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Original Research Article

Ramosetron vs Ramosetron with Dexmedetomidine for Prevention of Postoperative Nausea Vomiting and Shivering after Gynaecological Laparoscopic Surgery: A Comparative Study

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Abstract
Background: *Postoperative nausea and vomiting (PONV) and postanesthetic shivering (PAS) are common postoperative patient complaints that can be very distressing and may result in adverse physical outcomes. A combination therapy is more effective in dealing with PONV owing to its multifactorial etiology. Some antiemetics are reported to be effective in the management of PONV as well as PAS and pain. We evaluated the efficacy of dexmedetomidine added to ramosetron for prevention of PONV and shivering after gynaecological laparoscopic surgery.*
Methods: *One hundred and sixty patients scheduled for gynecologic laparoscopic surgery were randomly allocated to two groups. The patients of first group (group R, n = 80) were given ramosetron 0.3 mg and 50 ml normal saline; and the patients of second group (group D, n = 80) were given ramosetron 0.3 mg and 1µ/kg dexmedetomidine diluted in 50 ml normal saline before anaesthesia.*
Results: *Incidence of nausea, emesis and the need for rescue antiemetics was lesser in group D but the difference was insignificant. Incidence of shivering and interventions for shivering, one hour pain scores and*

total analgesic required in 24 hours were significantly lower in group D as compared to group R.
Conclusions: *Ramosetron 0.3 mg was as effective as combination of ramosetron 0.3 mg and dexmedetomidine 1µ/kg given before anaesthesia in reducing PONV. However, the combination of two drugs was more effective in reducing the incidence of post-operative shivering episodes, severity of pain, and total postoperative analgesic requirement compared to ramosetron alone in patients undergoing gynaecological laparoscopic surgery.*
Keywords: *Ramosetron, Dexmedetomidine, Post-operative nausea and vomiting, Shivering, Gynecological laparoscopic surgery.*

Introduction

Nausea, vomiting, and shivering are common problems after anesthesia, which can be very distressing and may cause adverse physical outcomes without proper intervention. The postoperative nausea and vomiting (PONV) occurs in 20% to 30% of the patients but the incidence can be as high as 70% to 80% in patients of high-risk groups[1]. It is seen in almost 90% of cases after gynecologic laparoscopic surgeries and is one of the major concerns of the recovery period[2]. Post anesthesia shivering (PAS) is commonly encountered after both general and regional anesthesia with an incidence range of 40% to 60%. It is distressing and uncomfortable and is associated with adverse effects on the normal recovery process[3,4]. Understandably, PONV and PAS diminish the advantage of rapid recovery expected in laparoscopic surgery.

Selective serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists are the first line of therapy in the prophylaxis and treatment of PONV due to their efficacy and fewer side effects compared to other antiemetics[5]. Ramosetron a newer agent of this class is more potent, has a longer effect and is found to be more effective than ondensetron and granisetron after major gynecological surgery[6,7]. It is the routinely used antiemetic for PONV in our institute. Research suggests that the serotonergic system has a role in the control of post anesthetic shivering and pain as well[8,9].

Laparoscopic surgeries under general anesthesia are associated with unique hemodynamic changes in the form of increased systemic vascular resistance, leading to hypertension[10]. Dexmedetomidine an alpha 2 agonist has been used as an effective anesthetic adjuvant to maintain hemodynamic stability during laparoscopic procedures[11]. It possesses unique sedative, analgesic, sympatholytic, amnestic, antiemetic and anti-shivering properties[12-14,].

Given the multifactorial etiologies of PONV and PAS; it was hypothesized that a combination of more than one class of drugs could be a more effective treatment modality of these conditions.

Till the present time there are no studies to show whether the combination of ramosetron and dexmedetomidine have a positive effect on prevention of PONV and PAS. So we designed a prospective randomized study to compare the effect of ramosetron with dexmedetomidine and ramosetron alone on PONV and PAS in gynecological laparoscopic surgeries. To the best of our knowledge, ours is the first study to evaluate the efficacy of ramosetron and dexmedetomidine combination for attenuating PONV and PAS in gynecological laparascopic surgeries.

Material and Methods:

Patient demographics- inclusion and exclusion criteria:

After obtaining an institutional ethical committee approval and individual written informed consent, 160 adult, female, ASA grade I and II patients, undergoing gynecological laparoscopic surgery were included in the study and randomly (envelope randomization) divided in two groups (80 subjects in each group) Group R received injection (inj) Ramosetron 0.3 mg and 50 ml normal saline intravenously. Group D received inj ramosetron 0.3 mg and inj dexmedetomidine as 1 mcg/kg bolus dissolved in 50 ml normal saline.

