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Original Research Article

Effect of Palonosetron monotherapy versus Palonosetron with Dexamethasone combination therapy for prevention of post operative nausea vomiting in children undergoing strabismus surgery

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Abstract

Background: Postoperative nausea and vomiting (PONV) is the most distressing symptom reported in 40–88% of patients subsequent to strabismus surgery. Newer antiemetic 5-HT3 receptor antagonist drugs palonosetron and its combination with dexamethasone for prevention PONV in chemotherapy patients having promising results, but has not been studied in children undergoing strabismus surgery.
Methodology: 120 patients were registered in this prospective, randomized double blind study. Group A received palonosetron 1.5 mcgkg^{-1} and Group B received an additional dose of Inj dexamethasone 0.25 mgkg^{-1} prior to anaesthesia. Post operative data of PONV and postoperative vomiting (POV) was recorded at pre defined intervals in different age groups**.**
Results: There is no difference of POV in both groups at different age groups. The incidence of post operative nausea in Group A was 44% and Group B was 11% (p=0.02). Considering the incidence of PONV in all age groups, our results showed that the overall incidence of PONV in Group A was found to be more than that with Group B (p<0.05). Also in age group 3 year to 9 year, the incidence of PONV was higher in Group A than Group B (p =0.01). The incidence of PONV was found to be 17% (6 out of 36), 21% (14 out of 68) and 6% (1 out of 16) when one, two and three extra ocular muscles were operated respectively (p=0.39).
Conclusion: Palonosetron with dexamethasone combination therapy is recommended to be used in children age > 3years undergoing strabismus surgery.
Keywords: Palonosetron, dexamethasone, strabismus.

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1. Introduction

Postoperative nausea and vomiting (PONV) is the most worrying symptom reported in 40–88% of patients consequent to strabismus surgery when antiemetic prophylactics are not prescribed [1]. PONV is generally self-limiting, associated with high level of patient dissatisfaction and may delay hospital discharge [2,3]. Since strabismus surgery is an obvious risk factor for PONV in children, prophylactic prescription of antiemetic is justifiable and has been described in literature [4]. None of the currently available antiemetic is capable of completely eliminating the incidence of PONV. Whereas all 5-HT3 receptor antagonists are considered to be similarly effective and the second-generation palonosetron is pharmacologically distinct with a longer half-life of approximately 40 hours [5]. Dexamethasone is a well

described potent antiemetic, which exerts its effects through central inhibition of the nucleus tractus solitarii and has a slow onset of action [6]. The etiology of PONV is multifactorial; hence use of only 5-HT3 receptor antagonists is insufficient. It is rational to give drugs which have divergent mechanism of action. The literature in children is lacking, and these generally focus on postoperative vomiting (POV) because the assessment of nausea can be difficult in younger children. In a recent study, combination of palonosetron with dexamethasone demonstrated better control of delayed chemotherapy induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy [7]. However studies comparing palonosetron monotherapy versus palonosetron plus dexamethasone combination therapy in children undergoing strabismus surgery are lacking.

2. Material and Method

After obtaining institutional ethics review board approval and informed parental consent, this prospective double blinded randomised control trial was carried out in a tertiary care hospital. Out of a total of 143 consecutive strabismus surgery patients listed for surgery during the study period from January 2015 to July 2016, 18 patients did not meet inclusion criteria and 03 patients were not included due to parental refusal and 2 cases were cancelled. A total of 120 patients were enrolled. Only patients in American physical status (ASA) grade I or II, between 6 months and 9 years of age, undergoing elective strabismus surgery under general anaesthesia (GA) were enrolled. Patients with known allergy or hypersensitivity to the study drug, history of motion sickness, prior severe PONV and on long term steroid therapy were excluded from the study. Patients with intestinal obstruction, hiatus hernia, renal and hepatic diseases and surgeries extending more than 30 minutes were also excluded from the study.

