlorpheniramine blocks histamine-mediated effects that may contribute in smooth recovery after nasal endoscopic surgeries by reducing the postoperative nasal congestion and obstruction in addition to its sedative effect as has been explained by Mochizuki H. et al. who proved that the administration of chlorpheniramine impaired visuomotor spatial discrimination and altered cortical and

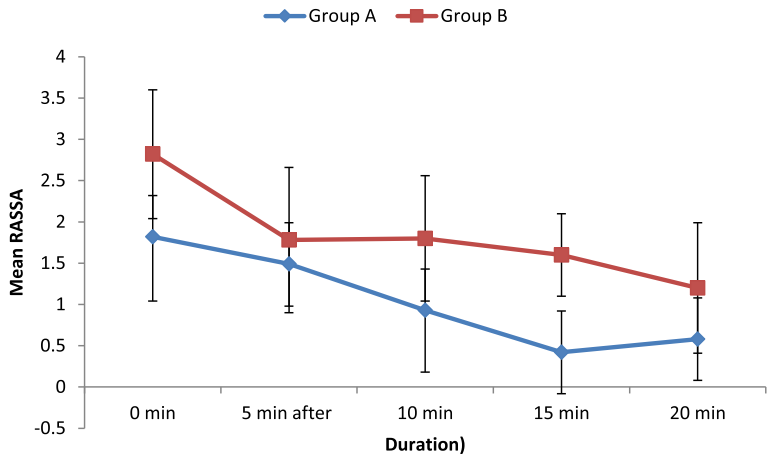

Fig. 2 Comparison between the two studied groups regarding agitation score on RASS at different periods time at PACU. Data are presented as mean ± SD

subcortical activity as measured by positron emission tomography (PET). Decreased and increased activities were observed in the right parietal cortex (BA 40) which is related to visuomotor spatial cognition and the posterior cingulate cortex which constitutes the attention system of the brain, respectively. In particular, the brain activities of BA 40 were negatively and positively correlated to those of bilateral caudate nuclei and the dorsolateral prefrontal cortex, respectively. These findings clearly suggest that the alteration in the cortical and subcortical activity contributes to impaired spatial cognition caused by treatment with d-chlorpheniramine. Thus, the administration of d-chlorpheniramine altered the brain activity in the cortical and subcortical regions that play an important role for cognition and movement (Mochizuki et al. 2002).

Although, our research being unique in studying the effect of chlorpheniramine maleate on the postoperative agitation however it gets along with many other researches which had studied the effect of other preoperative drugs on postoperative agitation. Jee et.al studied the effect of Nefopam infusion in preventing and reducing the severity of postoperative agitation after nasal surgery without a delay in extubation. However, caution is required regarding the increase in HR (Jee et al. 2017). Hina K et al. proved that the use of dexmedetomidine 0.4 mcg/kg/h as intraoperative infusion resulted in smooth emergence with more stable hemodynamics (Khurshid et al. 2015). Garg A et al. also proved that dexmedetomidine 1.0 μg/kg bolus followed by 0.4 μg/kg/h after induction of anesthesia significantly reduced the incidence of emergence agitation and requirement of desflurane in patients undergoing nasal surgery. However, it was associated with delayed extubation, residual sedation, and prolonged PACU stay (Garg et al. 2018). Other study checked the effect of elective preoperative external nasal compression and found that it reduced the incidence of emergence agitation and improve patient satisfaction with recovery after nasal surgery (Kasem and Abdelkader 2016).

Table 4 Comparison between the two studied groups regarding the need for midazolam and the total dose of midazolam needed

	Group A (n = 45)		Group B (n = 45)		P value
	No.	%	No.	%	
Need for midazolam	10	22.2	27	60.0	0.0027*
Dose of midazolam needed (mg)					
Mean±S.D.	1.60 ± 0.70		2.11 ± 0.80		0.042*

*P value ≤ 0.05

As secondary outcomes, it was noted that the studied drug had no any change in preoperative or postoperative mean blood pressure and did not improve or worsen the incidence of postoperative complications including desaturation, laryngospasm, and postoperative nausea and vomiting and also did not affect the time needed for extubation or the respiratory rate following it as shown in our results. This adds a great value for our proposed use of the chlorpheniramine maleate as regards its safety as an anesthetic adjunctive agent.

Concerning its analgesic or analgesic potentiating effects, it was observed that comparing NAS at 30 min and after 2 h postoperative there was a statistically significant difference between both groups (P value = 0.011, 0.048 respectively), while there was no statistically significant difference between both groups' NAS at 6 and 12 h postoperatively. Also, the number of patients needed rescue analgesia was lower in the studied drug group (P value 0.047).