Patients with a known hypersensitivity to the drugs used in the study; and those with a history of acid-peptic disease, gastrointestinal reflux disease, hepatic dysfunction or a history of motion sickness were excluded from the study. Pregnant, menstruating and lactating women were also excluded from the study.

Study Technique

Blinding method: The patients were uninformed about which drug they received for prophylaxis of PONV and PAS. An anesthesiologist who was otherwise not participating in the study prepared the drugs into a ready to use form in identical syringes and administered to the patients. The group of anaesthesiologists who examined the patients pre-operatively, monitored the patients intra-operatively and collected the data; and the statistician who analyzed the data; all were unaware of the group allocation to exclude any possibility of subjective bias.

Anesthesia Technique

No premedication was given to patients. On arrival to operating room, after establishment of intravenous (i.v.) and monitoring lines, the patients were preoxygenated and given i.v. inj glycopyrrolate 0.2 mg and inj midazolam 2 mg. Group R patients received 50 ml normal saline infusion over 10 minutes and inj ramosetron 0.3 mg; while Group D patients received an i.v. dexmedetomidine 1 mcg/kg dissolved in 50 ml normal saline infused over 10 minutes and inj ramosetron 0.3 mg. The anesthesia technique was same for both the groups. Induction was done with inj thiopentone 2mg/kg, intubation was facilitated with inj rocuronium 0.8 mg/kg, maintenance of anesthesia was done with N_2O: O_2 66:33 and isoflurane. Inj fentanyl 2µ/kg was used for analgesia and repeated as required. Muscle relaxation was maintained using inj rocuronium. At the end of surgery ports were infiltrated with 0.25% bupivacaine. Reversal of muscle relaxation was done with neostigmine 0.5 mg/kg and glycopyrrolate 0.01 mg/kg i.v. Heart rate, non-invasive blood pressure, oxygen saturation, electrocardiograph, and end-tidal carbon dioxide were monitored during surgery. Duration of anesthesia, duration of CO_2 insufflation and duration of surgery, and nasopharyngeal temperature before induction and after extubation were noted. After the surgery, the patients were transferred to the post anesthesia care unit (PACU).

Definition of outcome: Primary outcome measures included the incidence of nausea, emesis (retching and vomiting), and rescue antiemetic drug use within 24 h postoperatively, the number of complete responders, severity of PAS and the no of patients requiring treatment for PAS.

PONV was graded as Grade 0 (no symptoms), Grade 1 (nausea) and Grade 2 (emesis). When nausea or vomiting was present, patients were asked if they required rescue antiemetics, and metoclopramide 10 mg i.v. was administered. PAS in the recovery room was graded as Grade 0 (no shivering), Grade 1(mild fasciculation of the face and neck), Grade 2 (visible tremors involving more than one muscle groups) and Grade 3 (gross muscle activity involving whole body). PAS was treated using blanket and warmer. Injection tramadol and injection pethidine were avoided as it could affect PONV. Secondary outcome of the study was severity of postoperative pain VRS (Verbal Rating Scale) (0-100) during 1 h in PACU after surgery, and the total amount of rescue analgesic administered for 24 h post-operatively. If patients asked for analgesics or experienced pain with VRS exceeding 40, they received a bolus of diclofenac 75 mg i.v. slow infusion.

Statistical Analysis: Sample size calculation was done using Statistica Version 6 (Tulsa, Oklahoma: Statsoft Inc., 2001). Analysis of data was done using Statistical software Statistical package for social science (SPSS) version 17 (illinios, Chicago: SPSS Inc., 2008) for windows. Numerical variables between the two groups were compared using by unpaired t-test. Categorical

variables were compared using Chi square test or fisher's exact test as appropriate. All analyses were 2 tailed and p < 0.05 was considered statistically significant.

Results

Patient characteristics as well as operative data were similar in both the groups (Table-1). The incidence of emesis and nausea episodes was more frequent in Group R compared to group D but the difference was not significant (p>0.05). Similarly the consumption of rescue antiemetic was less in Group D compared to Group R with a non-significant difference (p>0.05). The number of complete responders was more in Group D than Group R but again the difference was statistically insignificant (p>0.05) (Table-2). Regarding Post anesthesia shivering, the incidence of Grade 1 and Grade 2 shivering was found to be significantly more in Group R compared to Group D (p=0.003 and p=0.006 respectively) and hence the overall number of patients who required treatment for shivering were significantly more in Group R compared to Group D (p=0.003) (Table-3).

