Original Article

A prospective, randomized, double blind and placebo-control study comparing the additive effect of oral midazolam and clonidine for postoperative nausea and vomiting prophylaxis in granisetron premedicated patients undergoing laparoscopic cholecystecomy

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Abstract

Background: Reduction of postoperative nausea and vomiting (PONV) continues to be a major challenge in perioperative care in spite of introduction of newer antiemetics with better efficacy and safety profiles. Therefore, we evaluated the additive effect of oral midazolam and clonidine for PONV prophylaxis in granisetron premedicated patients undergoing laparoscopic cholecystectomy.

Materials and Methods: In a prospective, randomized fashion, 120 selected cases were randomized into three groups: I, II or III to receive a tablet of midazolam (15 mg, $n = 36$), clonidine (150 mcg, $n = 40$), or glucose as placebo (5 g, $n = 44$) orally, 1 h before anesthesia. Occurrence of PONV along with need for rescue antiemetic during the first postoperative day was compared between groups as a primary outcome.

Results: Episodes of PONV reduced significantly in Group II (15%) as compared to group I and III (22.2%, 59%) at various time points during the period of observation ($P = 0.002$). Need for rescue antiemetic was significantly lower in group I (13.88%) and II (5%) as compared to group III (52.27%, $P < 0.001$).

Conclusion: Oral clonidine is better adjuvant for PONV prophylaxis, as compared to midazolam, in granisetron premedicated patients undergoing laparoscopic cholecystectomy.

Key words: Clonidine, granisetron premedicated, midazolam, PONV prophylaxis

Introduction

Postoperative nausea and vomiting (PONV) continues to be a major compliant after laparoscopic surgeries accounting for about 40 to 77% of cases.[1] There is a rising concern for PONV related complications like aspiration, hypoxia, bleeding, suture dehiscence, patient discomfort, increased hospital stay, and added health care costs. It is widely anticipated that a single antiemetic is less likely to be reasonable measure to prevent PONV than combination of drugs.[2] Many drugs like dexamethasone, droperidol and metoclopramide have been investigated to reduce the risk of PONV. Given the limited antiemetic efficacy of prophylactic antiemetic, Scuderi and coworkers were the first to investigate a multimodal approach in laparoscopic surgery.[3] Oral clonidine premedication was found to reduce vomiting in children after strabismus surgery.[4]

Although clonidine and midazolam are commonly used in adult patients as a premedication but literature review and Medline search did not reveal any study in adult patients, undergoing laparoscopic cholecystectomy, where comparison of additive effect of clonidine and midazolam has been evaluated for PONV prophylaxis in granisetron-premedicated patients. The present study was undertaken to investigate the additive effect of oral midazolam for PONV prophylaxis in

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granisetron-premedicated patients undergoing laparoscopic cholecystectomy and to compare it with oral clonidine. The primary outcome measure was PONV while secondary outcome measures were mean pulse rate, systolic blood pressure, postoperative visual analog score (VAS) and Ramsay sedation score (RAS).

Materials and Methods

After ethical approval and written informed consent, 120 female patients of American Society of Anesthesiologists physical status 1/2, aged 18-60 years, posted for laparoscopic cholecystectomy in between January 2010 and December 2010 were included in this trial. Exclusion criteria included known hypersensitivity to granisetron, significant systemic disease, obesity (BMI > 35) and patients already on antiemetics, steroids and opioids. Patients with previous history of motion sickness and PONV were included because they are the ones who are likely to get maximum benefit from prophylactic antiemetic therapy.

Using a sealed envelope technique, patients were randomized into three groups: Group I (n = 36): received midazolam 15 mg orally; Group II (n = 40): received clonidine 150 mcg orally; while Group III (n = 44): received glucose 5 g orally. Randomization and study drug administration was done by an investigator not involved in the management of the patients. Two blinded anesthesiologists familiar with the anesthetic technique participated in the procedure. The data collection was done by another investigator blinded to group allocation.

