

COMBINATION THERAPY IN THE PREVENTION OF PONV AFTER STRABISMUS SURGERY IN CHILDREN: GRANISETRON, ONDANSETRON, MIDAZOLAM WITH DEXAMETHASONE

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Summary

Background: Pediatric strabismus surgery is commonly associated with higher incidence of postoperative nausea and vomiting (PONV). Mixtures of different classes of antiemetics have been used successfully to decrease the incidence of PONV but there was no agreement on the optimal combination. The aim of this study was to investigate the effect of granisetron, ondansetron, midazolam combination with dexamethasone in the prevention of PONV following strabismus repair in pediatric population.

Method: Healthy 100 children ASA class I and II aged 4-12 years, scheduled for elective strabismus surgery, were enrolled in this study.

No premedications were given anesthesia was induced by inhalational technique using sevoflurane, nitrous oxide and oxygen mixture. After induction, fentanyl and atracurium were given and an endotracheal tube was inserted. Patients were randomly divided into four groups which received intravenously either: Placebo, or a combination of granisetron 10 $\mu\text{g}/\text{kg}^{-1}$, ondansetron 50 $\mu\text{g}/\text{kg}^{-1}$, midazolam 50 $\mu\text{g}/\text{kg}^{-1}$, plus dexamethasone 0.5 mg/kg^{-1} after induction of anesthesia and before start of surgery. All episodes of PONV during the first 24 hours after anesthesia were recorded.

Results: The incidence of postoperative nausea was 48%, 8%, 12% and 0% while the incidence of vomiting was 52%, 12%, 4% and 0% in placebo, granisetron, ondansetron, midazolam and dexamethasone combination groups respectively. No difference was detected between combination groups (P value >0.05).

Conclusion: Prophylactic administration of either of either granisetron, ondansetron, midazolam combined with dexamethasone markedly decreases the incidence of PONV following strabismus surgery in pediatrics. All combinations are equally effective.

Key words: PONV, Granisetron, Ondansetron, Midazolam, Dexamethasone, strabismus surgery

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Introduction

Post-operative nausea and vomiting (PONV) is one of the most frequent distressing complaints following surgery under general anesthesia¹. The incidence of PONV in day-case patients ranges from 8% to 45%². For some patients PONV is even more distressing than postoperative pain³.

PONV may increase hospital expenditure by prolongation of hospital stay, and management of vomiting related complications such as dehydration, electrolyte disturbances, and pulmonary aspiration⁴. Pediatric strabismus surgery is commonly associated with higher incidence of PONV, it ranges between 40 and 90%⁵.

A variety of methods have been tried in the management of PONV⁶. Some anesthesiologist manage PONV with a single prophylactic anti-emetic given during surgery. There is, however, a growing trend towards the use of a combination of antiemetic therapy in moderate to high-risk patients. The optimal combination is yet to be universally agreed upon⁷.

The role of serotonin receptors in drug-induced emesis has recently received increasing attention. Granisetron, a selective antagonist of serotonin receptor, has been proved to be effective in the prevention of PONV⁸. Ondansetron, also a selective serotonin receptor antagonist, is well tolerated and effective in preventing PONV in adults and children⁹. The anti-emetic effect of midazolam has been investigated by several investigators. Lee et al reported that in patients undergoing sevoflurane VIMA (volatile induction and maintenance of anesthesia), midazolam 2 mg given intravenously before the end of surgery was effective in decreasing the incidence of PONV¹⁰. Unlugenc and colleagues reported that sub-hypnotic dose of midazolam was effective in treating PONV¹¹.

The efficacy of prophylactic dose of dexamethasone in reducing PONV after strabismus surgery and tonsillectomy in children has been reported¹².

The current study was designed to investigate the effects of either of granisetron, ondansetron or midazolam when either is mixed with dexamethasone, in the prevention of PONV following strabismus surgery in pediatric population.