Regarding post-operative pain, it was observed that the mean VRS score of Group R at 1 hour was significantly higher than Group D (p=0.002). The first analgesic request time was earlier in Group R than Group D and it was statistically significant (p= 0.003). The mean value of total analgesic consumption during 24 hours was higher in Group R than group D and it was found to be statistically significant (p= 0.035, Table 4)

The incidence of the most common adverse events from 5HT3 receptor antagonist, such as headache and dizziness were similar between the 2 groups and some side effects like sedation bradycardia and dry mouth were present only in group D (Table 5).

Table1: Demographic characteristics of the two groups

	Group R (n=80)	Group D (n=80)	p-value
Age (years)	45.48±8.830	44.79±8.066	0.601
Weight(Kg)	52.93±6.178	51.45±7.465	0.314
Duration of surgery (mins)	61.30±16.145	60.90±15.709	0.874
Duration of anaesthesia (mins)	74.18±16.463	73.66±15.602	0.840
Duration of CO2 insufflation (mins)	48.24±16.138	48.39±14.962	0.951
Nasopharyngeal temperature pre-induction (^{0}C)	36.6±0.14	36.7±0.16	0.675
Nasopharyngeal temperature pre-extubation (^{0}C)	36.2±0.12	36.4±0.12	0.634

Values are mean±SD (standard deviation), Group R: Ramosetron Group, Group D: Ramosetron and Dexmedetomidine group. p value< 0.05 is considered significant.

Table 2: Frequency of emesis related episodes in the study groups, in 24 hours period

Variable &Time period	Group R (n=80)	Group D (n=80)	p-value
Nausea			
0-6 hrs	22(27.5)	16(20.0)	0.532
6-12 hrs	8(10)	7(8.75)	0.807
12-24 hrs	4(5)	3(3.75)	0.654
Emesis			
0-6 hrs	16(20)	11(13.75)	0.501
6-12 hrs	2(2.5)	1(1.25)	0.699
12-24 hrs	0(0)	0(0)	
Rescue antiemetic			
0-24 hrs	11(13.75)	6(7.5)	0.483
Complete responders			
0-24 hrs	48(60)	60(65)	0.624

Values are numbers (%). Group R: Ramosetron Group, Group D: Ramosetron and Dexmedetomidine group. p value<0.05 is significant

Table 3: Comparison of shivering episodes in the study groups

Shivering grade	Group R (n=80)	Group D(n=80)	P value
G0	42(52.5)	64(80)	
G1	28(35)	11(13.75)	0.003
G2	18(22)	5(6.25)	0.006
G3	1(1.25)	0	
Intervention for shivering	19(23.75)	5(6.25)	0.003

Values are numbers (%). Group R: Ramosetron Group, Group D: Ramosetron and Dexmedetomidine group. p value<0.05 is significant.

Table 4: Comparison of pain and requirement of rescue analgesics in the study groups

	Group R (n=80)	Group D (n=80)	P value
VRS score at 1 hr	34.03±14.167	27.93±9.496	0.002
First analgesia request time (mins)	72.39±39.353	87.83±21.917	0.003
Total analgesic requirement (mg)	82.75±33.541	65.38±26.971	0.035

Values are mean±SD (standard deviation), Group R: Ramosetron Group, Group D: Ramosetron and Dexmedetomidine group. p value< 0.05 is considered significant.

Table5: Incidence of side effects of the drugs used in the two study groups

Side effects	Group R (n=80)	Group D (n=80)
Bradycardia	0	4(5)
Sedation	0	6(7.5)
Dry mouth	0	8(10)
Headache	7(8.75)	6(7.5)
Dizziness	3(3.75)	2(2.5)

Values are numbers (%). Group R: Ramosetron Group, Group D: Ramosetron and Dexmedetomidine group.

Discussion

Various pathological gynecologic conditions are diagnosed and treated using laparoscopy. Though this procedure has potential advantage of early recovery and discharge but associated high incidence of PONV and PAS can diminish the aforesaid advantage. Orkin *et. al.* had stated that approximately three quarters of the patients felt that freedom from nausea and vomiting was the most important post-operative requirement. In a questionnaire analysis, nausea came only second to failure to wake up as reason for fear of general anesthesia[15]. PONV is multifactorial in origin[16] and some of the risk factors associated with our study were carbon dioxide insufflation, female sex, gynaecological surgery, use of opioids and inhalation anaesthetic[16]. Laparoscopic operations expose the peritoneal surface to large volumes of ambient CO_2 gas during pneumoperitoneum. Thus the patients undergoing laparoscopic surgery are at risk of intra-operative hypothermia and shivering thereafter[17].

