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THE EFFICACY OF A SINGLE PREANESTHETIC SUB HYPNOTIC DOSE OF PROPOFOL IN ADDITION TO RANITIDINE AND METOCLOPRAMIDE IN THE PREVENTION OF NAUSEA AND VOMITING IN SPINAL ANAESTHESIA FOR CAESAREAN SECTION

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Abstract

Background: The physiological changes of pregnancy deem nausea and vomiting infallible complications associated with obstetric anaesthesia, resulting in significant morbidity and longer recovery time. The aim of our randomised control trial was to investigate the efficacy of propofol in addition to the currently accepted regimen of ranitidine and metoclopramide in the prevention of nausea and vomiting in this high risk group undergoing spinal anesthesia during caesarean section.

Methods: Eighty fasted term pregnant women scheduled for elective caesarean section were given ranitidine 150mg and metoclopramide 10mg orally 2 hours prior to spinal anaesthesia following which they received either propofol 200µg /kg IV or placebo as a single bolus dose. Intraoperative and post-delivery emetic episodes experienced were recorded at intervals and the intensity of nausea was assessed using the visual analogue scale (VAS).

Results: The incidence of nausea during the intraoperative period in propofol group was 5 % as compared with placebo group in which it was 32.5%, while that of vomiting in propofol group was 5% as compared with placebo group in which it was 22.5%. Both were found to be statistically significant (p= 0.002, p= 0.023 respectively). The incidence of nausea and vomiting during the entire postoperative period of 0-24 hours between the two groups was found to be statistically insignificant.

Conclusion: The prophylactic administration of a subhypnotic dose of propofol with ranitidine and metoclopramide was effective in the prevention of nausea and vomiting after neuraxial blockade during the intraoperative period but not during the postoperative period.

Keywords:obstetric anaesthesia, caesarean section, nausea, vomiting, anesthetics i.v., propofol

Trial registry number

Clinical Trials Registry-India: CTRI/2018/05/013610

Introduction

Nausea and vomiting are distressing symptoms associated with anaesthesia, resulting in significant morbidity and longer recovery time[1].Although various antiemetics have been studied, none of the currently available prophylactic antiemetic regimens have entirely besuccessful in eliminating the incidence of nausea and vomiting[2]. This has led to the development of a concept of combination therapy known to be beneficial in high risk groups[3].The concept of a short-acting, specific antiemetic effect of propofol is a well recognised fact, regardless of the anaesthetic technique[4, 5].In order to bridge the liabilities in the present antiemetic regimens, we investigated the addition of propofol to the currently accepted regimen of ranitidine and metoclopramide in order to hypothesise a new multimodal regimen to prevent nausea and vomiting during obstetric anaesthesia. A secondary objective was to obtain the incidence of nausea and vomiting during and after spinal anaesthetic and compare the emesis free intervals.

Methods

Design

We conducted a double-blind, randomised control trial to evaluate the efficacy of a single preanesthetic subhypnotic dose of propofol in addition to ranitidine and metoclopramide (RMP) against the control, ranitidine

and metoclopramide (RM) given intravenously before spinal anaesthesia for caesarean section. The study was done at a tertiary care hospital after obtaining permission from the Research Ethics Board. All drugs used had regulatory approval from Drug Controller General of India.The study was registered with Clinical Trials Registry-India (CTRI/2018/05/013610). Informed written consent was obtained from all patients.
The inclusion criteria were ASA physical status 2 pregnant women at term, aged between 18-40 years scheduled for elective caesarean delivery under neuraxial anaesthesia having followed standard fasting guide-lines. Patients who were ASA physical status III and IV, who received antiemetics and opioids within 24 hours before surgery, who had a history suggestive of migraine/motion sickness/PONV, substance abuse or allergies to the drugs in the study were excluded.

Procedures

Pre-anesthetic checkup was done for all the patients and standard fasting guidelines adhered to. All patients were given tab. ranitidine 150mg and tab. metoclopramide 10mg orally 2 hours prior to surgery. Vital signs (heart rate, blood pressure and peripheral oxygen saturation) were recorded using standard non-invasive monitors and measurements taken at regular intervals throughout the procedure. Each patient received crystalloid infusion at 10ml/kg prior to spinal anaesthesia and crystalloids were continued during the procedure. Patients were allocated to receive either injection propofol 200µg/kg IV or placebo as a single bolus dose through a computer generated random number software. A non-investigator anesthesiologist and anaesthesia assistant not participating in patient care or data collection prepared the drug doses.
0.5% hyperbaric bupivacaine was injected intrathecally in left lateral position using 27G Quincke spinal needle at L3-L4 interspinous spaces to achieve a sensory blockade of T5 level. Patient was then placed in supine position with left uterine displacement. Oxytocin (20 units) infusion was started intravenously at the time of umbilical cord clamping. Hypotension (>20% decrease in MAP from baseline for one or more measurements) intraoperatively was treated with vasopressors and IV fluids. If two or more episodes of nausea-vomiting occurred, 4mg ofondansetron was provided intravenously as rescue antiemetic treatment. 6 Intraoperative andpost-delivery emetic episodes (nausea and vomiting) experienced by the patients were recorded by the investigator and the intensity of nausea was assessed using the visual analogue scale (VAS) categorised as 0 for no nausea, 1-3 for mild nausea, 4-7 for moderate nausea and 8-10 for severe nausea.[7] A score of 1 or more was recorded as an episode of nausea

