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Comparative study of efficacy of palonosetron, dexamethasone & glycopyrrolate in prevention of postoperative nausea and vomiting in patients undergoing lower abdominal surgeries under spinal anesthesia using bupivacaine with morphine

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Abstract

Introduction: Incidence of post-operative nausea vomiting (PONV) after spinal anesthesia is 21%, which increases to 50% when we add opioid (morphine) adjuvant intrathecally for better analgesia. This study is oriented to search a remedy for this commonest postoperative complication and to compare the efficacy of intravenous Palonosetron, Dexamethasone and Glycopyrrolate given preoperatively in prevention of PONV with intrathecal hyperbaric bupivacaine with morphine, in lower abdominal surgeries.

Methods: After Ethical committee clearance, Informed written consent was obtained from 90 ASA I or II patients, between ages 18 and 65 years undergoing surgery under spinal anaesthesia and randomized into three groups to receive either injection Palonosetron 0.075 mg (Group P), injection Dexamethasone 8mg (Group D) or injection Glycopyrrolate 0.2mg (Group G) 15 minutes prior to spinal anesthesia with injection bupivacaine 0.5% hyperbaric 15mg with 100 micrograms preservative free morphine and observed for complete responders, number of episodes of vomiting post operatively over 48 hrs. Pain and sedation assessed by Visual analogue score & Ramsey Sedation Scale respectively. Injection ondansetron 4mg is used as rescue drug.

Results: Demographic data and hemodynamic variables were similar in all the groups. The incidence of PONV in Palonosetron and Glycopyrrolate group was 13.3 % & in Dexamethasone group was 16.7% with p value 0.6 which was similar.

Conclusion: The efficacy of premedication with i.v. Dexamethasone or Glycopyrrolate in lower abdominal surgeries in prevention of PONV was comparable with Palonosetron.

Keywords: PONV, palonosetron, glycopyrrolate, dexamethasone, intrathecal bupivacaine, morphine

Introduction

Postoperative nausea and vomiting (PONV) is the most troublesome adverse event encountered in the recovery room, despite advances in prevention and treatment. The incidence of PONV has remained high and has a major negative impact on patient satisfaction about the overall surgical experience. General anesthesia has long been considered as causing a greater frequency and severity of PONV than regional anesthetic techniques. In spite of many advancements for treating PONV, this problem still continues to occur with unacceptable frequency in association with surgery and anesthesia and description of it as "Big little problem" encapsulates much of general perception^[1]. Spinal anaesthesia is most commonly criticized for limited duration of post-operative analgesia. Among local anesthetic, 0.5% Bupivacaine HEAVY or HYPERBARIC is the most commonly used drug for spinal anesthesia. The most important disadvantage of single injection SAB is the limited duration. Adjuvants have long been used along with local anesthetics to prolong the duration of anesthesia and analgesia like morphine, fentanyl, ketamine, and clonidine.

Since the introduction of intrathecal morphine in 1979, a multitude of medications, such as synthetic opioids, α_2 -agonists, and cholinesterase inhibitors, have been introduced in an attempt to enhance the action of local anaesthetics. The decision about their usefulness will not only rely on their effects on nerve blockade and pain relief, but also on their influence on

side effects such as PONV [2]. In lower abdominal surgeries intrathecal morphine is better than opioid analgesic in parenteral routes after surgery [3]. Using morphine 100 micrograms as analgesic is not associated with delayed respiratory depression whereas intrathecal morphine is associated with PONV distress which creates a risk of wound dehiscence, besides causing patient discomfort [2, 4]. Incidence of PONV after spinal anaesthesia is 21%, which increases to 50% when we add opioid (morphine) adjuvant intrathecally [2]. Lower abdominal surgeries are associated with postoperative pain, which are frequently done under spinal anaesthesia with variety of drugs which have their own inherent effects. Studies have shown that for spinal anaesthesia combination bupivacaine with morphine is better choice.

