Effect of ramosetron plus dexamethasone versus ramosetron alone for preventing nausea and vomiting after spine surgery in highly susceptible patients

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<ABSTRACT>

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Backgrounds : Opioid based patient-controlled analgesia (PCA) provides effective pain control after spine surgery, however is associated with a high incidence of postoperative nausea and vomiting (PONV). The antiemetic effect of 5-HT_3 antagonists against PONV is enhanced when used in combination with dexamethasone. Although the combination of dexamethasone and ramosetron is theoretically more advantageous than ramosetron alone, there are not enough reports to support this theory. In this study, we investigated the effectiveness of ramosetron plus dexamethasone against ramosetron alone to prevent opioid-based IV PCA related PONV in highly susceptible patients after spinal surgery using inhalational anesthetics.

Methods : Female nonsmoking patients (aged 18–65 years) were randomly allocated to ramosetron group (group R, n = 50) and ramosetron plus dexamethasone group (group RD, n = 50). Patients received normal saline 1ml (group R) or dexamethasone 5 mg (group RD) intravenously before induction. Anesthesia was maintained with remifentanil, rocuronium and sevoflurane. At the end of the surgery,

ramosetron 0.3 mg was given to all patients and fentanyl-based IV PCA was continued for 48 hrs postoperatively. The incidence and severity of PONV, pain score, amount of rescue antiemetics were assessed for 48 hrs after surgery.

Results : Patients' characteristics were similar between the groups. Although the overall incidence of nausea and severity of nausea were similar between the groups, the number of patients with moderate to severe nausea was significantly lower in the RD group (P = 0.029). The overall incidence of vomiting was significantly lower in the group RD than in the group R (P = 0.037). The frequency in use of rescue antiemetic was lower in RD group but not statistically significant. Pain scores were similar between the groups throughout the study period. The number of patients who experienced adverse events during postoperative period was similar between the groups.

Conclusions : Despite similar incidence of overall PONV, combination of ramosetron and dexamethasone significantly reduced the incidence of moderate to severe nausea and vomiting compared to ramosetron alone in highly susceptible patients for PONV using fentanly-based IV PCA and inhalation anesthetics.

Key words : dexamethasone, opioid based patient-controlled analgesia, postoperative nausea and vomiting, ramosetron

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I. INTRODUCTION

Despite the fact that postoperative nausea and vomiting (PONV) is one of significant causes of morbidity in patients undergoing general anaesthesia,[1] the optimal prophylactic antiemetic regimen has not yet been established. Multiple factors are associated with an increased incidence of PONV, including patient, anesthetic, and surgical factors.[2] General anesthesia using volatile anesthetics is associated with an average incidence of postoperative nausea and vomiting (PONV) ranging between 20% and 30%.[3] While total intravenous anesthesia (TIVA) is more effective for preventing PONV than inhaled anesthetic technique, it is expensive and requires standard delivery system resulting less frequent use for general anesthetic cases.[4,5] In case of spinal surgery, although the risk of PONV related to surgical factor is low, most of the patients receive intravenous patient controlled analgesia (PCA) using high dose of opioid and consequently PONV is significant, especially in highly susceptible patients undergoing inhalational anesthesia.[6-8]

Among the current antiemetics, 5-hydroxytryptamine receptor 3 (5-HT_3) antagonists has been the most frequently used antiemetic agents. Ramosetron is a newly developed 5-HT_3 antagonist with higher receptor affinity and longer duration of action than previously developed 5-HT_3 antagonists such as

ondansetron and granisetron.[9-11] In a previous study, ramosetron was reported to be superior to ondansetron for preventing PONV associated with opioid-based PCA.[11] Currently, the combination of antiemetics from different classes is popular for more effective antiemetic treatment in high risk patients regarding multifactorial etiologies of PONV. This multimodal approach was advocated for patients at high risk for PONV,[12] and the antiemetic efficacy of 5-HT_3 antagonists was known to be enhanced by its use in combination with dexamethasone.[13,14] Ramosetron decreases chemotherapy-induced emesis when added to dexamethasone,[15] while there is limited data comparing the effect of ramosetron plus dexamethasone to ramosetron alone on the prevention of PONV in patients undergoing general surgery.