Statistical analyses

Continuous variables, when normally distributed, were analysed using a Student's unpaired t- test. Continuous variables,if not normally distributed, were analysed with non-parametric Mann Whitney U-test.Categorical data was analysed using the chi square test. Continuous data are reported as mean (SD), or median and interquartile range, as appropriate. Categorical data are reported as frequencies (%). A $P<0.05$ was considered statistically significant. The statistical analysis was performed with SPSS version 17 statistical package.

Results

Ninety six patients were approached, of which 11 declined and 5 did not fulfil the inclusion criteria. The remaining 80 participants who consented to participate in the study comprised the randomised controlled trial cohort (Figure 1).There were no significant differences among subjects in the both study groups in terms of patients characteristics (Table 1). The mean duration of surgery in the propofol group was longer than the placebo group and was statistically significant ($p = 0.011$) with the propofol group showing lesser nausea and vomiting despite having longer duration of surgery (Table 2). The incidence of nausea and vomiting during the intraoperative period in the propofol group was profoundly lower when compared with placebo ($p=0.002$, $p=0.023$ respectively).During the postoperative period,no significant difference wasobtained between both groups (Table 3). The 3D up and-down line diagrams for each group are shown (Figure 2).

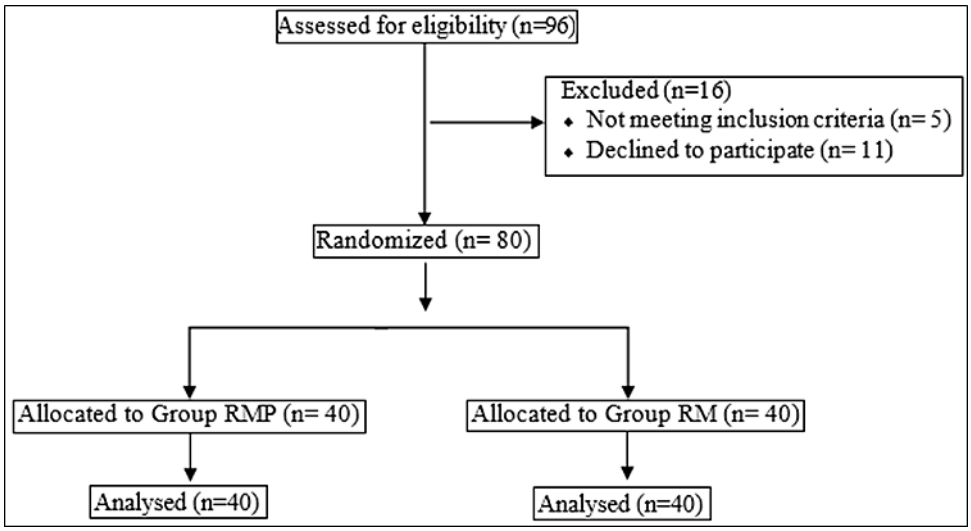
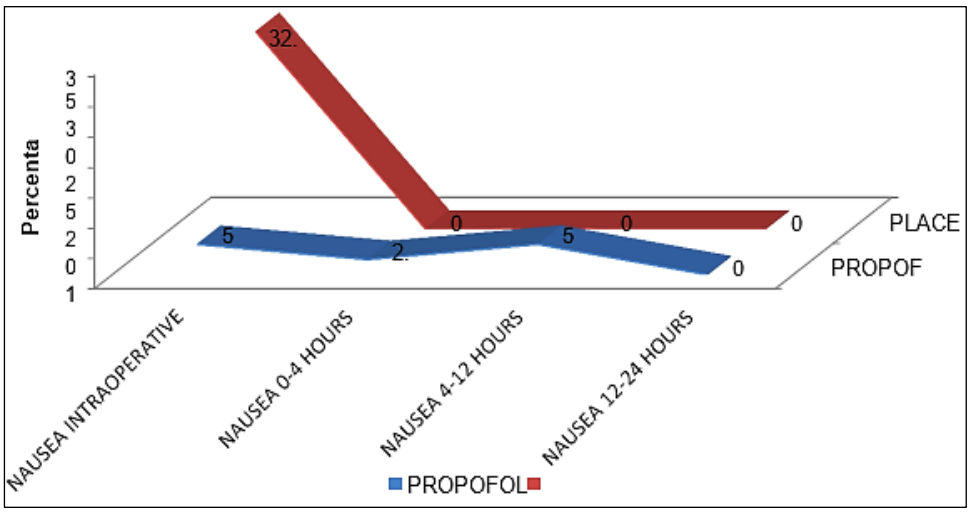