All the patients were administered studied drug as per group allocation, 60 minutes before induction of anesthesia. No antianxiety premedication was given to the patients, preoperatively. Perioperative monitoring included heart rate, oxygen saturation ($SpO_{2)}$, electrocardiography, noninvasive blood pressure and end-tidal carbon dioxide concentration ($EtCO_2$). All patients were given granisetron 1 mg intravenous (IV) 10 min before induction. Induction of anesthesia was done with fentanyl 2 mcg/kg and propofol 2 mg/kg IV. Vecuronium bromide 0.1 mg/kg IV was administered to facilitate endotracheal intubation. Ventilation was controlled mechanically and was adjusted to keep $EtCO_2$ 35-40 mmHg. Anesthesia was maintained using 70% nitrous oxide in oxygen and 0.5-1% isoflurane, and intermittent dosage of fentanyl 1 mcg/kg and vecuronium 0.02 mg/kg. At the end of surgery the neuromuscular block was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV and patients were transferred to the postanesthesia care unit (PACU). Sedation was assessed by RSS. The events in the recovery room vomiting, pain, heart rate, blood pressure, SpO_2, respiratory rate, antiemetic and analgesic requirements were recorded at every 30 minutes for the first 2 h and thereafter at 4 h, 6 h, and then 6 hourly up to 24 h. Pain was assessed by using VAS between 0-10; where 0 means no pain and 10 means worst imaginable pain. RSS was assessed by six point scale (1-6): 1- Anxious or restless or both; 2- Cooperative, orientated and tranquil; 3- Responding to commands; 4- Brisk response to stimulus; 5- Sluggish response to stimulus; 6- No response to stimulus. The severity of PONV was graded on a four point ordinal scale from 0 to 3 (0 = no nausea; 1 = mild nausea; 2 = moderate nausea; 3 = severe nausea with vomiting). For postoperative pain management fentanyl 0.5-1 mcg/kg IV was used in all patients for the first 24 h. All emetic episodes were noted by the blinded anesthesiologist. Total amount of IV metoclopramide used as rescue antiemetic was recorded.

Assuming that average incidence of PONV following laparoscopic cholecystectomy is 70%, to have 80% power α0.05), to detect a reduction to 35%, one would need to study 31 patients per group. Keeping in mind the drop out, we planned to study 36 patients in each group. Demographic and clinical data in three groups were analyzed using independent sample 't' test or Mann Whitney test where appropriate. The occurrence of PONV, rescue antiemetic therapy and rescue analgesic therapy were analyzed with the Chi-square test or the Fisher Exact test. The number of episodes of vomiting that occurred was measured by standard analysis of variance (ANOVA). P-value <0.05 was considered significant.

Results

All 120 patients completed the study without any dropout [Figure 5]. There was no significant difference in the demographic profile between the three groups (P > 0.05) [Table 1].

Significant reduction in incidence of PONV was observed in the Group II as compared with I and III, 15%, 22.2%, and 59%, respectively (P = 0.002). Requirements of rescue antiemetic in first 24-h postoperative period was more in the Group III (52.27%) as compared with (5%) and (13.88%) in Group II and I, respectively (P < 0.001) [Table 2].

Mean pulse rate was significantly low in Group I and II as compared to Group III (P = 0.003). Overall the mean pulse rate and its variation during the first 6 postoperative hours was lower in Group II and very high in Group III (P = 0.007) [Figure 1]. The mean systolic blood pressure was lower in Group II than Group I and III at all time-points [Figure 2]. The VAS was significantly lower in group I as compared to group II and III (P<0.001) for first hr during postoperative period [Figure 3]. In Group III, RSS at 2 h was lower as compared to Group I and II (P = 0.007) [Figure 4].