Materials and Method

Following Hospital Research and Human Ethics Committee approval, 100 healthy children ASA class I aged 4-12 years, scheduled for elective strabismus surgery under general anesthesia, were enrolled in this prospective, randomized, placebo-controlled, double blind study. Exclusion criteria included children who had experienced retching or vomiting, or have taken an anti-emetic medications, antihistaminics, steroids, or psychoactive drugs within 24 hours before surgery, and children who gave a history of motion sickness, allergy or previous adverse experiences with anesthesia. Children with cardiovascular, respiratory, metabolic, and central nervous system disease were also excluded from the study.

Solid food was not allowed 6 hours before operation and clear liquids were permitted up to three hours before induction of anesthesia. No premedication was given to the children. Upon arrival to the OR placement of routine monitors were established and baseline hemodynamic data were recorded after placement of routine monitors. Anesthesia was induced by inhalational technique using Sevoflurane, nitrous oxide and oxygen mixture. After induction, and establishment of intravenous line fentanyl 2 $\mu\text{g}/\text{kg}^{-1}$ and atracurium 0.5 mg/kg^{-1} were given an endotracheal tube was inserted under the appropriate anesthesia depth and degree of relaxation.

In a double-blind manner, patients were randomly, divided into four groups (25 patients each), received either:

(Group 1) - Placebo

(Group 2) - Combination of Granisetron 10 $\mu\text{g}/\text{kg}^{-1}$ plus Dexamethasone 0.5 mg/kg^{-1}

(Group 3) - Ondansetron 50 $\mu\text{g}/\text{kg}^{-1}$ plus Dexamethasone 0.5 mg/kg^{-1}

(Group 4) - Combination of Dexamethasone 0.5 mg/kg^{-1} plus Midazolam 50 $\mu\text{g}/\text{kg}^{-1}$

Maximum Dexamethasone dose given was 8 mg in all groups.

All drugs were delivered in equivalent volume in 5 ml syringe with a coded label. The anesthesiologist who anesthetized the patient and all involved nurses were unaware of the content of the syringe. The

study drugs were administered intravenously to all patients after induction of anesthesia and before start of surgery. Thereafter, anesthesia was maintained with 70% nitrous oxide, 30% oxygen with 0.5-3.0% inspired concentration of Sevoflurane. Ventilation was controlled mechanically to keep an end-tidal CO₂ between 35-45 mmHg measured using an anesthetic/respiratory gas analyzer (Capnomac Ultima, Datex, Finland). Intraoperative fluid was (D₅W in 1/4 strength NS) was administered at a standard rate defined as (one-half the deficit during the first hour, plus maintenance fluid). At the completion of surgery, muscle relaxant was reversed by a combination of 0.02 mg/kg⁻¹ atropine sulphate and 0.05 mg/kg⁻¹ neostigmine. Trachea was extubated when the child was fully awake and then transported to PACU for at least one hour until complete recovery, where assessment of vomiting was made by the recovery nurse and the attending anesthesiologist.

For the purpose of the current study, vomiting was defined as the forceful expulsion of liquid or solid gastric contents, while nausea defined as a subjective feeling which was reported by patients. No distinction was made between vomiting and retching (i.e., a retching event was considered a vomiting event).

Postoperatively, all children were admitted to the hospital where they remained for more than one

day. Oral intake was not allowed for four hours after recovery from anesthesia. All episodes of nausea, retching and vomiting during the first 24 hours after anesthesia were recorded by nursing staff who had no knowledge of which treatment each subject had received. Also, parents were asked about episodes of nausea and vomiting and any other potential surgical or anesthesia related complications. If two or more episodes of vomiting occurred, a rescue dose of metoclopramide 0.2 mg/kg⁻¹ was given intramuscularly. Postoperative pain was treated with 1 mg/kg⁻¹ rectal diclofenic sodium.