Fig 1: Flow diagram of included participants



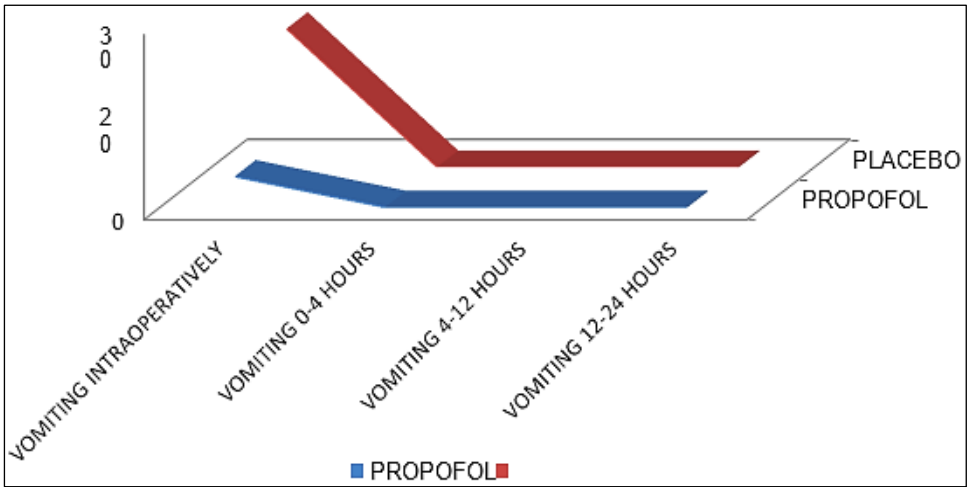


Fig 2: Line diagram of frequencies of nausea and vomiting at varying intraoperative and postoperative intervals

Table 1 Patient characteristics. Data are mean (SD), median (interquartile range), or n (%), as appropriate

	Propofol	**Placebo**
Number of patients	40	40
Age (years)	28.05 (5.119)	28.88 (5.297)
Weight (kg)	58.55 ± 10.223	56.43 ± 8.542
Height (cm)	153.55 ± 6.767	150.70 ± 6.634

Table 2: Intraoperative haemodynamic parameters. Data are expressed as mean (SD), median (interquartile range) or n (%). MAP, mean arterial pressure. Hypotension was defined as >20% decrease in MAP from baseline for one or more measurements. *P<0.05 vs baseline

	Propofol	**Placebo**
Duration of surgery (min)	70.4 (17.9)*	62.1(9.5)*
Uterus exteriorized (%)	45.0	55.0
Hypotension (%)	57.5	55.0
Total ephedrine dose (mg)	8.6(4.2)	9.7 (6.0)

Table 3: Intraoperative and postoperative frequency of nausea and vomiting. Data are expressed as n (%). *P<0.05 vs baseline

	Propofol		**Placebo**	
	Nausea	**Vomiting**	**Nausea**	**Vomiting**
Intraoperative	2 (5.0)	2 (5.0)*	13 (32.5)	9(22.5)*
Postoperative 0-4 hours	1 (2.5)	0 (0)	0 (0)	0 (0)
Postoperative 4-12 hours	2 (5.0)	0 (0)	0 (0)	0 (0)
Postoperative 12-24 hours	0 (0)	0 (0)	0 (0)	0 (0)

Discussion

The multifaceted causes of nausea and vomiting during the intraoperative and postoperative period and their subsequent treatment has been an intriguing topic of much celebrated discussion among anesthesiologists worldwide. The challenges faced have taken on several dimensions including identification of high risk groups, risk stratification, treatment efficacy, efficiency and consistency of the treatment process[8].The increasing understanding of nausea and vomiting associated with caesarean section and the related pathophysiology has led to the conception of a holistic approach which should be started before the operation and

Continued intraoperatively, encompassing a multimodal treatment regimen with risk reduction strategiesas well as pharmacy, according to the assessed individualised patient risk[9].We have tried to encompass these goals and subsequently evaluate the efficacy and viability of using a subhypnotic dose of propofol during caesarean section.