There is enough evidence in literature to show that combination antiemetics with different mechanisms of action act synergistically with a better control of PONV[18,19]. We used a combination of Ramosetron, which is a widely used 5-HT3 receptor antagonist; and dexmedetomidine, an alpha 2 agonist. Both the drugs are known to have an anti-shivering and analgesic effect as well[8,9,12,14]. Between the two study groups, the demographic factors were comparable and physical factors like operating temperature (24-25^{0}C), temperature of recovery room and i.v. fluids were well controlled to rule out any confounding bias which could have affected the results of the present study.

Among the antiemetic drugs, 5 HT3 antagonists have a well-reported and accepted role and are frequently used in clinical practice. Additionally, they have been effectively used to ease PAS. There are many studies which have pointed that perioperative dexmedetomidine administration could reduce the incidence of PONV and PAS. A

meta-analysis conducted by Wang G et al in 2016 clearly exhibited the role of dexmedetomidine in attenuating the incidence of PONV and shivering in patients undergoing laparoscopic surgeries[20].

In the present study we found a reduced incidence of PONV in the group where dexmedetomidine was administered along with ramosetron compared to the group where ramosetron was used solely but this difference was statistically insignificant. Among the possible explanations of the role of dexmedetomidine in reducing PONV, the most accepted ones are the reduced consumption of intra-operative and post-operative opioids, the reduced noradrenergic activity as a result of binding to alpha-2 presynaptic inhibitory adreno-receptors in the locus coeruleus and lastly an overall reduction in sympathetic outflow and catecholamine release[13,20]. In our study, we had deliberately avoided the use of opioids in the postoperative period either for pain or for shivering which can partly justify the non significance of the difference among the two groups.

Although the mechanism of 5 HT3 receptor antagonists on suppression of shivering is not clearly understood, it is probably through inhibition of serotonin re-uptake in the anterior hypothalamic region where the main thermoregulatory control occurs. Both heat loss and heat production pathways are influenced, thus changing the thermoregulatory set points without affecting the core or peripheral temperature[21,22]. Alpha-2 adrenergic agonists decrease the central thermo sensitivity by suppressing the neuronal firing rate of neurons and reduce the vasoconstriction and shivering thresholds[14,23]. The number of shivering episodes and the overall number of required interventions for shivering in 24 hours period were significantly less in the group where combination of the two drugs was used. Thus a synergistic effect of dexmedetomidine and ramosetron was observed.

Pain score (VRS) at one hour postoperative period and analgesic requirement in 24 hours post-operatively were the secendory outcomes studied in our study. Current research suggests an involvement of 5 HT3 receptors in peripheral and central perception and processing of pain as well as in inflammation. It has been reported that 5 HT3 receptors are involved in nociceptive pathways and bind to opioid receptors exhibiting agonist activity, resulting in a peripheral antinociceptive effect[9,24]. The mechanisms of the analgesic actions of α_2 agonists have not been fully elucidated. Dexmedetomidine acts at a number of sites, supraspinal, spinal and peripheral, thus reducing the transmission of nociceptive signals in the central nervous system and leading to analgesia[12]. There is enough evidence in the literature showing a reduced consumption of analgesics in the post-operative period with the use of dexmedetomidine in the intraoperative period[25,26].

Our results showed a significant reduction of VRS scores at one hour and a reduced requirement of analgesics in the 24 hours post-operative period, which was comparable to other studies in the literature[27,28]. Incidence of some minor side effects of the drugs like dizziness, headache related to ramosetron was seen alike in both the groups. Some side effects like sedation, dry mouth and bradycardia which were related to dexmedetomidine were present only in the combination group. Bajwa et al have previously reported that use of intra-operative dexmedetomidine was associated with postoperative side effects including sedation and dry mouth[14].

Conclusion

From the observations of the study we conclude that the combination therapy of ramosetron and dexmedetomidine significantly reduces the post-operative shivering episodes and severity, pain scores and total postoperative analgesic requirements in laparoscopic gynecological surgeries, as compared to ramosetron alone. A reduction in incidence of PONV was also seen in patients receiving the combination therapy, though the difference was not statistically

significant. To the best of our knowledge, this is the first study evaluating a combination of ramosetron and dexmedetomidine for attenuating PONV and PAS in gynecological laparascopic surgeries. More studies may be required to generate positive evidence for using this safe combination to relieve the patients from PONV, PAS and postoperative pain, thus enabling speedy recovery and discharge of the patients.

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