Comparative Study of the Effect of Concomitantly Administered Ondansetron on Duration of Post-Operative Analgesia of Tramadol Hydrochloride in Patients Undergoing Gynaecological Surgeries

Ajith Kumar G.[1], Prabhash R.[2], Rajeev D. S.[3], Baburaj C.[4], Sanjay Sahadevan[5]

[1]Associate Professor, Department of Anaesthesiology, Manjeri Medical College, Manjeri, Kerala, India.
[2]Associate Professor, Department of Anaesthesiology, Manjeri Medical College, Manjeri, Kerala, India.
[3]Associate Professor, Department of Anaesthesiology, Government Medical College, Trivandrum, Kerala, India.
[4]Associate Professor, Department of Anaesthesiology, Manjeri Medical College, Manjeri, Kerala, India.
[5]Assistant Professor, Department of Anaesthesiology, Government Medical College, Trivandrum, Kerala, India.

ABSTRACT

BACKGROUND
We wanted to determine the effect of concomitantly administered ondansetron on duration of post-operative analgesia of tramadol hydrochloride in patients undergoing gynaecological surgeries to compare the incidence of post-operative vomiting between Tramadol group and Tramadol-Ondansetron group.

METHODS
The study was approved by our Institutional Ethics Committee and all patients provided written informed consent. Sixty patients in the age group of 25 to 65 years belonging to ASA physical status I and II were induced in a prospective double-blind randomized study. All patients were scheduled for elective gynaecological surgeries under subarachnoid block.

RESULTS
The duration of analgesia in both groups was assessed with VAS pain score. Tramadol group had better mean duration of analgesia, 327 minutes than the concomitant group, 220 minutes. p value <0.001.

CONCLUSIONS
Post-operative use of Tramadol with ondansetron cannot be recommended, because ondansetron reduces the analgesic power of Tramadol.

KEYWORDS
Tramadol, Ondansetron Spinal Anaesthesia

Corresponding Author:
Dr. Prabhash R,
Associate Professor,
Department of Anaesthesiology,
Government Medical College,
Manjeri, Kerala, India.
E-mail: prabhashdrr@gmail.com

DOI: 10.18410/jebmh/2020/229

Financial or Other Competing Interests: None.

How to Cite This Article:
Ajith Kumar G, Prabhash R, Rajeev DS, et al. Comparative study of the effect of concomitantly administered ondansetron on duration of post-operative analgesia of tramadol hydrochloride in patients undergoing gynaecological surgeries. J. Evid. Based Med. Healthc. 2020; 7(22), 1058-1061. DOI: 10.18410/jebmh/2020/229

Submission 18-02-2020,
Peer Review 26-02-2020,
Acceptance 28-03-2020,
Published 28-05-2020.

BACKGROUND

We wanted to determine the effect of concomitantly administered ondansetron on duration of post-operative analgesia of tramadol hydrochloride in patients undergoing gynaecological surgeries to compare the incidence of post-operative vomiting between Tramadol group and Tramadol-Ondansetron group.

METHODS

The study was approved by our Institution of Ethics Committee and all patients provided written informed consent. Sixty patients in the age group of 25 to 65 years belonging to ASA physical status I and II were induced in a prospective double-blind randomized study. All patients were scheduled for elective Gynaecological surgeries under subarachnoid block.

Inclusion Criteria

- ASA PS – 1
- Age group between 25 – 65

Exclusion Criteria

- Body Weight > 70 Kg
- History of convulsions
- Patients on antidepressants
- H/o hypersensitivity to Tramadol or Ondansetron

Pre-Operative Evaluation

Thorough pre-operative assessment was done on the previous day of surgery and ASA status assessed. Body weight recorded and informed consent obtained from each patient. All patients were Instructed to use Visual Analogue Scale which is a 10 cms scale marked with no pain at one end and the worst possible pain at the other end.

Methodology

Sixty patients were randomly allocated into two groups, 30 each in a double blind randomized study.

GROUP O: Patients in this group received Tramadol 2 mg/Kg intravenously to a maximum of 100 mg and Ondansetron 0.08 mg/Kg IV to a maximum of 4 mg, 90 minutes after the onset of block.

GROUP T: Patients in this group received Tramadol 2 mg/Kg IV to a maximum of 100 mg and 1 ml saline IV, 90 minutes after the onset of block.