The purpose of this study was to evaluate the efficacy of a combination of ramosetron and dexamethasone against ramosetron alone on opioid-based IV PCA related PONV in highly susceptible patients undergoing spinal surgery using inhalational anesthetics in a prospective, randomized and double-blind trial.

II. MATERIALS AND METHODS

Approval of the institutional review board and informed consent from patients were obtained. We recruited 100 female patients with high risk of PONV, aged 18 to 65, scheduled for elective lumbar spinal surgery using standard posterior approach, between March 2008 and January 2009. To minimize the confounding effect of surgery, only the patients undergoing less than two levels of lumbar spinal surgery were studied.

Before anesthesia, patients with a risk of PONV exceeding 60% according to the expected risk for PONV using the simplified risk score of Apfel et al.[16] The 4 risk factors considered in this score are female gender, nonsmoking, the use of postoperative opioids, and prior history of motion sickness or PONV; the presence of 0, 1, 2, 3, or 4 of these risk factors correspond to approximately 10, 20, 40, 60, and 80% risk for PONV, respectively. Basic inclusion criteria were non-smoking and female patients because all the patients are anticipated to use postoperative opioid-based PCA. Exclusion criteria were severe impairment of bowel motility, insulin-dependent diabetes mellitus, pregnancy or breastfeeding, administration of antiemetic medication within 24 hr before surgery, systemic treatment with steroids within 24 hr before surgery or during 48 hr after surgery, a history of cardiovascular or respiratory disease, active alcohol or drug usage, obesity (body mass index $\geq$ 35 kg/m^2), as well as impaired renal and/or hepatic function. Patients with inadvertent tear of the dura mater during the surgery were also excluded. Patients were randomly allocated into either ramosetron group (group R, n = 50) or combination group (group RD, n = 50) by a computerized randomization table.

Patients were premedicated with midazolam 0.05mg/kg and glycopyrrolate 0.004 mg/kg. Before the induction of anesthesia, 1 ml of normal saline was injected in patients assigned to the group R, and dexamethasone 5 mg in 1 ml was injected in patients assigned to the group RD. Injected drugs were prepared in 1 ml syringe by anesthetic nurses who were not involved in this study.

Anesthesia was induced with 1.5-2.5 mg/kg of propofol, and 0.5-1 μg/kg of remifentanil, and tracheal intubation was facilitated with 0.9 mg/kg of rocuronium. Patients' lungs were mechanically ventilated with oxygen and air (inspired oxygen fraction 0.5), a tidal volume of 8-10 ml/kg, I:E ratio of 1:1.9 at a respiratory rate of 8-12 breaths/min to maintain normocarbia throughout the surgery. Anesthesia was maintained with continuous infusion of remifentanil (0.05-0.2 μg/kg/min), rocuronium (5-6 μg/kg/min), and sevoflurane (1.8-2 %). At the end of the surgery, all patients received ramosetron 0.3 mg and PCA was commenced. The PCA regimen was consisted of fentanyl 25 μg/kg, ketorolac 120 mg and ramosetron 0.3 mg (total volume including saline: 100 ml). The IV PCA was programmed to deliver 2 ml/hr as background infusion and 1 ml per demand with a 15 min lockout during 48 hr period. As the patients were placed in supine position and sevoflurane was discontinued and remifentanil was infused continuously at a reduced infusion rate (0.02-0.05 μg/kg/min). Neuromuscular blockade was antagonized with pyridostigmine (0.1 mg/kg) and glycopyrrolate (0.2-0.3 mg) and remifentanil was discontinued after extubation.

