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Clinical Investigation

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

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Abstract
Background and Aims: *To determine the effect of concomitantly administered ondansetron on duration of post operative analgesia of tramadol hydrochloride in patients undergoing gynarcological 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 induded 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 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.*
Conclusion: *Is the post operative use of Tramadol cannot be recommended with ondansetron as the first choice of the antiemetic, because ondansetron reduces the analgesic power of Tramadol on post operative pain.*
Keywords: *Tramadol, ondansetron spinal anaesthesia.*

Introduction

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.

Materials and Methods

Inclusion Criteria

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

Exclusion Criteria

- Body Weight > 70kg
- 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 10cms 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 0: Patients in this group received Tramadol 2mg/kg intravenously to a maximum of l00mg and Ondansetron 0.08mg/kg IVto a maximum of 4mg, 90 minutes after the onset of block.

GROUP T: Patients in this group received Tramadol 2mg/kg IV to a maximum of l00mg and 1ml 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 0.5mg given at HS on previous day and at 6 AM on the day of surgery.
- Inj. Pethidine1mg/kg and Phenergan O.5mg/kg both given 1M 45 minutes before surgery.
- Baseline blood pressure, pulse rate and respiratory rate were recorded or to surgery.
- An intravenous access was established and 500ml of Ringer's Lactate was infused in the pre medication room.

Anesthetic Technique

In the operating room blood pressure checked using non invasive 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 23Gauge spinal needle with 3.2 to 3.5cc 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.

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 12hours was recorded. The incidence of post operative nausea and vomiting was recorded for the same period. Vomiting was treated with metoclopramide l0 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 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.

Observation and Results

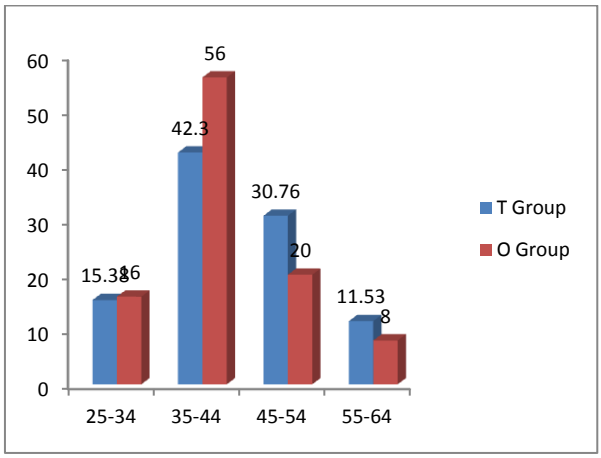
Fifty one patients were studied. 26 in Group T and 25 in 0 group. Four subjects In Group T and 5 subjects in group 0 were excluded from the study because of the following reasons.

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.

Demographic Data of Patients

Age Distribution of Patients

Age groups (in years)	T Group		O Group	
	Number	Percentage	Number	Percentage
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	
t = 0.22			p>0.1	

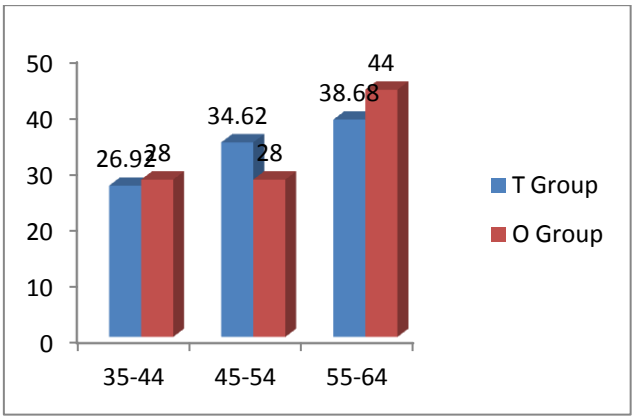


Bar Diagram Showing Age Distribution

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.

Weight Distriblition of Patient

Weight in (Kg)	T Group		O Group	
	Number	Percentage	Number	Percentage
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	
t = 0.59			p>0.1	



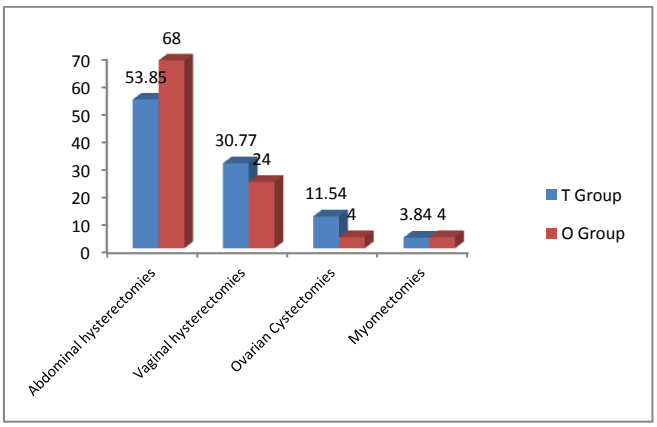
The mean body weight in T group was 50.8. The mean body weight in 0 group was 52.44. The maximum number of patients in either group b longs to 55- 64kg.

