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A Randomized Clinical Trail to Compare Palonosetron and Ondansetron for Prevention of Post Operative Nausea and Vomiting

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Abstract

Abstract: Nausea and vomiting is known to be associated with the use of anaesthetic technique for many years. Ondansetron a gold standard drug used for treatment of post operative nausea and vomiting (PONV) is short acting and multiple doses are needed. Objective of the present study is to compare the efficacy of palonosetron and ondansetron for prevention of PONV in patients undergoing abdominal surgery under general anaesthesia.

Methods: 140 patients undergoing abdominal surgery under general anesthesia were randomised and allocated into two groups after taking into consideration inclusion and exclusion criteria. Group I received ondansetron 8mg intravenously and Group II received palonosetron 0.075mg intravenously 5 min before the induction of anesthesia. In all patients general anaesthesia given using thiopentone as inducing agent. Occurrence of PONV was noted and was scored for 24 hrs.

Results: The incidence of PONV was significantly lower in the palonosetron group compared with the ondansetron group (24.3% vs 78.6%, respectively). Emetic episodes were observed in 5.71% of patients in palonosetron group compared to 61.4% of patients in ondansetron group (P value <0.001). The results were clinically and statistically significant.

Conclusion: Incidence of PONV and emetic episodes is less in patients who had received palonosetron in comparison to those who had received ondansetron. From the study we conclude that palonosetron is more efficacious than ondansetron for prevention of PONV in patients undergoing abdominal surgery under general anesthesia.

Keywords: Post Operative Nausea and Vomiting; Palonosetron; Ondansetron; General Anaesthesia.

Introduction

Post operative nausea and vomiting (PONV) remains a significant problem even in the modern day anaesthesia practice and continues to be a significant. During the past decade, anaesthesiologists have been modifying their anaesthetic techniques to ensure a more rapid and smooth recovery. However in-spite of these advances, nausea and vomiting still occurs with unacceptable frequency in association with surgery and anaesthesia and description of it as "the big little problem" [2] encapsulates much of the general perception. Post operative nausea and vomiting in addition to being distressing and unpleasant to the patients, has a potential to adversely affect the patient in the form of delayed recovery, unexpected hospital stay and can also cause post surgical morbidities like wound dehiscence, pulmonary aspiration, surgical site bleeding and dehydration [3].

Various drugs have been used to prevent PONV namely antihistamines, phenothiazine derivatives, anticholinergic and dopamine receptor antagonists. Use of these drugs is associated with unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness and tachycardia

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[4,5,6]. The management of nausea and vomiting has improved greatly in recent years, with the introduction of 5 Hydroxytyptamine (5-HT_3) receptor antagonists. The commonly used drug of this group is Ondansetron [7]. Ondansetron is being considered as a gold standard drug for treatment of PONV. 2nd generation drug Palonosetron has been recently introduced and has higher receptor affinity and longer half life which confers it prolonged duration of action [5]. Studies evaluating efficacy and safety of palonosetron for PONV revealed that a single dose of palonosetron 0.075mg significantly decreased the emetic episodes, nausea severity and use of rescue medication in patients undergoing abdominal surgeries under general anesthesia for first 24 hours. Further studies were done to demonstrate the continued effect of palonosetron for 24 to 72 hrs. Palonosetron was also reported to be as effective as ondansetron for prevention of chemotherapy induced nausea and vomiting (CINV) following use of highly emetogenic chemotherapeutic agents. The incidence of PONV is relatively high in patients undergoing abdominal surgeries under general anesthesia. Still no studies were found which evaluated the relative efficacy of palonosetron and ondansetron in preventing PONV.

Hence the present study was done to compare the efficacy of palonosetron and ondansetron for prevention of PONV in patients undergoing abdominal surgeries under general anaesthesia.

Methodology

Institutional ethical committee approval was taken and consent was taken from enrolled 140 patients. Patients aged between 18 to 60 years, with ASA status 1 and 2 were scheduled to undergo elective abdominal surgeries under general anesthesia were randomly allocated into two groups. All patients had one of the PONV risk factors like female gender, history of PONV, motion sickness, nonsmoking status. Patients who have already received antiemetics or had nausea and vomiting 24 hrs preceding the surgery were excluded from the study.