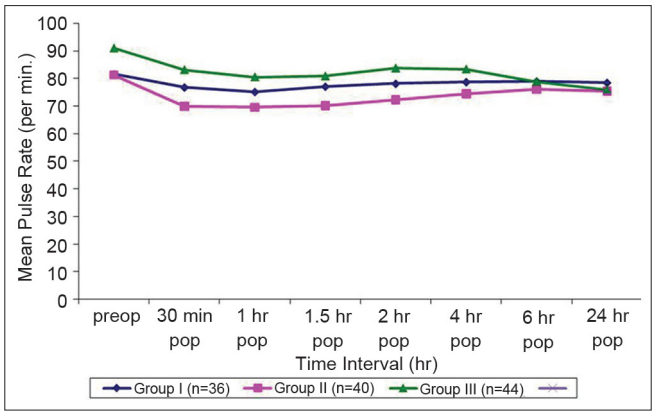

Figure 1: Mean pulse rate at various time points during postoperative period

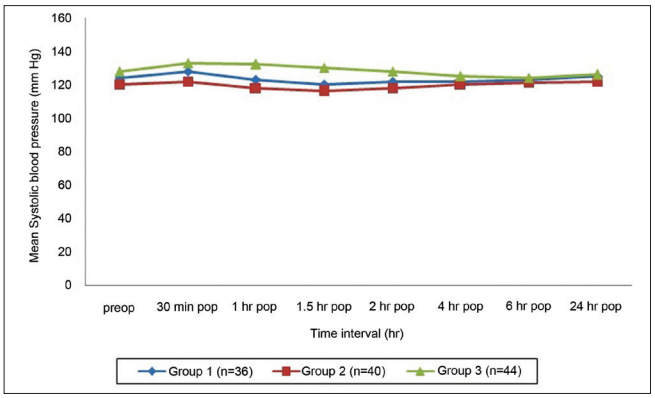

Figure 2: Mean systolic blood pressure at various time points during postoperative period

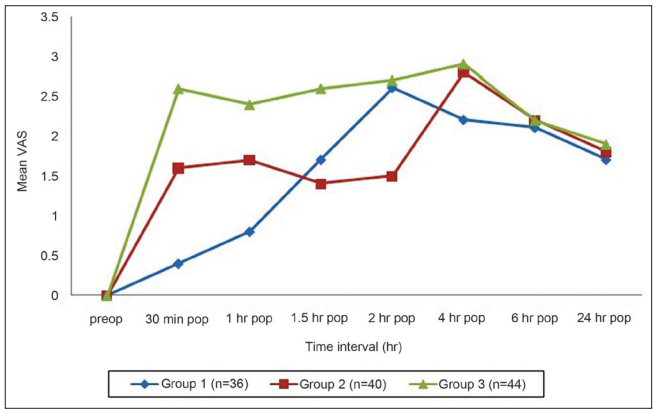

Figure 3: Visual analogue score at various time points during postoperative period

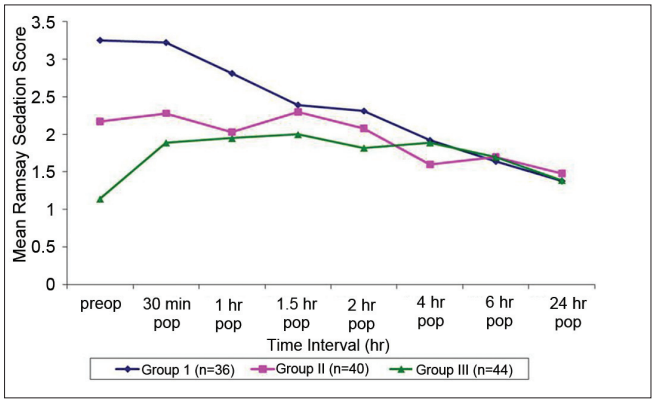

Figure 4: Showing mean Ramsay sedation score (RSS) in Group III at preoperative period was lower as compared to Group I and II

Table 1: Demographic data (Mean ± SD)

Variables	Group I (*n* = 36)	Group II (*n* = 40)	Group III (*n* = 44)
Age (years)	36.94 ± 12.109	41.85 ± 12.213	39.48 ± 10.926
Weight (kg)	54.25 ± 9.811	54.09 ± 9.637	59.32 ± 10.726
Height (cm)	153.92 ± 5.050	154.18 ± 5.358	153.59 ± 5.235
BMI (Kg/mt^2)	22.4 ± 5.6	22.9 ± 4.9	23.5 ± 5.8

**P-value less than 0.05 were taken as significant*

Table 2: Incidence of post-operative nausea and vomiting (PONV) in the three groups atdifferent time intervals (%)

Time interval (hours)	Group I (*n* = 36)		Group II (*n* = 40)		Group III (*n* = 44)		χ^2	*P*-value
	No.	%	No.	%	No.	%		
0	0	0	0	0	0	0	-	-
0.5	0	0	1	2.5	2	4.5	1.678	0.432
1	1	2.8	1	2.5	1	2.3	0.021	0.990
1.5	4	11.1	1	2.5	5	11.4	2.674	0.263
2	0	0	0	0	4	9.1	7.147	0.028*
4	2	5.6	1	2.5	8	18.2	6.994	0.030*
6	0	0	2	5.0	13	29.5	15.883	0.000*
24	6	16.7	3	7.5	14	31.8	12.499	0.002*

**statistically significant (P < 0.05)*

Discussion

We observed significant reduction in incidence of PONV in clonidine group as compared to midazolam and placebo group.