Assessed primary efficacy variables include the incidence and severity of nausea and incidence of vomiting 48 hrs after surgery. Secondary efficacy variables included use of additional antiemetic rescues, pain intensity, and medication-associated complications. These variables were assessed by two investigators, who were blinded to the patients' groups, in the first 48 hr following emergence from general anesthesia. Evaluations were performed at the following 4 time periods; during the stay in recovery room, 0-6 hr, 6-24 hr, and 24-48 hr. Nausea was defined as subjectively unpleasant sensation associated with awareness of the urge to vomit and an emetic episode was defined as a single episode of vomiting (the forceful expulsion of gastric contents through the mouth). Retching was defined as an expulsive movement of the stomach muscles when no stomach contents are expelled but was considered as vomiting. The intensity of nausea was graded on verbal rating

scales (VRS) using an 11 point scale, with 0 = no nausea to 10 = worst possible nausea. Pain intensity scores were measured on a visual analog scale (VAS) that ranged from 0 mm (no pain) to 100 mm (worst pain imaginable). Antiemetic efficacy was assessed by monitoring the incidence and severity of nausea and vomiting as well as the need for rescue antiemetic medication. Rescue antiemetic therapy (metoclopromide 10 mg IV) was given at the discretion of the attending physicians, who were blinded to the patients' group, in response to nausea, vomiting, or patient's request. IV PCA was discontinued when severe nausea persisted and/or upon patient's request after 2 consecutive boluses of metoclopromide. The most frequently reported side effects of the 5-HT_3 antagonists used in conjunction with opioid-based IV PCA such as headache, dizziness, drowsiness, constipation, flushing, heat and general weakness were also assessed during the study period.

Sample size estimation was performed in accordance with the results of the study comparing the effect of ondansetron with dexamethasone on PONV in high risk group of patients.[16] At 43 patients per group, there is an 80% chance to detect an absolute risk reduction of 50 percentage points of vomiting using a two-sided Fisher's exact test with a type I error of 0.05. Statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation (SD) or number or median (range). Data between the groups were compared using Chi-square test, Fisher's exact test, independent t-test or the Mann-Whitney U test, as appropriate. A P value of less than 0.05 was considered statistically significant.

III. RESULTS

Patients' characteristics including history of PONV and/ or motion sickness, and operative data were similar between the groups (Table 1). None of the patients had inadverent tear of the dura mater. PCA pumps were discontinued in 1 patient of group R between 6 and 24 hr after surgery and in 1 patient of group RD between 24 and 48 hr after surgery due to intractable nausea and/ or vomiting.

Table 1. Patients' characteristics

	Group R (n = 50)	Group RD (n = 50)	P value
Age (yr)	49 ± 12	50 ± 9	0.626
Body mass index (kg/m^2)	24 ± 3	24 ± 3	0.220
Surgery time (min)	112 ± 46	125 ± 52	0.213
Anesthesia time (min)	149 ± 53	167 ± 56	0.104
Amount of fentanyl used (μg)	1384 ± 160	1360 ± 144	0.432
History of PONV	6	1	0.111
History of motion sickness	13	16	0.507

Values are mean ± SD or number of patients. Group R: ramosetron only. Group RD: combination of ramosetron and dexamethasone. PONV: postoperative nausea and vomiting.

The overall incidence of nausea was 52% in the group R and 44% in the group RD. Although the severity of nausea was similar between the groups, the number of patients with moderate to severe nausea was significantly lower in the RD group (P = 0.029). The overall incidence of vomiting was significantly lower in the group RD than in the group R (P = 0.037). The frequency of rescue

antiemetic medication was less in the RD group than in the R group without significance (P = 0.096) (Table 2).

Table 2. Incidence of nausea, vomiting, and requirement for rescue antiemetic treatment

	Group R (n = 50)	Group RD (n = 50)	P value
PONV	29 (58)	24 (48)	0.316
Nausea	26 (52)	22 (44)	0.423
RR	5 (10)	6 (12)	0.521
0-6 hr	21 (42)	15 (30)	0.184
6-24 hr	19 (38)	17 (34)	0.732
24-48 hr	14 (28)	13 (26)	0.821
Nausea ≥ VRS 4	20 (40)	10 (20)	0.029
RR	2 (4)	0	0.124
0-6 hr	16 (32)	7 (14)	1.000
6-24 hr	12 (24)	6 (12)	0.118
24-48 hr	7 (14)	4 (8)	0.338
Vomiting	13 (26)	5 (11)	0.037
RR	1 (2)	0	0.367
0-6 hr	8 (16)	3 (6)	0.102
6-24 hr	7 (14)	3 (6)	0.318
24-48 hr	3 (6)	1 (2)	0.617
Rescue antiemetic	22 (44)	14 (28)	0.096
RR	2 (4)	2 (4)	0.622
0-6 hr	13 (26)	6 (12)	0.066
6-24 hr	13 (26)	7 (14)	0.147
24-48 hr	5 (10)	4 (8)	1.000