According to a computer-generated randomization chart, the patients were assigned to one of the two treatment groups. Patients in group A (n=60) received intravenous palonosetron 1.5 mcg kg^{-1} and patients in group B received combined palonosetron 1.5 mcg/kg^{-1} and dexamethasone 0.25mg kg^{-1} prior to induction of GA. The test drug was prepared and administered by a nurse who was blinded to drug assignment. In both groups, drugs were diluted with normal saline to a volume of 3 ml in a 5 ml syringe and labeled as 'Test Drug'. The study population was given premedication with glycopyrrolate 10 $mcgkg^{-1}$ and midazolam 0.1 $mgkg^{-1}$. Standardized anaesthetic management for induction of GA using thiopentone sodium 5 $mgkg^{-1}$, fentanyl 1 $mcgkg^{-1}$ and atracurium 0.5 $mgkg^{-1}$ followed by tracheal intubation was done for both the groups. Maintenance was done with 2% Sevoflurane in 50% nitrous oxide and 50% oxygen. At the end of surgery, residual neuromuscular blockade was antagonized with glycopyrrolate 20 $mcgkg^{-1}$ and neostigmine 50 $mcgkg^{-1}$, and the trachea was extubated while the child was awake.

In our study, children aged < 3 years had only one baseline risk factor for POV which is strabismus surgery. Children aged > 3yrs had two risk factors for POV, which were strabismus surgery and age > 3 years. Therefore age becomes an important limiting factor and the study has been analyzed for POV in two subgroups, namely age 6 months to 03years and age 3 years to 9years. Post operative data was assessed for 24 hours after which the patients got discharged. Nausea in patients aged 06 to 09 years was assessed at the intervals of 0–2, 2–6 and 06–24 hours using six point pictorial Baxter Retching Faces (BARF) Scale. All episodes of vomiting were assessed at the intervals of 0–2, 2–6 and 6–24 hours using a three point numeric POV scoring system (1=No vomiting, 2=Vomiting once in 30 min, 3 = Two or more episodes of vomiting in 30 min). Children having a POV score of 3 were considered to have severe vomiting and given metoclopramide 0.15$mgkg^{-1}$ as a rescue antiemetic.

Data analysis was done with the help of SPSS software version 20.0.Quantitative data was presented with the help of mean, standard deviation and median. Assuming level of significance set as 0.05, power of the study 80%, number of groups 2 and number of measurements 2, the total sample size was calculated to be 60 in each group. Power analysis was done for the estimated effect size and sample size recruited, which reveled the power of the study as 90%.The duration of surgery, number of extra ocular muscles operated upon, incidence of nausea and vomiting, adverse effects and number of patients needing rescue antiemetic was compared using Pearson Chi Square test. For statistical comparison, the difference was considered significant when the p-value was found to be less than 0.05.

3. Observation and Results

Efficacy of palonosetron and its combination with dexmedetomidine before induction for GA was studied in 120 pediatric patients. Demographic parameters and clinical characteristics were comparable between the groups (Table 1). Both the study groups had 60 patients each. Of them 76% were males and 24% were females and most of them belonged to ASA physical status I (91%). All patients received premedication and GA as per protocol after randomization.

There is no difference in POV in both groups at different age groups (Table 2). Nausea could only be assessed in children aged 07 to 09years.Also children who had vomited were not assessed for nausea. The incidence of post operative nausea in group A was 44 % (7 out of 16 children) and in group B was 11% (2 out of 19 children) ($p=0.02$). Considering PONV without age group our results showed that the overall incidence of PONV in group A was found to be more than with group B ($p<0.05$) (Table 2).

However in age group 03 – 09year the incidence of PONV is higher in group A compared to group B(p =0.01)(Table 2).The incidence of PONV was found to be 17% (6 out of 36), 21% (14 out of 68) and 6% (1 out of 16) when one, two and three extra ocular muscles were operated respectively (p=0.39). The incidence of PONV was found to be 13% (8 out of 62) and 21% (12 out of 58) in males and females respectively(p=0.25).

The incidence of adverse reaction such as flushing, headache, constipation and diarrhea was comparable in both the groups and there was no increase in incidence of adverse events with combination therapy. 04(7%) patients in group A and 02 (3%) patients in group B needed a rescue antiemetic.

Table 1: Demographic profile and baseline clinical characteristics of patients in both the group

Patient data	Group A (n=60) mean±SD	Group Y (n=60) mean±SD	P value
Age (yrs)	6.94±2.1	6.68±2.3	0.54
Weight (kg)	14.8 ±5.28	15.32 ± 5.35	0.65
Gender M/F	33/27	29/31	
Duration of surgery	17.80 ± 5.16	18.42 ±4.83	0.50

M= Male, F= female, yrs= years, SD= Standard deviation

Table 2: Incidence of postoperative vomiting (POV) and postoperative nausea and vomiting (PONV) in both groups at different age group

Age Group		Group A	Group B	Total	p-value
6m - 3 Yrs	No Vomiting	28	28	56	1
	Vomiting	2	2	4	
3yr - 9yrs	No vomiting	25	28	53	0.22
	Vomiting	5	2	7	
6m- 9 yrs	No PONV	46	54	100	0.05
	PONV	14	6	20	
6m - 3 Yrs	No PONV	28	28	56	1
	PONV	2	2	4	
3 yr- 9 yr	No PONV	18	26	44	0.01
	PONV	12	4	16	
7 yr-9 yr	No Nausea	9	17	26	0.025
	Nausea	7	2	9	

PONV= Postoperative nausea vomiting, yrs= years.