Table 5 Comparison between the two studied groups regarding pain assessment at different period of follow-up

Pain assessment (VAS)	Group A (n = 45)	Group B (n = 45)	P value
30 min postop.	5.56 ± 1.39	6.53 ± 1.24	0.011*
2 h	4.62 ± 1.17	4.96 ± 0.71	0.048*
6 h	3.22 ± 0.90	3.44 ± 0.78	0.108
12 h	2.62 ± 0.61	2.80 ± 0.84	0.128
Total no. of patients received rescue analgesia	8.9%	24.4%	0.047*

*P value ≤ 0.05

Study limitation

Our study had some limitations such as sample collection for this study required accurate patient selection based on inclusion and exclusion criteria. In addition, smaller sample size hence our findings still need more interpretation for further study. This should be addressed by future prospective studies to verify and clarify the role of chlorpheniramine maleate to reduce the incidence of postoperative agitation.

Conclusion

We concluded that preoperative single dose of chlorpheniramine maleate is an effective medication that may be used to prevent or reduce the severity of emergence agitation with minimal cardio-respiratory depression.

Abbreviations

FESS: Functional endoscopic sinus surgeries; ENT: Anesthesia for ear, nose, and throat; PACU: Postanesthesia care unit; RASS: Richmond Agitation-Sedation Scale; SAS: Sedation-Agitation Scale; NMDA: N-methyl-D-aspartate; ASA: American society of anesthesiologists; BMI: Body mass index; NAS: Numerical pain analog scale; OR: Operating room; IV: Intravenous; O2: Oxygen; Mbp: Mean arterial blood pressure; NIBP: Noninvasive blood pressure; PET: Positron emission tomography

Acknowledgements

We thank our colleagues from ENT and anesthesia departments who provided help, insight, and expertise that greatly assisted the research, although they may not agree with all of the interpretations/conclusions of this paper.

We would also like to show our gratitude to Dr. Ayman Abdellatif, professor of Anesthesia and Intensive Care and Pain Management, Ain Shams University, for sharing his pearls of wisdom with us during the course of this research and for his comments on an earlier version of the manuscript, although any errors are our own and should not tarnish the reputations of this esteemed person.

Authors' contributions

TNA contributed to the conception and design of the study, organized the data collection, reviewed and greatly contributed to the interpretation of results, checked the statistical analysis, and revised the manuscript critically for important intellectual content. AAK performed data collection and organized data preparation. Both authors actively discussed the manuscript, critically reviewed its comprehensive content, and finally approved the version to be submitted for publication.

Funding

This research was self-funded, and no external funds were obtained.

Availability of data and materials

Not applicable

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee at the Faculty of Medicine, Ain Shams University Hospital, Cairo, Egypt (FAMSU R 01/2019). It is registered on Clinical Trials.gov with ID (NCT04293081). Informed written consent to participate in the study was provided by all participants.

Consent for publication

Not applicable

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Received: 2 March 2020 Accepted: 9 June 2020
Published online: 02 July 2020

References

Barr J, Fraser LG, Puntillo K, Wesley E et al (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 41:263–306

Chen JY, Jia JE, Liu TJ et al (2013) Comparison of the effects of dexmedetomidine, ketamine, and placebo on emergence agitation after strabismus surgery in children. Can J Anesth 60:385–392

Cho EJ, Yoon SZ, Cho JE, Lee HW (2014) Comparison of the effects of 0.03 and 0.05 mg/kg midazolam with placebo on prevention of emergence agitation in children having strabismus surgery. Anesthesiology 120:1354–1361 https://doi.org/10.1097/ALN.0000000000000181

Dahmani S, Stany I, Brasher C, Lejeune C, Bruneau B, Wood C et al (2010) Pharmacological prevention of sevoflurane and desflurane related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth 104:216–223 https://doi.org/10.1093/bja/aep376

Feldman MA, Patel A (2010): Anesthesia for eye, ear, nose and throat surgery. In: Miller RD (ed) Miller's Anesthesia, vol 2. Churchill Livingstone Elsevier, aa Philadelphia.

Garg A, Kamal M, Mohammed S, Singariya G, Chouhan DS, Biyani G (2018) Efficacy of dexamedetomidine for prevention of emergence agitation in patients posted for nasal surgery under desflurane anaesthesia: a prospective double-blinded randomized controlled trial. Indian J Anaesth 62:524–530

Gruetter CA, Lemke SM, Anestis DK, Szarek JL, Valentovic MA (1992): "Potentiation of 5-hydroxytryptamine-induced contraction in rat aorta by chlorpheniramine, citalopram and fluoxetine". Eur J Pharmacol. Department of Pharmacology, Marshall University School of Medicine, Huntington, WV. 217: 109–18. Doi: https://doi.org/10.1016/0014-2999(92)90827.