Values are expressed as number (%). Group R: ramosetron only, Group RD: combination of ramosetron and dexamethasone. PONV: total number of patients who experienced nausea or vomiting during study period. VRS: verbal rating scale. RR: recovery room.

Pain scores assessed for 48 hr after surgery were less than 40 in both groups and were similar between the groups (Table 3).

Table 3. Pain intensity scores

	Group R (n = 50)	Group RD (n = 50)	P value
Pain scores			
RR	22 ± 21	30 ± 20	0.092
0-6 hr	41 ± 27	36 ± 19	0.336
6-24 hr	30 ± 25	34 ± 20	0.328
24-48 hr	33 ± 42	28 ± 19	0.434

Values are mean ± SD. Group R: ramosetron only. Group RD: combination of ramosetron and dexamethasone. RR: recovery room.

No patient was withdrawn from the study due to adverse events associated with antiemetic medications. The number of patients who experienced adverse events during postoperative period was similar between the groups (Table 4).

Table 4. Side effects of antiemetic drugs

	Group R (n = 50)	Group RD (n = 50)	P value
Headache			

RR	0	0	
0-6 hr	3 (6)	3 (6)	1.000
6-24 hr	6 (12)	4 (8)	0.741
24-48 hr	6 (12)	4 (8)	0.505
Dizziness			
RR	0	2 (4)	0.529
0-6 hr	5 (10)	5 (10)	1.000
6-24 hr	7 (14)	4 (8)	0.356
24-48 hr	6 (12)	5 (10)	0.749
Drowsiness			
RR	0	0	
0-6 hr	3 (6)	1 (2)	0.362
6-24 hr	3 (6)	2 (4)	1.000
24-48 hr	1 (2)	3 (6)	0.617
Constipation			
RR	0	0	
0-6 hr	1 (2)	0	0.495
6-24 hr	1 (2)	0	1.000
24-48 hr	1 (2)	1 (2)	1.000
Flushing			
RR	0	0	
0-6 hr	1 (2)	0	0.495
6-24 hr	1 (2)	0	0.246
24-48 hr	1 (2)	0	0.234
Heat			
RR	0	0	
0-6 hr	2 (4)	1 (2)	0.131
6-24 hr	2 (4)	0	0.058
24-48 hr	0	1 (2)	1.000

General weakness			
RR	0	0	
0-6 hr	0	0	
6-24 hr	1 (2)	0	0.246
24-48 hr	0	1 (2)	1.000
Total adverse event	22 (44)	17 (34)	0.386

Values are expressed as number (%). Group R: ramosetron only. Group RD: combination of ramosetron and dexamethasone. RR; recovery room.

IV. DISCUSSION

In this prospective study, we compared the antiemetic efficacies of ramosetron or ramosetron plus dexamethasone for preventing fentanyl-based IV PCA related PONV in patients under highly susceptible conditions for developing PONV. The combination of ramosetron and dexamethasone significantly reduced the incidence of moderate to severe nausea and vomiting compared to that of ramosetron alone, however there were no significant differences among groups for incidence of total PONV.