Four major neurotransmitter system appear to play important roles in mediating the emetic response viz. dopaminergic, histaminic (H1), cholinergic/muscarinic and serotonergic (5 HT_3). As there are four different types of receptors, there are at least four sites of actions at more than one receptor, but the commonly used drugs have a more prominent action at one or two receptors.[5] Midazolam possibly acts as an antiemetic by decreasing dopamine input at the chemoreceptor trigger zone in addition to decreasing anxiety. It may also decrease adenosine reuptake. This leads to an adenosine-mediated reduction in the synthesis, release, and postsynaptic action of dopamine at the chemoreceptor trigger zone.[6,7] Moreover it may also decrease dopaminergic neuronal activity and 5-hydroxytryptamine (5-HT) release by binding to the γ-amino butyric benzodiazepine complex.[8]

The mechanism of antiemetic effects of clonidine is not known and probably multifactorial. It decreases sympathetic outflow, reduces anxiety, provide sedation and decreases anesthetic and analgesic requirements.[9] High sympathetic tone and catecholamine release may trigger nausea and vomiting.[10,11] The analgesic effect of clonidine, by a reduced need for opioid as

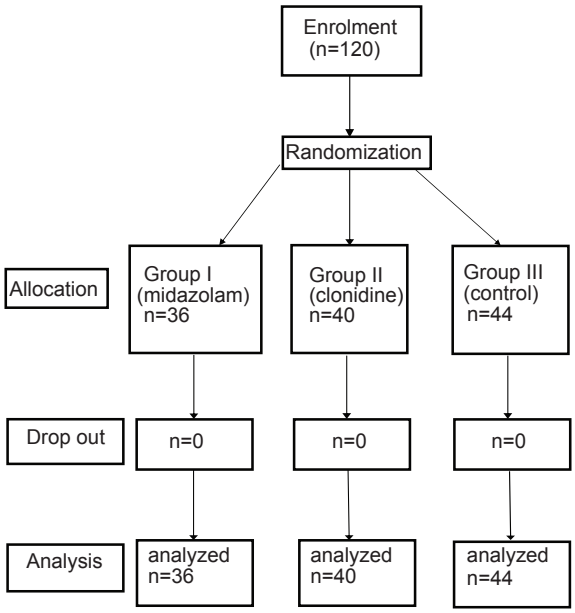

Figure 5: Flow chart of patient studied

known emetogens,[10,12] might influence the incidence of PONV.

Clonidine decreases sympathetic tone, attenuates heart rate, arterial blood pressures, and plasma renin activity were lower during and after pneumoperitoneum.[9] Preoperative clonidine decreases intraoperative stress response and improves hemodynamic stability.[9,13,14] The hemodynamic effects of midazolam are dose related: the higher the plasma level, the greater the decrease in systemic blood pressure.[15] The mechanism by which midazolam maintain a relatively stable hemodynamic involves the preservation of homeostatic reflex mechanisms.[16]

Apnea and respiratory depression occurs with benzodiazepines in a dose-dependent manner[16] and more likely to occur in the presence of opioids. Clonidine have minimal depressant effects on ventilation and it does not significantly potentiates opioid induced depression of ventilation.[17]

Clonidine use resulted in lower VAS, better pain relief and lesser rescue analgesic requirements. This was possibly because of activation of post-synaptic $\alpha 2$ receptor in substantia gelatinosa of spinal cord, as well as the descending noradrenergic pathway.[18,19]

Limitations of this study are that we have used nitrous oxide, isoflurane and fentanyl which are known to potentiate emesis. According to the pharmacokinetics of midazolam and clonidine, a different length of preoperative observation was necessary. Different age groups have different emesis potential. We did not use antianxiety premedication, which is also limitation of our study.

This study supports the study done by Mikawa *et al*.[4] in children which found that clonidine to be better than midazolam. The additive effect of oral midazolam and clonidine for PONV prophylaxis in granisetron-premedicated adult patients undergoing laparoscopic cholecystectomy has not been adequately studied and further research in this field is needed.

To conclude, clonidine has higher antiemetic efficacy than midazolam. Clonidine decreases the sympathetic discharge and act as a preemptive analgesic. Oral clonidine is better adjuvant, than midazolam, for PONV prophylaxis, in granisetron-premedicated patients undergoing laparoscopic cholecystectomy.

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