Palonosetron is a 5HT₃ receptor antagonist a proven antiemetic, that has demonstrated superiority in preventing both acute and delayed emesis. Palonosetron uniquely triggers 5-HT₃ receptor internalization and induces prolonged inhibition of receptor function [5]. Dexamethasone is an inexpensive, effective and safe which has antiemetic and additional anti-inflammatory action. Efficacy of dexamethasone in reducing PONV, pruritus, and enhancing postoperative analgesia in patients receiving neuraxial anaesthesia with neuraxial morphine has been studied [6]. Glycopyrrolate is cost effective; easily available has less incidence of bradycardia with antiemetic action. Antiemetic effect may be due to heart rate mediated increase in cardiac output and subsequent reduction in hypotension episodes [7]. According to the data from various studies [2] suggest that, at least in more extensive surgery where effective postoperative pain relief is warranted, intrathecal morphine was not associated with higher PONV rates than opioid based systemic analgesia, especially if a dose of 100 microgram or less was chosen. By undertaking this study we can use safer dose of 100 micrograms of intrathecal morphine to find out the best method to overcome the most unwanted side effect of morphine i.e. nausea and vomiting. Many options are available for the treatment of PONV, among which we chose best of them, easily available & cost effective for our study.

This study was aimed to compare the effectiveness of different group of drugs in prevention of PONV in patients undergoing lower abdominal surgeries using intrathecal bupivacaine with morphine.

Material and Methods

After approval from institutional ethical committee, this prospective randomized double blind study was conducted in a tertiary teaching hospital from March 2018 to October 2019 in patients undergoing lower abdominal surgeries under spinal anaesthesia. Those patients who gave written informed consent of either sex in the age group of 20-60 years with ASA physical status I and II were included in the study. Patients with GI disorders, pregnancy, with h/o motion sickness and previous postoperative events, who have taken other antiemetic last 24hrs prior to surgery, with co-morbid disorders & all emergency cases and surgical cases with vomiting as symptom were excluded from the study.

Sample size was calculated as 30 in each group, considering 50% nausea in Dexamethasone and 10% in Glycopyrrolate group studied by Thomas R *et al.* [8] & Jain R *et al.* [9] (ref, 90% power and 5% alpha error, by hypothesis testing of two

or more large proportions with equal allocation, so total 90 divided into 3 groups).

After taking written informed consent, patients were allocated into two groups based on computer generated randomized sequence (www.random.org).

Their demographic data, history, clinical and systemic examination findings were recorded. Patients were advised to be nil orally for 6 hours. Among 90 patients, 30 patients in each group were given one of the study drugs. The drugs are given intravenously, only once, preoperatively 15 min before spinal anaesthesia.

- Group P: Patients received Inj. Palonosetron 0.075 mg
- Group D: Patients received Inj. Dexamethasone 8 mg
- Group G: Patients received Inj. Glycopyrrolate 0.2 mg

Spinal anesthesia in the L₂-L₃ or L₃-L₄ interspace was given with injection bupivacaine 0.5% hyperbaric 15mg with 100 micrograms preservative free morphine. The patients and the anesthesiologist observing the data were blinded. The duration and level of motor and sensory block were noted. Intraoperative monitoring of vital signs – heart rate, blood pressure, SpO₂, respiratory rate is done. Patients were observed for complete responders (no emesis, no rescue antiemetic), Number of episodes of vomiting post operatively over 48 hours (every 15 min till 2 hours. then every 6th hourly for 48 hours). Our Primary Outcome Measure was to control PONV.

Nausea and vomiting was assessed, An emetic episode defined as vomiting or retching or any combination that occurred in rapid sequence of less than 1 min between episodes.

Verbal rating scale for PONV, Nause scale 0 = none, 1 = mild, 2 = moderate, 3 = severe. No. of episodes of vomiting were recorded. Rescue antiemetic given was Inj. Ondansetron 4mg iv. Pain was assessed by Visual Analogue score (VAS) and Sedation by Ramsay sedation scale.