Since the opioid-based IV PCA has been most widely used for postoperative pain management after surgery, PONV is a common cumbersome problem. The incidence of PONV reaches about 60% in non smoking female patient receiving opioid based IV PCA[16] and, thus appropriate prophylactic antiemetic treatment is important in this subset of patients. 5-HT_3 antagonists are most commonly used antiemetic agent and frequently used for the prevention of PONV. However, previously reported results about their effect on preventing IV PCA related PONV were not satisfactory.[17-19] It seemed to be associated with the fact that 5-HT_3 antagonists possess anti-vomiting efficacy better than anti-nausea efficacy.[20.21] In our previous study,[11] the incidence of PONV was 60-70% in patients with multiple risk factors for PONV in spite of receiving ondansetron or ramosetron. The need for more effective antiemetic therapy is thus increasing and the limited efficacy of single antiemetics treatment has prompted evaluations of a combination of antiemetic drugs acting at different receptor sites to prevent PONV.[22] The antiemetic efficacy of a combination of dexamethasone with earlier serotonin receptor antagonists such as ondansetron, granisetron, and dolasetron was reported to be beneficial for reducing the incidence of PONV in previous studies.[14,23-25] The suggested hypothesis for a better effect of the combination therapy are as follows: corticosteroids may reduce the levels of serotonin in neural tissue by depleting its precursor

tryptophan; antiinflammatory properties of corticosteroids may prevent the release of serotonin in the gut; dexamethasone may potentiate the main effect of other antiemetics by sensitising the pharmacological receptor.[23,26-28] Addition of 8 mg of dexamethasone to granisetron reduced the incidence of PONV for 24 hrs after anesthesia about 12%-15% when compared to granisetron alone.[13,14] On the contrary, a combination of dolasetron and dexamethasone (4 mg) did not reduce the incidence of PONV when compared to dolasetron, but improved quality of recovery and resulted in greater satisfaction for the management of PONV.[25]

Ramosetron is a newly developed 5-HT_3 antagonist with a higher affinity and longer duration of action than that of the previously developed 5-HT_3 antagonists such as ondansetron, granisetron and tropisetron.[9-11] There is limited data on the benefits of ramosetron plus dexamethasone combination compared to ramosetron alone. We observed that the combination of ramosetron and dexamethasone could reduce the incidence of moderate to severe PONV and vomiting significantly compared to ramosetron alone, although the total PONV incidence was similar in both groups. Patients might be less tolerant to moderate and severe nausea and vomiting than mild nausea and there was a trend for less use of rescue antiemetic agents in the group RD. Vomiting may cause dehydration, electrolyte imbalance, disruption of the surgical repair, and increase the perception of pain, resulting magnification of postoperative pain affecting patients' outcome.[3,17] And moderate and severe nausea comes just before vomiting, therefore, the result of current study seems to have significant clinical implication.

The incidence of moderate to severe nausea was low but half of the patients in the group RD developed PONV and the possible reasons are as follows. First, although dexamethasone is effective against both early and late (2-24 hr) nausea and vomiting, its late efficacy is more pronounced. In this study, we assessed the effect of drugs for 48 hrs postoperatively because the incidence of PONV

usually decreases after 48 hr period. Considering the duration of dexamethasone's effect on preventing PONV lasts more than 72 hrs,[29] if the observation time was prolonged, the incidence of PONV could have been less in the group RD. Second, ramosetron has been demonstrated to possess better anti-vomiting efficacy than anti-nausea efficacy, and the incidence of vomiting was significantly reduced with the combination of ramosetron and dexamethasone in the present study. We may assume that synergistic effect of ramosetron and dexamethasone primarily acts on the pathways associated with vomiting. Lastly, the dose of the dexamethasone could have not been enough to prevent PONV sufficiently. Minimum effective dose of dexamethasone to reduce the incidence of PONV when combined with ondansetron has been reported to be 4 mg in patients undergoing gynecological laparoscopy.[23] Although 4–10 mg of prophylactic doses of dexamethasone is used popularly, the cautious use of dexamethasone is recommended in surgical patients due to the concerns about surgery-related side effects, such as delayed wound healing and increased incidence of wound infection. Thus, we used 5 mg of dexamethasone for a combination therapy in this study.[23,24] Considering that 8-10 mg of dexamethasone was used for a combination therapy with other 5-HT_3 antagonists which demonstrated positive effect,[13,14,30] using higher dose of dexamethasone for combination therapy could possibly achieve better prophylactic effect.