Statistical analysis

The results were analyzed using SPSS version 14 (SPSS Inc., Chicago, IL, USA). Power analysis indicated that 25 patients are required per each group based on 85% incidence of PONV in strabismus surgery if no prophylaxis is given with an anticipated reduction in the incidence of emesis up to 25% which was the therapeutic outcome for dexamethasone when given as a sole prophylaxis agent³. The alpha error was set at 0.05 and Type II error was set at 0.20. Statistical analysis was done using Kruskal-Wallis Test (Nonparametric ANOVA). If Kruskal-Wallis Test was significant, Dunn's Multiple Comparisons Test

Table 1
Demographic and clinical data

Group		1	2	3	4
		Placebo (n = 25)	Granisetron Dexamethasone Combination (n = 25)	Ondansetron Dexamethasone Combination (n = 25)	Midazolam Dexamethasone Combination (n = 25)
Age (years)		6.7 (2.9)	6.6 (2.1)	7.3 (2.5)	8.3 (3.9)
Sex	M	14 (56%)	14 (56%)	13 (52%)	11 (44%)
	F	11 (44%)	11 (44%)	12 (48%)	14 (56%)
No. of operated muscles (%)					
1		4 (16%)	1 (4%)	4 (16%)	11 (44%)
2		19 (76%)	15 (60%)	18 (72%)	9 (36%)
3 or 4		2 (8%)	9 (36%)	3 (12%)	5 (20%)
Anesthesia time (min)		60 (18)	40.6 (22.2)	62 (21)	57 (26)
Oculocardiac reflex requiring atropine (%)		3 (12%)	10 (40%)*	2 (8%)	0 (0%)

Data expressed as a mean and standard deviation (SD) or number and percentages.

* P value = 0.01

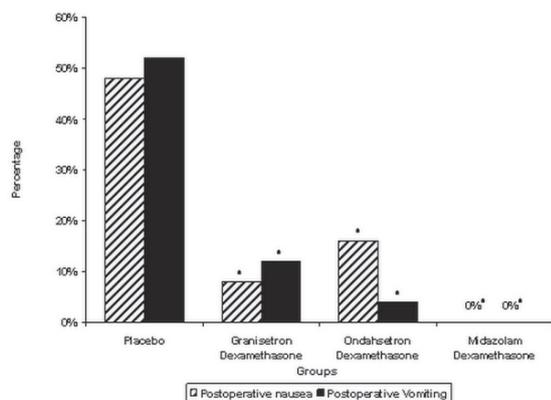
was used to compare different groups. For all tests of significance, a *P* value of 0.05 was used as the level of significance. Data were presented as a mean and standard deviation (SD) or number and percentages.

Results

The demographic and clinical data of the 100 enrolled children are shown in Table 1. There was no difference among the groups with regard to age, sex, duration of surgery, number of operated muscles. The incidence of oculocardiac reflex was significantly higher in Granisetron-Dexamethasone group (*P* value = 0.01).

The data relating to PONV during the study are presented in Fig. 1. The incidence of PONV was significantly greater in the Placebo Group 1 compared to other combination groups (*P* value <0.01) Patients in the Placebo group had incidence of nausea and vomiting of 48% and 52% respectively, while the same incidence was 8% and 12% in the Granisetron-Dexamethasone Group 2. Children of Ondansetron-Dexamethasone Group 3 reported 16% nausea and 4% vomiting. Neither nausea nor vomiting was observed in midazolam-dexamethasone combination Group 4. No difference recorded between combination groups (*P* value >0.05). No major respiratory or hemodynamic adverse effects were observed in the studied groups.

Fig. 1
Incidence of postoperative nausea and vomiting



Against placebo * *P* value <0.01,
No difference between group 2, 3 and 4 (*P* value >0.05)

Discussion

The main finding of the present study was that there were no significant differences between

different combinations groups in reducing PONV after strabismus surgery in pediatric patients. Combinations of drugs have become a proven strategy for prevention of PONV with good response, as compared to monotherapy¹³. Different classes of anti-emetics with different mechanisms of action were shown to act independently when given prophylactically and therefore can be combined to enhance anti-emetic efficacy¹⁴.