Statistical analysis was done by means of proportions for categorical/binary variables (gender, PONV) and mean, Standard deviation for continuous variables which are normally distributed (age, duration of surgery, weight, heart rate, SBP, DBP, MAP, post-operative sedation, VAS). Inferential statistics was done by using chi square test to compare percentage (proportion) between three groups (e.g. gender, PONV). Fisher exact test was used when expected values in the cells are less than 5. One way ANOVA was used to compare the difference in means between more than two independent groups (heart rate, SBP, DBP, MAP etc.). Post hoc test within one way ANOVA was used to make intergroup comparisons. Post hoc test (Bonferroni) was used, only when there is $P < 0.005$ in one way ANOVA. All the statistical methods were done using SPSS 21.0 version for windows. $P < 0.05$ was considered statistically significant. All the graphs were done either in SPSS or Microsoft Excel.

Results

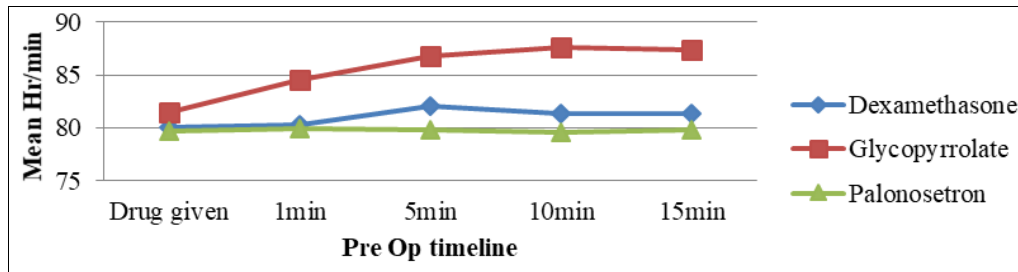
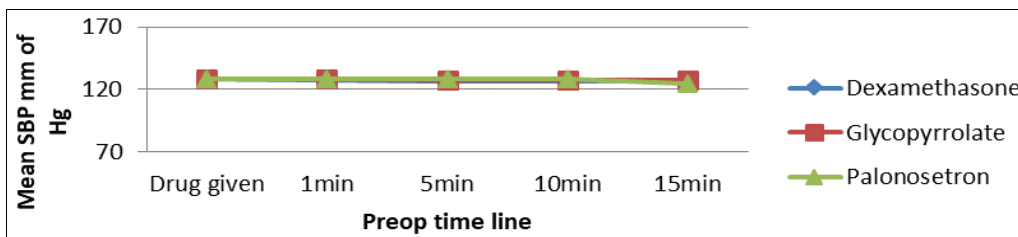
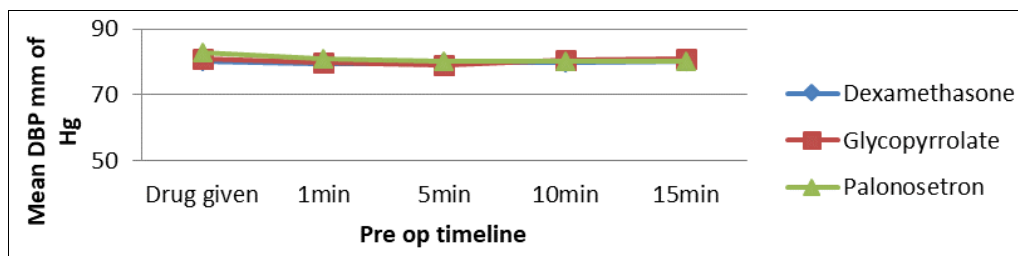
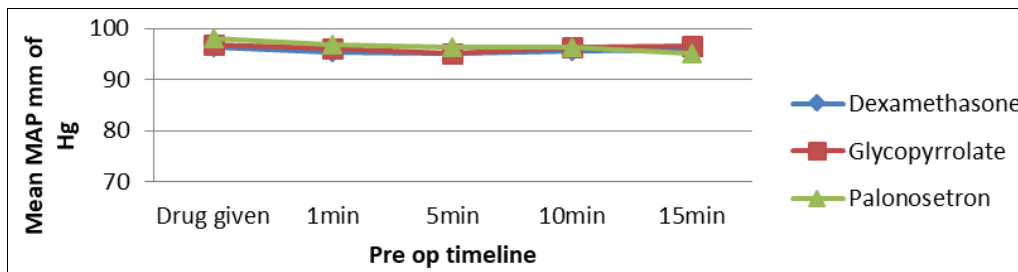
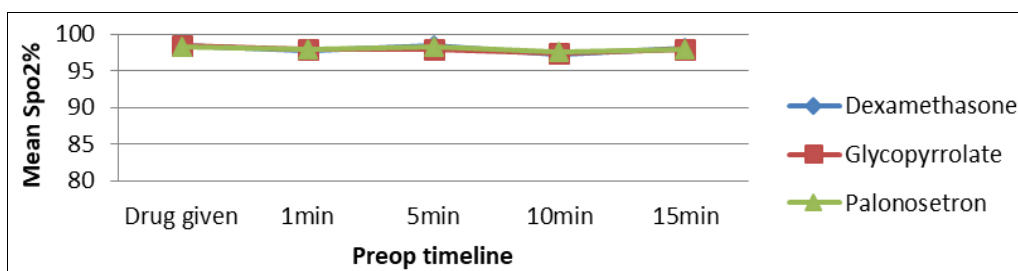
A total of 90 patients were enrolled for the study. There were no exclusion in the study. Demographic data comparing the age, gender, weight, height, ASA grade and type of surgery were comparable between the 3 groups and did not show any significant statistical difference. Mean duration of surgery for patients in Group D was 75.5±14.70, in Group G was 75.50±21.87, in Group P was 86.33±25.43. (Table 1).