Gynaecological Procedure Done

Surgical procedure	T Group		O Group	
	Number	%	Number	%
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

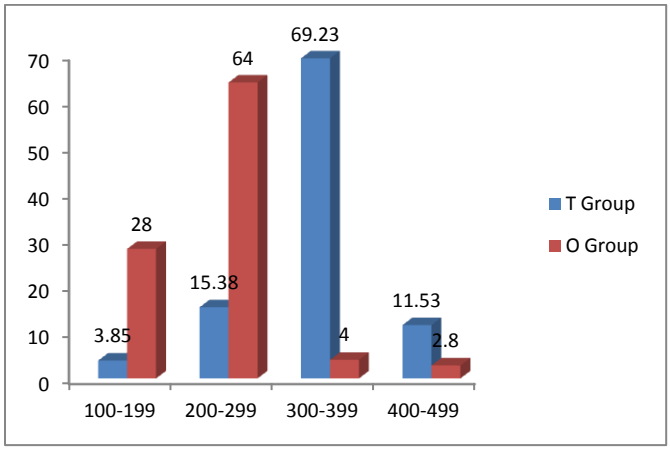
Maximum number of Gynaecological procedures done was Abdominal hysterectomies.

Bar Diagram Showing Gynaecological Procedures



Duration of Post Operative Analgesia

Duration in minutes	T Group		O Group	
	Number	Percentage	Number	Percentage
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	
t = 3.94				p < 0.001



Bar Diagram Showing Duration of Post Operative Analgesia

The minimum duration of analgesia in T group was 120 minutes and maximum duration was 420minutes.

The minimum duration in 0 group was 120 minutes and maximum duration was 405 minutes.

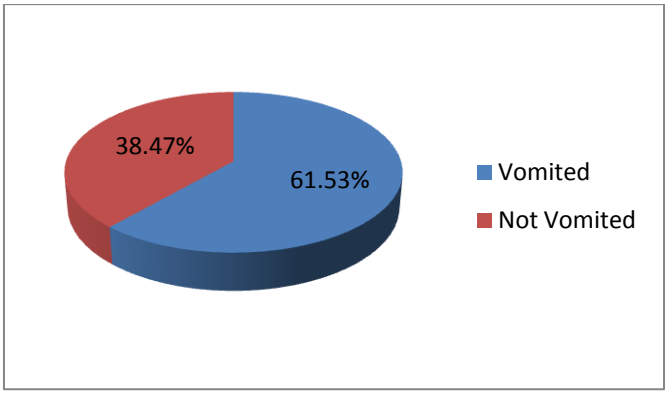
Rescue Analgesic for First 12 Hours

No. of rescue doses of Tramadol	T Group	O Group
	No. of patients	No. of patients
1	19	6
2	5	14
3	2	5
Mean dose	1.36	1.96
t = 0.0053		p > 0.1

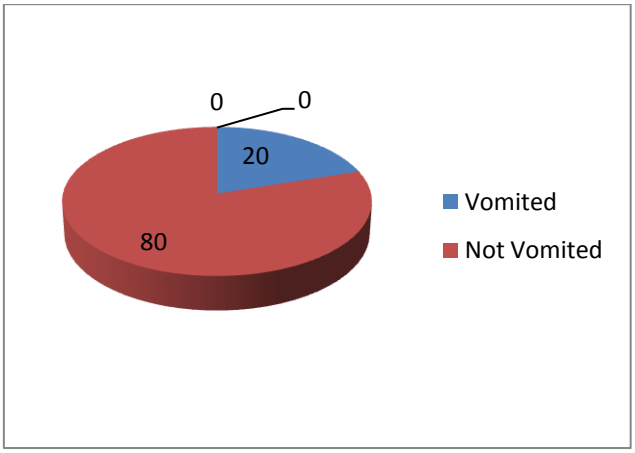
Incidence of Vomiting

Patients	T Group		O Group	
	Number	Percentage	Number	Percentage
Vomited	**16**	**61.53**	**5**	**20**
Not Vomited	10	38.47	20	80
$x^2 = 20.01$		p < 0.01		

T Group



O Group



PIE Diagram Showing Incidence of Vomiting

61.53% in Tramadol group had vomiting, where as in concomitant group only 20% had vomiting.

Discussion

Acute post operative pain and PONV are the important concerns of the care giver in the post operative care unit. 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 activity1 Tramadol is a centrally acting synthetic analgesic which is used in various routes to control post operative pain because of tower 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 SHT3 antagonist is used as an antiemetic in controlling PONV. Tramadol block neuronal uptake of noradrenaline and SHT

(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 SHT3 receptor mediated serotoninergic transmission and particularly that of Ondansetron induced receptor antagonism could either enhance or weaken Tramadol induced analgesia. But clinically it is observed that analgesic effect of Tramadol decrease with Ondansetron.