In the absence of a placebo control group, we did not know the baseline risk of PONV without prophylaxis in our study population, which had predictive risk factor scores of 3. The observed incidence of PONV of 44% in the group RD was higher that might be expected on the basis of a 33% relative risk reduction for two intervention (ondansetron and dexamethasone) calculated with estimated incidence of PONV.[31] This result is in accordance with the previous study reporting observed incidence of PONV of 47% in patients treated with dexamethasone and ondansetron,[23] which was also higher than

might be expected on the basis of 25% relative risk reduction calculated with estimated incidence of PONV. Those results demonstrated that the combination of dexamethasone and 5-HT_3 antagonists might not produce even additive effect. The higher incidence of PONV in the present study was probably associated with frequent assessment of nausea and classification of any score above zero (on a 0–10 scale) as positive for the presence of nausea. Since the inhalation anesthetics is one of the main causes of early postoperative vomiting, administration of nonvolatile agents to maintain anesthesia may be helpful to improve patients' satisfaction in this subset of patients. TIVA with propofol was associated with less PONV when compared to inhaled drugs, especially in the early postoperative period.[32-34] Additionally, the use of a multimodal approach incorporating both TIVA and a combination of antiemetic drugs was reported to be associated with an incidence of PONV less than 10%.

V. CONCLUSION

Combination of ramosetron and dexamethasone significantly reduced the incidence of moderate to severe nausea and vomiting compared to ramosetron alone, although the overall incidence of PONV was similar in both groups in highly susceptible patients for PONV using fentanly-based IV PCA and inhalation anesthetics.

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< ABSTRACT(IN KOREAN)>

척추수술 후 오심 및 구토의 고위험군 환자에서 Ramosetron과 Dexamethasone의 혼합투여시의 예방효과

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서론 : 척추수술을 받는 환자에서 아편양 제제를 사용한 자가통증조절법은 적절한 통증조절에 도움을 주나 수술 후 오심 및 구토를 종종 유발할 수 있다. $5HT_3$ 수용체 길항제의 항구토제로서의 효과는 dexamethasone을 병용투여시 증강된다고 알려져 있다. Ramosetron은 새로 개발된 $5HT_3$ 수용체 길항제로서 dexamethasone과의 병용투여에 대한 연구는 아직 미비한 수준이다. 척추수술 후 오심 및 구토의 고위험군 환자에서 아편양 제제를 사용한 무통주사와 관련된 수술 후 오심 및 구토에 대한 ramosetron과 dexamethasone의 예방효과를 ramosetron 단독투여시와 비교해 보고자 하였다.

재료 및 방법 : 척추수술이 예정된 환자중 자가통증조절법을 시행받는 18-65세 사이의 비흡연 여성환자 70명을 무작위로 ramosetron군(R군, n = 50)과 ramosetron dexamethasone 혼합투여군(RD군, n = 50)으로 나누었다. 마취유도전 R군에는 생리식염수를 RD군에는 dexamethasone 5 mg을 투여하였고

수술이 끝난 후 양 군 모두 ramosetron 0.3 mg을 정주하였다. 마취는 sevoflurane, remifentanil, rocuronium으로 유지하였다. 수술 후 48시간 동안 오심의 정도 및 빈도, 구토의 유무와 횟수, 통증정도, PCA 사용량, 추가적 항구토제 사용량 및 부작용의 발생 유무 등을 조사하였다.

결과 : 오심의 정도 및 발생 빈도는 두 군간에 유의한 차이가 없었으나 중등도 이상의 오심의 발생은 RD군에서 유의하게 적었다(P= 0.029). 또한 구토의 횟수 역시 R군과 RD군에서 각각 13명(26%), 5명(11%)로 RD군에서 의미있는 감소를 보였다(P = 0.037). 통증정도와 추가적 항구토제 사용량 및 부작용은 두 군간에 유의한 차이를 보이지 않았다.

결론 : Ramosetron과 dexamethasone의 병용투여는 흡입마취를 이용하여 척추수술을 시행받는 자가통증조절법과 관련된 수술 후 오심 및 구토 발생의 고위험군 환자에서 ramosetron의 단독투여보다 중등도 이상의 구역 및 구토를 예방하는 효과가 뛰어난 것으로 보여진다.

핵심되는 말 : dexamethasone, 자가통증조절, 수술 후 오심 구토, ramosetron,