The combination of granisetron and dexamethasone had been used in both adult and pediatric populations. The present work in a pediatric population showed an incidence of 8% nausea and 12% vomiting in children of granisetron-dexamethasone Group 2. Fujii and associates reported that prophylactic use of this mixture produced 2% incidence of PONV during the first 24 hours following thyroidectomy in 130 female patients. However the dose of granisetron in Fujii report¹⁵ was 40 µg/kg⁻¹ compared to 10 µg/kg⁻¹ used for the present work. The same result was reported following middle ear surgery in adult¹⁶ and in children undergoing inguinal hernia and phimosis surgery¹⁷. The reported frequency of PONV was 7% after the use of 40 µg/kg⁻¹ granisetron and 4 mg dexamethasone combination in pediatric subjects undergoing strabismus repair, tonsillectomy and adenoidectomy¹⁸.

The present work showed an incidence of 16% and 4% for postoperative nausea and vomiting, respectively, for ondansetron-dexamethasone combination. Splinter et al¹⁹ reported that low-dose ondansetron plus dexamethasone was a more effective prophylactic antiemetic when compared with dexamethasone alone following strabismus repair. They used 150 µg/kg⁻¹ dexamethasone together with ondansetron 50 µg/kg⁻¹ and the incidence of PONV was 9%.

Although the minimum effective dose of dexamethasone for the prevention of PONV was suggested to be 2.5 mg in a recent study²⁰, an 8 to 10 mg dose of dexamethasone was most frequently used. In the current trial the same dose of ondansetron was used but the dose of dexamethasone increased to 0.5 mg/kg with a maximum of 8 mg. Peach and colleagues reported that the efficacy of the smallest dose combination (dexamethasone 2 mg with ondansetron 2 mg) did not significantly differ from that of larger dose combinations (dexamethasone 4 mg with ondansetron

4 mg) in women who had day-surgical gynecologic laparoscopy²¹.

Midazolam is commonly used as a premedicant to relief anxiety. Previously it was suggested that midazolam may have a role in the management of PONV. Di Florio and Goucke²² studied the effect of intravenous midazolam infusion on persistent PONV on twenty patients aged 18-82 years. They reported that low-dose intravenous infusion of 1.0 mg h⁻¹ midazolam after a 1 mg IV bolus was determined to be safe and effective treatment for resistant PONV in adult population. Splinter et al²³ found that midazolam and droperidol at a dosage of 50 µg/kg⁻¹ appear to have a similar effect on vomiting after strabismus surgery. The reported incidence of PONV following single

intravenous injection of 2 mg midazolam was 3.3% in adult patients undergoing abdominal or gynecological procedures¹¹. Palmer and Cameron²⁴ reported the effectiveness of intravenous midazolam-clonidine infusion for treatment of cyclical vomiting syndrome in a 12 years old child²⁴. Our combination of midazolam and dexamethasone produced good response.

Conclusion

Prophylactic administration of granisetron, ondansetron, midazolam combined with dexamethasone decreases the incidence of PONV following strabismus surgery in pediatric population. No recorded differences between different combinations.