4. Discussion

The reported incidence of PONV after pediatric strabismus surgery has been reported to be 60%to 85% in previously published studies, when no prophylactic antiemetic is given [1, 8]. None of the currently available antiemetic is capable of completely eliminating the incidence of PONV. In the IMPACT trial, 4123 patients were randomly assigned to 01 of 64 possible combinations of 06 prophylactic antiemetic medications. It was demonstrated that effectiveness primarily depends on the patient's baseline risk rather than on the choice of antiemetic, and each additional antiemetic in a combination regimen adds less and less additional benefit, as the patients risk decreases [9]. Our study also provides additional benefit but this additional benefit decreases significantly as the patient's baseline risk decreases. The key message here is that the patient's baseline risk is the main determinant of the effectiveness of antiemetic interventions. Therefore, prophylaxis is rarely justified in patients at low risk, a single antiemetic is likely to be reasonable for patients with a moderate risk, and patients at high risk are likely to benefit from combination treatment [10]. Various combinations of drugs have therefore been tried to obtain optimal results. Also there are multifactorial causes for PONV and antagonising only one type of receptor is not enough in many patients. It is rational to give drugs which have dissimilar mechanism of action. Given the limited antiemetic efficacy of prophylactic antiemetics, Scuderi and co-workers were the first to investigate a multimodal approach [11]. Fewer studies have been conducted in children, and they usually focus on POV because the assessment of nausea can be complex in younger children [12,13]. A limited number of studies investigated risk factors, but only one well-designed multicenter prospective survey developed predictive model for POV [14, 15]. Although the impact of the type of surgery remains controversial in adults, strabismus surgery and Faden surgery for myopexy appear to be independent predictors of POV in children [16,17]. In a recent study, compared with the first-generation 5-HT3 receptor antagonist granisetron,

palonosetron in combination with dexamethasone demonstrated better control of delayed CINV in patients receiving highly emetogenic chemotherapy [7].

Another study compared different doses of palonosetron for prevention of PONV in children undergoing strabismus surgery. Based on the results of this study, fixed palonosetron doses of 0.5, 1.0, and 1.5 $mcgkg^{-1}$ appear to be effective doses and 0.5 $mcgkg^{-1}$ of palonosetron was as effective as higher doses in reducing the incidence of PONV [18]. However to the best of our knowledge a comparison of palonosetron monotherapy versus palonosetron plus dexamethasone combination therapy has never been studied in children undergoing strabismus surgery.

The limitation of this study is that it did not compare the effect of palonosetron with a placebo, **as** more than half of all patients undergoing pediatric strabismus surgery experience PONV, and it would be not be ethical to use a placebo group in this pediatric population. Another possible limitation of this study may be the short duration of the study period which was 24 hours. Due to both the long half-life and long-lasting functional effects of palonosetron compared with other 5-HT3 receptor antagonists, PONV may be assessed for 72 hours; however, in our study, patients were discharged from the hospital after 24 hours. Another limitation was that nausea could only be assessed only in the age group 7yr – 9yrs.

5. Conclusion

Based on the results of our study palonosetron with dexamethasone combination therapy is recommended to be used in children age more than 03years undergoing strabismus surgery. The reported incidence of PONV after pediatric strabismus surgery was 60% and 85% in previously published studies when no prophylactic antiemetic is given. It can be concluded that palonosetron with dexamethasone combination therapy is recommended to be used in children with more than 02 risk factors and a single antiemetic like palonosetron monotherapy is likely to be reasonable for children with less than 02 risk factors.

Ethics Committee Approval:

Ethics committee approval was received for this study from the ethics committee of Institutional Ethics Committee Army Hospital (R&R), Delhi Cantt, India (Date: 23.09.2014).

Informed Consent:

Written informed consent was obtained from patients who participated in this study.

Conflict of Interest:

No conflict of interest was declared by the authors.

Financial Disclosure:

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