Table 1: Comparison of demographic parameters, ASA and duration of surgery

	Group D		Group G	Group P
Age in years	41±13.8		41±9.7	45.3±11.3
Weight in kg	60.33±4.41		60.53±4.95	58.73±3.63
ASA	1	11	11	8
	2	19	19	22
Duration of surgery	75.50±14.7		75.5±21.87	86.33±25.43

The hemodynamic parameters like Heart rate, SBP, DBP, MAP, SpO₂ were comparable between the 3 groups. Intra operative heart rate p value for all 3 group is < 0.005 from 2

min to 20 min. Between Inj. Glycopyrrolate & Inj. Palonosetron P value was <0.001 which were significant. (Fig 1, 2, 3, 4, 5).

**Fig 1:** Pre-operative heart rate in all 3 groups**Fig 2:** Preoperative systolic blood pressure (SBP) in all 3 groups**Fig 3:** Preoperative diastolic blood pressure (DBP) in all 3 groups**Fig 4:** Preoperative mean arterial pressure (MAP) in all 3 groups**Fig 5:** Preoperative SpO₂ in all 3 groups

During intraoperative period of our study the incidence of nausea was 2 (6.7%) and vomiting was 2 (6.7%) in Dexamethasone group, incidence of nausea was 4 (13.3%) and vomiting was 3 (10%) in Glycopyrrolate group and incidence of nausea was 1 (3.3%) & vomiting was 1 (3.3%)

in Palonosetron group. Compared to Palonosetron group incidence of intra-operative nausea and vomiting is more in Glycopyrrolate group followed by Dexamethasone group. (Fig 6).