Despite recent advances in identifying patient factors, superior operative techniques, newer antiemetic drugs, nausea and vomiting associated with surgery and anesthesia continues to occur with unacceptable frequency. This has been particularly profound and exacerbated especially in LSCS under subarachnoid block. Postoperatively, nausea and vomiting correlated with the incidence of pulmonary aspiration of gastric contents, surgical bleeding, impaired fluid balance, wound dehiscence and electrolyte disturbance[10].Hence our study was targeted to reduce the distress caused by nausea and vomiting associated with caesarean section and allay the anxiety it causes in the maternal population.

An injection of 2.5 mg/kg bolus of propofol was studied in order to determine the placental transfer of the drug and its neonatal effects during general anesthesia in parturients. Mean concentration of propofol in the maternal vein was 0.56 ±0.08 μg/ml and in the umbilical vein was 0.39 ±0.05 μg/ml. The mean duration between the injection of propofol and delivery of fetus was 25±3.6 minutes. The ratio of plasma concentration measuring the maternal to fetal transfer was determined to be 0.70[11].Plasma concentrations of propofol in a neonate at birth are dependent on the level in maternal plasma, and consequently on the induction dose in tandem with the interlude between the administration of the drug and the delivery of the foetus.[12] Extrapolating the results of these studies, we choose a minimalistic dose of 200 μg/kg to be used in our study which would not give any undesirable fetal transfer in the short duration of uterine incision to delivery time.

Borgeat and colleagues had in their randomised placebo controlled study demonstrated that patients experienced profound diminution in nausea and vomiting with propofol (81%) against the placebo (35%). The mean operating time was 98 minutes for the propofol group and 89 minutes for the placebo group.However the relapse rate within 30 minutes was significant with propofol[1].Our study had a similar conclusion wherein the RMP group had significant reduction during the intraoperative period. The mean duration of surgery in our study was alsolonger with propofol group showing no emesis for a duration of 70 minutes and placebo group for 62 minutes. It should be mentioned that there was no incidence of relapse in our study and the postoperative period remained insignificant between both groups.

Gan TJ and colleagues studied the reduction in nausea scores to 50 percent and postulated it to be 343 ng/ml for 50th percentile and 592 ng/ml for 90th percentile for the plasma concentration of propofol infusion[13].Our study found even a bolus at a very minimal dose of 200 мg/kg made a difference in the intraoperative period to allay the sensation of nausea and subsequent episodes of vomiting.Both Schulman *et al*. and Campbell *et al*. had investigated the concentration of propofol to be maintained in the plasma for the successful treatment of nausea in a postoperative patient. While the first found it to be 197 ng/ml for successful treatment, the latter determined that 0.3 mg/kg propofol at the end of surgery was not effective [14, 15].Our study had concluded 200 мg/kg was efficacious during the intraoperative duration of 70 minutes with no effect on the postoperative period. However, should we have given the dose towards the end of the surgery as was done by Campbell *et al*., we could possibly extrapolate the findings and assume a further 70 minutes of emesis free duration.

Shi JJ *et al*. in a study of 50 pregnant mothers found that a single 10 mg bolus of propofol after the delivery of the baby did not validate its efficiency in the preventing either nausea or vomiting intraoperatively. 24% patients had nausea with propofol and 40% had nausea in the control group. Similarly 16% patients had vomiting with propofol and 20% had vomiting in the control group, neither of these were significant[16].In stark contrast our study had proven that incidence of both were reduced during the intraoperative period. Vomiting in mothers who received propofol was 5% as compared with 22.5% in those who did not and nausea was 5% as compared to 32.5%.Rudra and colleagues found that 26 of 30 patients (86%) who hareceived propofol 1mg/kg/hr remained emesis free, compared with 12 of 30 (40%) who had received placebo during the intraoperative and early post delivery period, which spanned a duration of 0-3 hours. Nausea was also found to be a less disconcerting symptom in those who received propofol with a reduction in severity scores[17].Our study showed similar statistical findings with 95% patients in the propofol group remaining emesis free as compared to 77.5% of those who received placebo.

It might be pertinent to conclude that our results have equally matched similar studies done in the past with infusion dosages and refuted the past studies against a single bolus dose. Certain non-anesthetic causes including surgical bleeding, medications such as uterotonic agents and antibiotics have not been factored in during the assessment of the study and hence could have biased the results. Thus the authors recommend the usage of a single subhypnotic dose of propofol in the prevention of nausea and vomiting during caesarean section to lay the foundation for a new multimodal prophylactic regimen.

Authors' contributions

Study design: P.K, R.R.
Patient recruitment: P.K, R.R.
Data collection: P.K, R.R.
Table and figure design:R.R.
Writing of manuscript: all authors.
Approval of final manuscript: all authors.

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Declaration of interest

The authors declare that they have no conflicts of interest.

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