Tae Soo Hahm, Chung Soo Kim, Myong Shin Koo, Byung Seop Shin, Hee Youn Hwang, Sang Min Lee, Hyun Sung Cho (2006): The effect of H1-receptor antagonist on hemodynamic changes during anesthesia. Korean J Anesthesiol. 2006; 51(4):395-399. https://doi.org/10.4097/kjae.2006.51.4.395

Jee YS, You HJ, Sung TY, Cho KY (2017): Effects of nefopam on emergence agitation after general anesthesia for nasal surgery: a prospective, randomized, and controlled trial. Medicine (2017) 96:47. Doi: https://doi.org/10.1097/MD.0000000000008843

Kasem A, Abdelkader A (2016) Preoperative external nasal compression: does it decrease emergence agitation after nasal surgery? Ain-Shams J Anaesthesiology 9:593–597. https://doi.org/10.4103/1687-7934.198250

Khurshid H, Muneer K, Malla MS (2015) Effect of dexmedetomidine on emergence agitation after nasal surgeries. Indian Journal of Clinical Anaesthesia 2(3):126–130. https://doi.org/10.5958/2394-4994.2015.00013.X

Kim SY, Kim JM, Lee JH, et al. (2013): Efficacy of intraoperative dexmedetomidine infusion on emergence agitation and quality of recovery after nasal surgery. Br J Anaesth 2013;111:222–228.
Kim HJ, Kim DK, Kim HY, et al. (2015): Risk factors of emergence agitation in adults undergoing general anesthesia for nasal surgery. Clin Exp Otorhinolaryngol 2015;8 (1):46–51. doi: https://doi.org/10.3342/ceo.2015.8.1.46
Mallampati, SR; Gatt, SP; Gugino, LD; Desai, SP; Waraksa, B; Freiberger, D; Liu, PL (1985): "A clinical sign to predict difficult tracheal intubation: a prospective study". Canadian Anaesthetists' Society Journal 32 (4): 429–434. DOI: https://doi.org/10.1007/BF03011357. PMID 4027773.
Hideki Mochizuki, Manabu Tashiro, Masaaki Tagawa, Michiko Kano, Masatoshi Itoh, Nobuyuki Okamura, Takehiko Watanabe and Kazuhiko Yanai (2002): The effects of a sedative antihistamine, d-chlorpheniramine, on visuomotor spatial discrimination and regional brain activity as measured by positron emission tomography (PET). Hum Psychopharmacol Clin Exp 2002; 17: 413–418. DOI: https://doi.org/10.1002/hup.430
Naclerio RM, Bachert C, Baraniuk JN (2010) Pathophysiology of nasal congestion. International Journal of General Medicine 3:47–57. https://doi.org/10.2147/IJGM.S8088
Pieters BJ, Penn E, Nicklaus P, Brucgger D, Meht B et al (2010) Emergence delirium and postoperative pain in children undergoing adenotonsillectomy: a comparison of propofol vs sevoflurane anesthesia. Pediatr Anesth 20(10): 944–950
Polat R, Peker K, Baran I et al (2015) Comparison between dexmedetomidine and remifentanil infusion in emergence agitation during recovery after nasal surgery: a randomized double-blind trial. Anaesthesist 64:740–746. https://doi.org/10.1007/s00101-015-0077-8
Rim JC, Kim JA, Hong JI, et al. (2016): Risk factors of emergence agitation after general anesthesia in adult patients. Anesth Pain Med 2016;11:410–416
Sessler CN, Grap MJ, Brophy GM (2002) The Richmond agitation-sedation scale. American J Respir Crit Care Med 2002 16(10):1338–1344. https://doi.org/10.1164/rccm.2107138
Simons, F. E. (November 18, 2004). "Advances in H1-antihistamines". N Engl J Med. 351. (21): 2203–2217. doi:https://doi.org/10.1056/NEJMra033121
Vlajkovic GP, Sindjelic RP.(2007): Emergence delirium in children: many questions, few answers. Anesth Analg. 2007 Jan; 104(1):84-91.
Yasuda SU, Wellstein A, Likhari P, Barbey JT, Woosley RL (1995) Chlorpheniramine plasma concentration and histamine H1-receptor occupancy. Clin Pharmacol Ther 58(2):210–220. https://doi.org/10.1016/0009-9236(95)90199
Yu D, Chai W, Sun X, Yao L. (2010): Emergence agitation in adults: risk factors in 2,000 patients. Can J Anaesth. 2010 Sep; 57(9):843-848.

Publisher's Note