After thorough pre-anaesthetic evaluation and clinical examination patients were randomized to receive either ondansetron 8mg (Group I) or palonosetron 0.075mg (group II) intravenously using computer generated randomization table. A trained nurse who was not involved in the study prepared the drug and numbered them. Normal saline was added to palonosetron to make total volume of 4 ml. Patients did not receive any premedication. Patients received either palonosetron 0.075 mg or ondansetron 8 mg intravenously 5 min prior to induction of anesthesia. Standard anesthesia regime was used for all the patients. Patients were premeditated with glycopyrrolate 0.004mg/kg, midazolam 0.05mg/kg fentanyl 2µ/kg. Following pre oxygenation anaesthesia was induced with thiopentone sodium 5mg/kg and intubation facilitated with injection Suxamethonium 2mg/kg. Endotracheal intubation was done with appropriate size endotracheal tube. Anaesthesia was maintained with N_2O 50% and oxygen 50% and vecuronium 0.1 mg/kg. Neuromuscular blocked was reversed with injection glycopyrrolate 0.04mg/kg and neostigmine 0.05mg/kg. Pulse rate, blood pressure, SpO_2 and $ETCO_2$ were monitored throughout perioperative period. Post operative analgesia was provided by diclofenac sodium 75 mg IM or with paracetamol infusion of 10 mg/ kg four times daily in patients who donot tolerate diclofenac. Post operatively patients were monitored for Nausea and vomiting every hourly for first 24 hours. Incidence of the ponv was compared according to nausea and vomiting score. 0 = No emetic symptoms,1 = Nausea (defined as unpleasant sensation associated with awareness of urge to vomit) 2 = Retching (labored, spasmodic and rhythmic contraction of respiratory muscles without expulsion of gastric contents,) 3 = Vomiting. (Forceful expulsion of gastric contents from mouth). Patients received intravenous Dexamethasone 0.1mg/kg as rescue antiemetic and were administered when PONV score was ≥ 2. A complete response was defined as absence of ponv and no use of rescue antiemetic Occurrence of side effects like headache, dizziness, constipation were recorded.

Statistical Analysis Sample size was calculated by power analysis with α error of 0.05, β error of 0.2 and power of study being 80%. Minimum of 70 patients were included in each group. All data was expressed as mean +/- standard deviation. Demographic data was analyzed using unpaired 't' test. Efficacy of drugs was compared using chi square test with P value of < 0.05 being considered significant.

Results

140 patients undergoing abdominal surgery under general anaesthesia were enrolled in the study and all of them completed the study. Demographic profiles in both the groups were comparable with regards to the patient characteristics, duration of the procedure and ponv risk factors. (P value > 0.05) (Table 1) It was observed that the incidence of post operative nausea

and vomiting in group I is 78.57% (55) as compared to 24.29% (17) in group II with p value < 0.001 (Table 2). It was observed that the incidence of vomiting in group I is 61.43% (43) as compared to 5.71% (04) in group II (P value of <0.001) which is statistically significant. (Table 3).

Discussion

Post operative nausea and vomiting (PONV) is very common sequelae of general anaesthesia and is very unpleasant and distressing for the patient. It is leading cause of delayed discharge andunanticipated hospital admission after ambulatory surgical procedure [8]. Incidence of postoperative nausea and vomiting in an untreated adult surgical population receiving general anaesthesia is around 20-30%, but it increases up to 80% in patients with risk factors for PONV. PONV is very frequent in abdominal surgeries leading to the recommendation of routine prophylactic administration of antiemetics [9]. The etiology of nausea and vomiting after abdominal surgeries under GA are multifactorial in origin. Age, type of surgery, anaesthetic procedure and duration of surgery may influence PONV.

Numerous interventional methods have been studied for the prevention of nausea and vomiting. Non pharmacological methods include acupuncture, electropuncture, transcutaneous electrical nerve stimulation, acupoint stimulation and acupressure. Pharmacological methods include Dopamine receptor antagonists (phenothiazines, buterophenones and benzamides), Histamine receptor antagonists (dimenhydrinate), Muscarinic receptor antagonists (scopolamine), and serotonin receptor antagonists (ondansetron). Miscellaneous drugs like propofol, clonidine, dexamethasone and ephedrine are also tried for prevention of nausea and vomiting. Above drugs are effective in reducing PONV with varying efficacy and are associated with unwanted side effects.

Hence introduction of 5-HT_3 receptor antagonists in 1990s was heralded as the major advance in prophylaxis of PONV as they lack the major adverse effects which were observed commonly with traditionally used antiemetic drugs [10,11]. These 5-HT_3 receptor antagonists produced no sedation, extrapyramidal reactions, adverse effects on vital signs or laboratory tests or drug interactions [12]. Half life of Palonosetron is 40 hrs [5], this confers Palonosetron prolonged duration of action and less frequent dosing as compared to Ondansetron. Studies were done to find out for the optimal dose of Palonosetron. White PF et al did a placebo controlled randomized study to evaluate palonosetron across a range of doses for prophylaxis against PONV. 1µg/Kg and 30µg/Kg doses produced a significantly better complete response in the first 24 hours (44% p=0.004) and 45%(p=0.002) vs 19%) and a lower incidence of nausea during the same period.[5]Second study to optimise the dose of Palonosetron was done in 2008