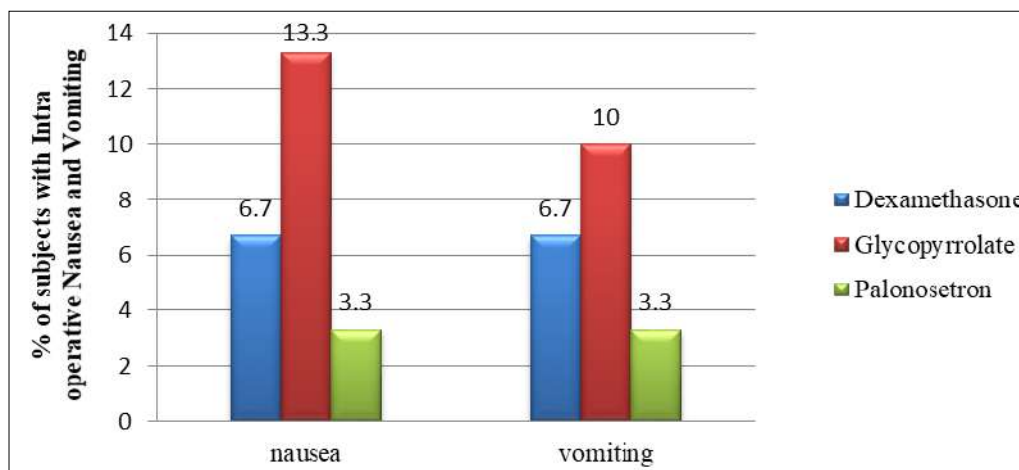


Fig 6: Intra-operative nausea and vomiting in all 3 groups

In our study patients who complained of nausea was followed by vomiting incidence. In first 2 hrs of post-operative period in Dexamethasone group 2 (6.7%) patients, in Glycopyrrolate group 4 (13.3%) of patients and in Palonosetron group 3 (10%) of patients had PONV. In 2 to 24 hrs, the incidence of PONV was 3 (10%) in Dexamethasone group, 1 (3.3%) in Palonosetron group and

Glycopyrrolate group was symptom free. From 24 to 48 hrs patients in all the 3 groups were free of PONV complaints. Over- all patients in Dexamethasone group had total incidence 16.67 % of PONV and patients in both Glycopyrrolate group & Palonosetron group had 13.3% of incidence post-operative nausea and vomiting. (Fig 7)

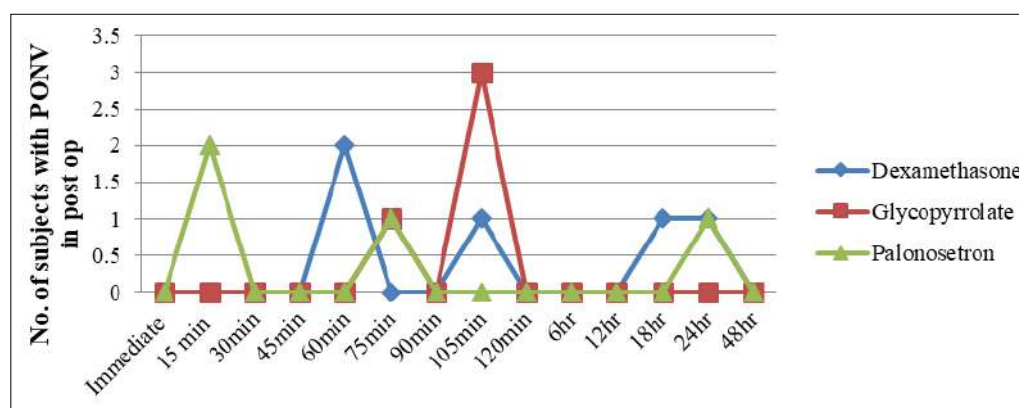


Fig 7: Post-operative nausea and vomiting in all 3 groups

Palonosetron was already a specific antiemetic drug. In our study we compared the efficacy of inj. Dexamethasone & Inj. Glycopyrrolate in prevention of PONV with Palonosetron which are easily available and cheaper & routinely used for other purposes other than antiemetic action. When we observed the incidence of PONV and complete responders in all the 3 groups, results in Dexamethasone group and Glycopyrrolate group were comparable with Palonosetron group and they are equally efficacious.

Requirement of rescue antiemetic is also comparable in all the groups. There is no significant difference in Ramsey Sedation Score and Visual Analog Scale between the groups.

Discussion

Post-operative nausea and vomiting is a common problem

and distressing symptom in surgical patient population. Many surgeries are associated with high incidence of PONV. This has led to many hypothesized causal mechanism of PONV in various types of surgeries. The incidence largely depends on pre-operative patient characteristics, operation, type of anaesthesia, gender, intensity of pain and its postoperative management. Postoperative vomiting will harm skin flaps, abdominal wall sutures, vascular anastomoses, and other areas recently operated on. It increases intra-ocular, intra-cranial pressure and may also cause tachycardia, electrolyte imbalance, wound dehiscence, oesophageal tears and aspiration pneumonitis. PONV after minor and ambulatory surgery delays the hospital discharge. Incidence of PONV after spinal anaesthesia is 21%, which increases to 50% when we add opioid (morphine) adjuvant intrathecally [2]. Antiemetics drugs including antihistamines, butyrophenones, and