Pre-Operative Preparation

All patients were kept fasting for 8 hours prior to surgery.

- Tab Diazepam 0.5 mg given at HS on previous day and at 6 AM on the day of surgery.
- Inj. Pethidine 1 mg/Kg and Phenergan 0.5 mg/Kg both given IM 45 minutes before surgery.
- Baseline blood pressure, pulse rate and respiratory rate were recorded or to surgery.
- An intravenous access was established, and 500 ml of Ringer's Lactate was infused in the premedication room.

Anaesthetic Technique

In the operating room blood pressure checked using noninvasive BP cuff and three lead ECG attached for continuous monitoring of the heart rate. The patients were placed in the lateral decubitus position. Under strict aseptic precautions, lumbar subarachnoid block was performed by a median approach at l2 3/l3-4 interspace using 23 Gauge spinal needle with 3.2 to 3.5 cc 0.5% heavy Bupivacaine. After the subarachnoid injection patients were turned to supine and blood pressure, heart rate and respiratory rate were monitored immediately at 5 minutes for first 15 minutes and thereafter at regular intervals. After assessing the level of block, the surgeon v.: as allowed to proceed with surgery.[1]

90 minutes after the onset of block patients were randomized to Group 0 and Group T and drugs were administered accordingly. Post operatively the pulse rate, blood pressure and respiratory rate were monitored every 15 minutes for a period of 2 hours in the recovery room. There after every 2 hours for the first 12 hours. The duration of post-operative analgesia was calculated as the time interval between the administration of drugs and appearance of discomfort due to pain which corresponds to a score of 6 in VAS. Tramadol was repeated IV as the patient complained of discomfort due to pain at VAS of 6. The number of supplemental doses of Tramadol for first 12 hours was recorded. The incidence of post-operative nausea and vomiting was recorded for the same period. Vomiting was treated with metoclopramide 10 mg intravenously. Patients were closely monitored for sedation and checked the level of sedation.

The arithmetic mean and standard deviations of the various parameters were calculated. The comparison[2] between the two groups were accomplished using 't test and Chi square test, whenever applicable a p value of <0.05 was calculated to be significant.

RESULTS

Fifty one patients were studied. 26 in Group T and 25 in 0 group. Four subjects In Group T and 5 subjects in group 0 were excluded from the study because of the following reasons. One subject in T group, 3 subjects in 0; group needed other anaesthetic technique after the administration of the study drugs. One subject in T group needed IV midazolam to control some abnormal movement that developed after IV Tramadol. Two subjects in either group did not respond to (their pain score did not decrease) second dose of Tramadol. Results were analysed in remaining 51 subjects as follows.

The mean age in T group was 43.77. The mean age in 0 group was 40.63. The maximum number of patients in either group were in 35 to 44 years age group. The mean body weight in T group was 50.8. The mean body weight in 0 group was 52.44. The maximum number of patients in either group b longs to 55- 64 kg. Maximum number of Gynaecological procedures done was Abdominal hysterectomies. The minimum duration of analgesia in T group was 120 minutes and maximum duration was 420 minutes. The minimum duration in 0 group was 120 minutes and maximum duration was 405 minutes. 61.53% in Tramadol group had vomiting, whereas in concomitant group only 20% had vomiting.

Age Groups (In Years)	T Group		O Group	
	No.	%	No.	%
25-34	4	15.38	4	16
35-44	11	42.30	14	56
45-54	8	30.76	5	20
55-64	3	11.53	2	8
Mean age	43.77		40.63	

Table 1. Age Distribution of Patients

t = 0.22 p>0.1

Weight in (Kg)	T Group		O Group	
	No.	%	No.	%
35-44	7	26.92	7	28
45-54	9	34.62	7	28
55-64	10	38.68	11	44
Mean weight	50.8		52.44	

Table 2. Weight Distribution of Patients

t = 0.59 p>0.1

Surgical Procedure	T Group		O Group	
	No.	%	No.	%
Abdominal hysterectomies	14	53.85	17	68
Vaginal hysterectomies	8	30.77	6	24
Ovarian Cystectomies	3	11.54	1	4
Myomectomies	1	3.84	1	4