Table 1: Demographic data of the patients

	Group I (N= 70)	Group II (N= 70)	P value
Age	41.1±15.16 yrs	43±13.86 yrs	0.444
Sex			
Males	34 (48.6%)	31 (44.3%)	
Females	36 (51.4%)	39 (55.7%)	0.611
Body weight	57.5±8.57 Kg	58.7±8.11 Kg	0.13
ASA status I,II	32, 38	32, 38	1.0
Duration	2.66±0.83 hrs	2.93±0.82 hrs	0.055

Table 2: Incidence of post operative nausea and vomiting

Nausea & Vomiting	Group I		Group II	
	Number	%	Number	%
Yes	55	78.57	17	24.29
No	15	21.43	53	75.71

Table 3: Incidence of Emetic episodes

Emetic episodes	Group I		Group II	
	Number	%	Number	%
Vomiting	43	61.43	04	5.71
No Vomiting	27	38.57	66	94.29

by Kovac AL et al. In the study palonosetron in dose of 0.025 mg, 0.05 mg and 0.075 mg was used and were compared in 546 patients undergoing laparoscopic surgery. The palonosetron 0.075mg dose was statistically superior to placebo for all end points during the first 24 hrs, including CR (complete remission), emesis, nausea rates and reduction in nausea severity. Based on these two studies minimum effective dose of palonosetron in the setting of PONV is 0.075mg [13]. Present study was done to compare the efficacy of palonosetron 0.075mg and ondansetron 8mg administered 5 min prior to the induction of anaesthesia in the patients undergoing abdominal surgeries under general anaesthesia. The study was designed in such a way as to control all the factors that can interfere with the interpretation of the results of the study with a standardized anaesthesia regimen like (avoiding use of propofol for induction, avoiding use of tramadol and opoids for post operative analgesia). The duration of anaesthesia, surgery and the anaesthetic used were similar in both the groups. Therefore it is likely that the difference in the incidence of emetic episodes in both the groups were attributable to Ondansetron and Palonosetron. In the study both the groups were comparable with respect to age, sex, body weight, ASA grading and duration of the surgery (Table 1). The duration of anaesthesia and surgery has a bearing on post operative nausea and vomiting as prolonged duration of surgery with frequent bowel handling will increase the incidence of post operative nausea and vomiting, hence increasing the requirement of antiemetic. In the study it was found that the incidence of PONV was 79% in Ondansetron group and 24% in Palonosetron group (P value = <0.001). The results were both clinically and statistically significant (Table 2). The study confirms the finding that Palonosetron at a dose of 0.075 mg improves the control of nausea and vomiting. Control over nausea and vomiting is even seen to extend over second and third day, an effect that may be most marked after major operations requiring inpatient stay. From the study we can also say that Palonosetron 0.075mg reduces the severity of delayed nausea, which is particularly relevant in day surgery population, in whom it is difficult to identify those at risk of post discharge PONV and for whom early return to normal activities is important. From the study it was also found that the incidence of emetic episodes were 6% in Paolnosetron group and 61% in Ondansetron group (p value = <0.001), in 24 hrs post operative period in the patients undergoing abdominal surgeries under general anaesthesia (Table 3). The results were both clinically and statistically significant. In the study it was noticed that incidence of vomiting was high in the Ondansetron group mainly between 3-6 hours. This is mainly due to its relative short life of 3.5 to 5 hrs. In the patients who received Palonosetron, the incidence of vomiting was less because it has longer duration of action of 40 hrs. Both Palonosetron and Ondansetron has non serious adverse effects like short duration head ache, constipation, dizziness and prolongation of QTc interval. But no side effects were observed in patients of both the groups in our study.

Limitation in the present study are; 1. We did not include in the study the phase of the menstrual cycle of the female patients. All antiemetic have effect on the incidence of vomiting on different phases of the menstrual cycle, with the studies showing the incidence of vomiting less in women in postovulatory phase. 2. We did not include in our study the patients undergoing ear surgeries and strabismus surgeries who are also at high risk of having PONV.

Scope of the study: Seeing the results, study can be done on patients undergoing day care surgeries where single dose of palonosetron is highly effective for PONV. On the basis of promising results for combination therapy with Palonosetron in CINV, similar combination studies can be done for prevention of PONV in surgical patients. Combination of Palonosetron with Dexamethasone is very effective in prevention of nausea, and when neurokinin–1 antagonists such as Aprepitant is added to the above combination, incidence of vomiting is still further reduced to low levels even in high risk patients. So from the results of the present study and from the results of other cited studies, it can be concluded that Palonosetron is more effective than Ondansetron to prevent post operative nausea and vomiting in patients undergoing abdominal surgeries under general anaesthesia.

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