References

1. HOFER CK, ZOLLINGER A, BUCHI S, ET AL: Patient well-being after general anaesthesia: a prospective, randomized, controlled multi-centre trial comparing intravenous and inhalation anaesthesia. *Br J Anaesth*; 2003, 91:631-7.
2. JOHNS RA, HANOUSEK J, MONTGOMERY JE: A comparison of cyclizine and granisetron alone and in combination for the prevention of postoperative nausea and vomiting. *Anaesthesia*; 2006, 61:1053-7.
3. DARKOW T, GORA-HARPER ML, GOULSON DT, RECORD KE: Impact of antiemetic selection on postoperative nausea and vomiting and patient satisfaction. *Pharmacotherapy*; 2001, 21:540-8.
4. APFEL CC, LÄÄRÄ E, KOIVURANTA M, GREIM CA, ROEWER R: Simplified Risk Score For Predicting Postoperative Nausea and Vomiting. *Anesthesiology*; 1999, 91:693-700.
5. TRESCHAN TA, ZIMMER C, NASS C, STEGEN B, ESSER J, PETERS J: Inspired Oxygen Fraction of 0.8 does not attenuate postoperative nausea and vomiting after strabismus surgery. *Anesthesiology*; 2005, 103:6-10.
6. TAYLOR R, PICKFORD A: Postoperative nausea and vomiting. *Anaesth Intens Care Med*; 2003, 4:335-337.
7. JOHNS RA, HANOUSEK J, MONTGOMERY JE: A comparison of cyclizine and granisetron alone and in combination for the prevention of postoperative nausea and vomiting. *Anaesthesia*; 2006, 61:1053-7.
8. FUJII Y, TANAKA H, TOYOOKA H: Reduction of postoperative nausea and vomiting with granisetron. *Can J Anaesth*; 1994, 41:291-94.
9. KHALIL SN, ROTH AG, COHEN IT, ET AL: A Double-Blind Comparison of intravenous ondansetron and placebo for preventing postoperative emesis in 1-to 24-Month-Old pediatric patients after surgery under general anesthesia. *Anesth Analg*; 2005, 101:356-61.
10. LEE Y, WANG JJ, YANG YL, CHEN A, LAI HY: Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomised controlled trial. *Anaesthesia*; 2007, 62:18-22.
11. UNLUGENC H, GULER T, GUNES Y, ISIK G: Comparative study of the antiemetic efficacy of ondansetron, propofol and midazolam in the early postoperative period. *Eur J Anaesthesiol*; 2004, 21:60-5.
12. MADAN R, BHATIA A, CHAKITHANDY S, ET AL: Prophylactic Dexamethasone for Postoperative Nausea and Vomiting in Pediatric Strabismus Surgery: A Dose Ranging and Safety Evaluation Study. *Anesth Analg*; 2005, 100:1622-6.
13. GAN TJ, MEYER T, APFEL CC, ET AL: Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg*; 2003, 97:62-71.
14. RÜSCH D, ARNDT C, MARTIN H, KRANKE P: The addition of dexamethasone to dolasetron or haloperidol for treatment of established postoperative nausea and vomiting. *Anaesthesia*; 2007, 62:810-17.
15. FUJII Y, TANAKA H, KOBAYASHI N: Granisetron/dexamethasone combination for the prevention of postoperative nausea & vomiting after thyroidectomy. *Anaesth Intensive Care*; 2000, 28:266-9.
16. FUJII Y, TOYOOKA H, TANAKA H: Prophylactic antiemetic therapy with a combination of granisetron and dexamethasone in patients undergoing middle ear surgery. *Br J Anaesth*; 1998, 81:754-56.
17. FUJII Y, SAITOH Y, TANAKA H, TOYOOKA H: Prophylactic therapy with combined granisetron and dexamethasone for the prevention of postoperative vomiting in children. *Eur J Anaesth*; 1999, 16:376-9.
18. FUJII Y, TOYOOKA H, TANAKA H: Granisetron and dexamethasone provide more improved prevention of postoperative emesis than granisetron alone in children. *Can J Anaesth*; 1996, 43:1299-32.
19. SPLINTER WM, RHINE EJ: Low-dose Ondansetron with Dexamethasone More Effectively Decreases Vomiting after Strabismus Surgery in Children than Does High-dose Ondansetron. *Anesthesiology*; 1998, 88:72-5.
20. WANG JJ, SHUNG T, TZENG JJ, TANG CS: The Effect of Timing of dexamethasone Administration on Its Efficacy as a Prophylactic Antiemetic for Postoperative Nausea and Vomiting. *Anesth Analg*; 2000, 91:136-9.
21. PAECH MJ, RUCKLIDGE MW, LAIN J, DODD PH, BENNETT EJ, DOHERTY DA: Ondansetron and dexamethasone dose combinations for prophylaxis against postoperative nausea and vomiting. *Anesth Analg*; 2007, 104:808-14.
22. DI FLORIO T, GOUCKE CR: The effect of midazolam on persistent postoperative nausea and vomiting. *Anaesth Intensive Care*; 1999, 27:38-40.
23. SPLINTER WM, NOEL LP, ROBERT D, RHINE E, BONN G, CLARKE W: Antiemetic prophylaxis for strabismus surgery. *Can J Ophthalmol*; 1994, 29:224-26.
24. PALMER GM, CAMERON DJ: Use of intravenous midazolam and clonidine in cyclical vomiting syndrome. *Pediatr Anesth*; 2005, 15:68-72.