Table 3. Gynaecological Procedure Done

Duration in Minutes	T Group		O Group	
	No.	%	No.	%
100-199	1	3.85	7	28
200-299	4	15.38	16	64
300-399	18	69.23	1	4
400-499	3	11.53	1	4
Mean Duration	327 minutes 5 hours 27 minutes		220 minutes 3 hours 40 minutes	

Table 4. Duration of Post-Operative Analgesia

t = 3.94 p < 0.001

No. of Rescue Doses of Tramadol	T Group No. of Patients	O Group No. of Patients
1	19	6
2	5	14
3	2	5
Mean dose	1.36	1.96

Table 5. Rescue Analgesic for First 12 Hours

t = 0.0053 p > 0.1

Patients	T Group		O Group	
	No.	%	No.	%
Vomited	16	61.53	5	20
Not Vomited	10	38.47	20	80

Table 6. Incidence of Vomiting

$x^2 = 20.01$ p < 0.01

DISCUSSION

Acute post-operative pain and PONV are the important concerns of the care giver in the post-operative care unit.[3] There are many drugs by various route available to control post-operative pain. But majority of systemic analgesics used to improve pain relief have significant emetogenic activity. Tramadol is a centrally acting synthetic analgesic which is used in various routes to control post-operative pain because of lower sedation, less addiction, less nausea and vomiting than with other opioids. Since PONV is expected with certain surgical procedures and anaesthetic techniques, antiemetic drugs are used for the treatment and prophylaxis of PONV. Ondansetron a $5HT_3$ antagonist is used as an antiemetic in controlling PONV.[4] Tramadol block neuronal uptake of noradrenaline and 5HT (Serotonin). These drugs are administered during peri-operative period in our institutions for elective as well as for emergency surgeries. The drug combination could induce mutually contrasting modification on the $5HT_3$ receptor mediated serotoninergic transmission and particularly that of Ondansetron induced receptor antagonism could either enhance or weaken Tramadol induced analgesia.[5] But clinically it is observed that analgesic effect of Tramadol decreases with Ondansetron.

In the present study, an attempt has been made to evaluate the effect of concomitant use of Ondansetron on the duration of post-operative analgesia of Tramadol in patients undergoing Gynaecological surgeries. The result obtained has been compared with patients who got Tramadol and Placebo.

The duration of analgesia in both groups were assessed with VAS pain score. Tramadol group had better mean duration of analgesia, 327 minutes than the concomitant, group, 220 minutes. P value <0.001. In the study by Dewitte JL et al 1 mg/Kg of Tramadol when administered along with Ondansetron 0.1 mg/Kg or placebo 15 minutes before induction of anaesthesia resulted in impaired analgesic efficacy of Tramadol.[6]

R Arcioni et al in their study of 59 patients undergoing ear, nose and throat surgery were given Tramadol for 24 hours post operatively with patient controlled analgesia.[7] They were randomly allocated either to a group receiving Ondansetron continuous infusion (1 mg/hr) to a control group or receiving saline. Results showed a reduced overall analgesic effect of Tramadol in Ondansetron group.

However J Broome et al studied the analgesic efficacy and occurrence of nausea and vomiting when Tramadol is added to NSAID drug to provide analgesia in day care oral surgery.[8] All patients received oral Diclofenac pre operatively and were included in the following treatment group intra operatively: Fentanyl and Ondansetron, Fentanyl and Metoclopramide, Tramadol and Metoclopramide or Tramadol and Ondansetron. There were no significant difference between groups in score for pain in early post-operative period.

In his study Dr Manoj Bhardwaj of PGIMS Rohtak, compared Tramadol and Morphine in Gynaecological surgeries. A single bolus dose of intravenous Tramadol 1.5 mg/Kg produced satisfactory pain relief for 360 minutes. Whereas study by Dr. Monica G et al at CMC Vellore got a mean duration of 269 minute when 100 mg Tramadol and 4

mg Ondansetron were administered to patients undergoing abdominal hysterectomies. Even though the difference in duration is not statistically comparable there exists a definite clinical difference. These durations are comparable in the present study.