In the present study, an attempt has been made to evaluate the effect of concomint use of O dansetron 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 1mg/kg of Tramadol when administered along with Ondansetron 0.lmg/kg or placebo 15 minutes before induction of anaesthesia resulted in impaired analgesic efficacy of Tramadol•

R Arcioni et al in their study of 59 patients undergoing ear, nose and throat surgery were given Tramadol for 24hours post operatively with patient controlled analgesia. They were randomly allocated either to a group receiving Ondansetron continuous infusion {lmg/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. 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 l.5 mg/kg produced satisfacto'ry pain relief for 360minutes. Whereas study by Dr Monica G et al at CMC Vellore got a mean duration of 269 minute when l00 mg Tramadol and 4mg 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[40].

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 analgesiy could consist of reduction of binding SHT3 receptor at the spinallevel.

Another mechanism for Ondansetron induced analgesic effectiveness of Tramadol, involve competition for CYP2D6 for metabolism[22]• Tramadol is metabolized to M_1, by the CYP2D6 iso enzyme of the cytochrome P450 enzyme. M_1 metabolite is more potent than rarnadol. 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 nRArcioni et al's study. Where as in this study incidence is less \"it., Ondansetron group. P value< 0.01, so the difference is statistcally significant. This may be because the intensity of Tramadol used in the initial few hours was more in the Ondansetron group in their study (2U ver.:Jus71mg by in 1st 4 hours). Where as in the present study during tt1e above period maximum dose of Tramadol administered was only lOOmg::lnd the got more Ondansetron initially.

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

Conclusion

Concomitant administration of Tramadol and Ondansetron.

- Reduces Tramad of analgesic power on post operative pain
- Incidence of post operative. vomiting is less.
- Conclusion is that, post operative use of Tramadol cannot be recommended with Ondansetron as the first choice of antiemetic.

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Conflicts of Interest: There are no conflicts of Interest.

References

1. L. Brain Ready, Acute peri operative pain, Anaesthesia 5th edition RD Miller 2000; p. 2325.
2. Carlc hag Jr. MD PhD. Clinical anaesthesiology, 3rd edition, G. Edward Morgan, Jr. MS Mikhail, MJ Mury. 2002; p. 344.
3. Michal Errante, Acute post operative pain management, Principles and practice of Anaesthesiology, JH, ED. Longneckor, GE Morgen. 2nd edition. P. 2347.
4. S MoiedAhamed, RM Khan, S Banu, MH Siddiqui, AH Haq. Therapeutic suggestion under general anaesthesia reduce the incidence of post operative emesis. Ind. J. Anaeth (41) 1997; 158.
5. Robert K Stoelting, Pharmacology and Physiology in Anaesthetic practice 3rd Edition. 1999. P. 103.
6. MN Sadiq, PC Rath, N Pani. Efficany of Tramdaol hydrochloride as pre operative analgesia. Ind. J. Anaesthe. 42, 1998. P. 99.
7. KL Tulsiani, Premila Malik, OP Garg Comparison between Tramadol hydrochloride and pentazocine lactate for post operative pain, Ind. J. Anaesthe. 41, 1997. P.44.
8. Crighten IM, Martin PH, Hobbs GJ, Cobby TF, Fleteher, AJP, Steward PD. A comparison of the effects of intravenous Tramadol and morphine on gastric emptying in human volunteers. Analg 1998, 87:445-449.
9. Olle Fortung G et al, Ketorlac Versus Tramadol comparative study of analgesic efficacy in the postoperative pain in abdominal hysterectomy. Rev. Esp. Anaesthesiol Reamin 2000. April 47 (4) 162-7 (Spanish).

10. Sunshine A, Olson NZ, Zighelboiml, Decarto A, Minn FC, Analgesic oral efficacy of Tramadol hydrochloride in post operative pain. Clin Pharmacol Ther. 1992 June, 51.
11. MH Pearman. Single dose intravenous Ondansetron in the prevention of post operative nausea and vomiting. Anaesthesia 1994 vol. 49. S011.
12. De Witte JL, Schoemakers B, Sesseler DI, Deloof "The analgesia efficacy of Tramadol is impaired by concurrent administration of Ondansetron", Anaesthesia Analgesia, 2001 Dec. 93,1626.
13. Arcioni R, Della Rocca M, Romano S, Romano R, Pietropali P, Gasp aretoo, "Ondansetron inhibit the analgesic effects of tramadol. A possible $5HT_3$spinal Receptor involvement in Acute pain in humans", Anaesthesia Analgesic, 2002 June, 1553-7.
14. J Boome, HM Robb, N Ray, Y Girigis& G J Wardall " The use of Tramadol following day case oral Surgery" Anaesthesia, March 1999, 283.