dopamine receptor antagonists were used a few years ago. These antiemetics had undesirable side effects like excessive sedation, hypotension, dry mouth, dysphasia, hallucinations and extra-pyramidal symptoms and they are now rarely used ^[10]. In 1981, Dexamethasone was found to be an effective antiemetic in patients undergoing chemotherapy with limited side effects and its use in prophylaxis for PONV was started two years later. In 1990, 5-HT₃ antagonists were introduced. Anticholinergic Glycopyrrolate was also studied to be used as antiemetic ^[11]. Biswas BN *et al.* ^[7] observed the incidence of nausea and vomiting in patients who received inj. Glycopyrrolate (group A), inj. Dexamethasone (group B), inj. Metaclopramide (group C) and saline (group D). He found that patients who received inj. Glycopyrrolate (group A) incidence of nausea was 2 (10%), vomiting was 1 (5%), total 3 (15%) and complete responders were 17 (85%); patients who received inj. Dexamethasone (group B) the incidence of nausea was 2 (10%), vomiting was 2 (10%), total 4 (20%) and complete responders were 16 (80%); patients who received saline (group D) the incidence of nausea was 8 (40%), vomiting was 3 (15%), total 11 (15%) and complete responders were 9 (45%). The incidence of nausea and vomiting in A, B and C groups were compared with group D (placebo) and it was found that incidence of nausea and vomiting in Glycopyrrolate group was much less compared to all groups. p value less than 0.05 was considered significant. In our study the patients who complained of nausea were followed by vomiting. The patients who received inj. Glycopyrrolate (group G) the incidence of nausea was 4 (13.3%), vomiting was 4 (13.3%), total 4 (13.3%) and complete responders were 26 (86.7%); the patients who received inj. Dexamethasone (group D) the incidence of nausea was 5 (16.6%), vomiting was 5 (16.6%), total 5 (16.6%) and complete responders were 25 (83.4%). P value 0.6 which we considered not significant and efficacy inj. Glycopyrrolate and inj. Dexamethasone were comparable.

SKS, Shaikh S *et al.* ^[12] in 2012 investigated and compared the efficacy of newer 5HT₃ antagonist Palonosetron with placebo, in preventing Postoperative Nausea and Vomiting in patients undergoing gynaecological surgeries under spinal anaesthesia. The efficacy of study medication was assessed in terms of Complete Response (No emesis and no rescue antiemetic), incidence of emetic episodes, the incidence and severity of nausea in the postoperative study periods 0-6 hours, 6-24 hours and 24-72 hours. They found that incidence of a Complete Response (no emesis, no rescue antiemetic) in 0-6 hour study period was 82.9% with Palonosetron group and 45.7% with placebo group (P value-0.001 strongly significant). The corresponding incidence in 6-24 hour was 74.3% with Palonosetron and 37.1% with placebo group. During 24-72 hour, the incidence was 97.1% in Palonosetron and 94.3% in the placebo group. In our study that incidence of a Complete Response in 0-6 hour study period was 90% with Palonosetron group. The corresponding incidence in 6-24 hour was 96.7%. We observed till 48 hrs postoperatively during that period, the incidence was 100%. Therefore inj. Palonosetron is better drug in prevention of Post-Operative Nausea and Vomiting. Cardoso M *et al.* in 2013 ^[13] studied that during the first 24 hours, nausea occurred in 12/35 (34.4%) patients receiving dexamethasone and in 32/35 (91.4%) receiving placebo (P<0.001). During the same time period, vomiting occurred

in 12/35 (34.4%) patients receiving dexamethasone and in 29/35 (82.9%) receiving placebo (P<0.001). Pain at rest and pain on movement was lower in patients who received dexamethasone at some time points during the study period. In our study there was not much significant difference in VAS score for pain between 3 groups.

This study had few limitations like Discomfort related to morphine were not studied which confounds observation of our study. Use of same drug as rescue antiemetic for each group, instead of ondansetron as common drug would have helped in better assessment of efficacy of the drug and Larger sample size would have given more specific derivations. To conclude our study demonstrates that the efficacy of premedication with i.v. Dexamethasone or Glycopyrrolate in lower abdominal surgeries in prevention of Post-Operative Nausea and Vomiting is comparable with Palonosetron.

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