The $5HT_3$ receptors are presumed to have a role in peripheral neuronal pathways that are involved in visceral pain mechanisms and central neuronal pathways that are involved in emesis, appetite, addiction pain and anxiety.[9]

Serotonin plays a key role in pain control mechanisms and affect nociception through a variety of specific receptors including SHT1r A-D, 5HT 2, A-C, SHT3 and SHT4. The antiemetic properties of Ondansetron are based on the block of the CTZ and enteric neuron SHT3 receptors. Identical receptors are expressed by the nociceptive primary afferent fibers either on the peripheral free terminal or centrally on their spinal terminal and by the neurons of the superficial laminae of the dorsal horn.

In mouse Tramadol antinociceptive activity on the spinal ascending fibers and that produced. by 2 methyl SHT (a SHT3 agonist) are poorly antagonize? By naloxone. But the intrathecal Tramadol analgesia is reversed by the antiserotonergic ritanserin. Thus, it seems that between the two modes of action of Tramadol, the monoaminergic mode seems to be crucial at the dorsal horn level. The SHT released by the action of Tramadol binds all SHT receptor subtypes/ but because of selective Ondansetron antagonism, it is assumed that, the described inhibitors of Tramadol analgesia could consist of reduction of binding SHT3 receptor at the spinal level.

Another mechanism for Ondansetron induced analgesic effectiveness of Tramadol[10] involves competition for CYP2D6 for metabolism. Tramadol is metabolized to M1 by the CYP2D6 isoenzyme of the cytochrome P450 enzyme, M1 metabolite is more potent than Tramadol. So the competition for CYP2D6 results in increased concentration of Tramadol and decreased concentration of M_1.

Incidence of post-operative vomiting is more in Ondansetron group in R. Arcioni et al's study. Whereas in this study incidence is less than Ondansetron group.[11] P value <0.01, so the difference is statistically significant. This may be because the intensity of Tramadol used in the initial few hours was more in the Ondansetron group in their study. Whereas in the present study during the above period maximum dose of Tramadol administered was only 100 mg and got more Ondansetron initially.

Mean rescue injection of Tramadol used in the first 12 hour period in T group is 1.3 times and in 0 group is 1.96 times. There is not much difference in sedation score at the end of 12 hours period.

CONCLUSIONS

Concomitant administration of tramadol and ondansetron reduces Tramadol's analgesic power on post-operative pain.[12] Also incidence of post-operative vomiting is less. Post-operative use of Tramadol with Ondansetron cannot be recommended.

REFERENCES

[1] Ready LB. Acute perioperative pain. In: Miller RD, ed. Anaesthesia. 5th edn. Philadelphia: Churchill Livingstone 2000: p. 2325.

[2] Morgan GE, Mikhail MS, Murray MJ. Clinical anaesthesiology. 3rd edn. McGraw Hill 2002: p. 344.

[3] Ferrante FM. Acute postoperative pain management. In: Longnecker DE, Tinker JH, Morgan GE, eds. Principles and practice of anesthesiology. 2nd edn. St. Louis, MO: Mosby 1998:2331-2351.

[4] Ahmed SM, Khan RM, Bano S, et al. Therapeutic suggestion under general anaesthesia reduce the incidence of post-operative emesis. Indian J Anaesth 1997;41(3):158-161.

[5] Stoelting RK. Pharmacology and physiology in anaesthetic practice. 3rd edn. Philadelphia: Lippincott-Raven 1999: p. 103.

[6] Sadiq MN, Rath PC, Pani N. Efficany of Tramdaol hydrochloride as pre-operative analgesia. Indian J Anaesth 1998;42:99.

[7] Arcioni R, della Rocca M, Romano S, et al. Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT3 spinal receptor involvement in acute pain in humans. Anaesth Analg 2002;94(6):1553-1557.

[8] Broome IJ, Robb HM, Raj N, et al. The use of tramadol following day case oral surgery. Anaesthesia 1999;54(3):289-292.

[9] Stoelting RK. Pharmacology and physiology in anaesthetic practice. 3rd edn Philadelphia: Lippincott-Raven 1999: p. 403.

[10] De Witte JL, Schoenmaekers B, Sessler DI, et al. The analgesic efficacy of Tramadol is impaired by concurrent administration of Ondansetron. Anesth Analg 2001;92(5):1319-1321.

[11] MH Pearman. Single dose intravenous Ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia 1994;49 Suppl:11-15.

[12] Sunshine A, Olson NZ, Zighelboim I, et al. Analgesic oral efficacy of tramadol hydrochloride in postoperative pain. Clin Pharmacol Ther 1992;51(6):740-746.