Original Research Article

A comparative study of effect of oral tapentadol versus oral gabapentin for postoperative pain relief in adult patients undergoing abdominal surgeries under general anaesthesia

Vinaya Rahul Kulkarni[1], Rohit Sancheti[2*]

[1]Associate Professor, [2]Assistant Professor, Department of Anesthesiology, BJ Government Medical College, Pune, Maharashtra, INDIA.
Email: vinayabjmc@yahoo.com,dr.rohitsancheti@gmail.com

Abstract

Gabapentin is a second generation anticonvulsant drug which is used for the treatment of chronic neuropathic pain syndrome as well as postoperative pain with good results.1Tapentadol a novel analgesic with dual mode of action has been used for many chronic pain conditions.2 The study is done to compare the analgesic effects of oral tapentadol with oral gabapentin as premedication for postoperative pain relief in adult patients posted for abdominal surgeries under general anaesthesia. Gabapentin produced better anaesthesia sparing effects with better quality postoperative analgesia while tapentadol produced a longer duration of postoperative analgesia with minimal side effects.
Key Words: Tapentadol, gabapentin, postoperative analgesia,

[*]**Address for Correspondence:**
Dr. Rohit Sancheti, Assistant Professor, Department of Anesthesiology, BJ Government Medical College, Pune, Maharashtra, INDIA.
Email: dr.rohitsancheti@gmail.com
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INTRODUCTION

Pain is an unpleasant sensation that originates from ongoing and impending tissue damage. Adequate pain relief in the postoperative period provides a quick return to normal physiologic function and prevents the development of chronic pain. Traditional analgesia in the postoperative period is based on opioids, nonsteroidal anti-inflammatory drugs(NSAIDS) and regional techniques. Administration of high doses of opioids during the perioperative period can result in higher incidence of complications like respiratory depression, sedation, vomiting, constipation, pruritus, immune dysfunction and urinary retention. NSAIDS may lead to gastrointestinal bleeding, renal toxicity and thromboembolic complications. Tapentadol is a relatively new analgesic. It is a mu agonist and has additional norepinephrine reuptake inhibition properties. It has both central and peripheral actions.[2]It is reported to be an important addition in the management of moderate and severe pain. It has been used for postoperative analgesia for knee and shoulder arthroscopy surgeries. Its advantages over other opioids including tramadol are:

1. It has a quicker onset of 32 minutes as compared with that of tramadol (60 mins)
2. It has no cytochrome 450 interaction and has much greater norepinephrine reuptake inhibition besides mu agonist activity.[2,3]
3. It is metabolised 70% by the liver,95% excreted by the kidneys and has an elimination half life of four hours.
4. Due to its synergistic effects with mu agonist, it leads to opioid sparing and decreases the gastrointestinal side effects besides providing good analgesia.[4]

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5. Tapentadol has been reported to cause lesser confusion than tramadol.[5]
6. Tapentadol has no active metabolites.
7. Tapentadol has better gastrointestinal tolerability than other opioids.[6]
8. The incidence of postoperative nausea and vomiting ranges from 12% to 38%.[7]

Gabapentin is an antiepileptic drug that has demonstrated analgesic effect in diabetic neuropathy, postherpetic neuralgia and neuropathic pain.8Gabapentin does not bind to GABA or GABA B receptor but to the alpha 2 delta subunit of the presynaptic voltage gated calcium channels responsible for the inhibition of the calcium influx. The inhibition of calcium release then prevents the release of excitatory neurotransmitters involved in the pain pathways. Tippana et a9 found that the opioid sparing effect during the first 24 hours after a single 300 to 1200 mg dose of gabapentin administered one to two hours preoperatively, ranged from 20 percent to 62 percent. Gabapentin and similar drugs seem to have a strong potential for perioperative use as an analgesic adjuvant and antihyperalgesic agent when used in conjunction with opioids. Gabapentin has been used for postoperative analgesia.[10,11,12] Gabapentin was shown to be effective in neuropathic pain, incisional injury and inflammatory injury.[13,14,15,16] As a result of the saturable transport mechanism , the bioavailability of gabapentin is inversely dependent on the dose.[17] It ranges from approximately 60% for a 300 mg18 and 35% at steady state with doses of 1600 mg three times daily.20 Mean maximum plasma gabapentin concentrations of 2.7+/-2.99 mgper liter are reached in healthy volunteers approximately 3 hours after a single oral 300 mg dose.[18,21]Unlike GABA, gabapentin readily penetrates the blood brain barrier. The drug is excreted unchanged in urine and undergoes first order kinetic elimination.[17,21] Plasma clearance of gabapentin is directly proportional to creatinine clearance. Consequently ,renal impairment reduces gabapentin excretion and increases plasma gabapentin concentrations in a linear fashion.[21,22,23,24] The elimination half life of gabapentin is between 5 and 9 hours and as a result three divided doses are usually required per day but steady state is rapidly achieved.[17] Gabapentin is unique among anticonvulsant drugs as it lacks hepatic metabolism, exhibits low protein binding and does not induce or inhibit hepatic microsomal enzymes or inhibit the metabolism of other antiepileptic drugs.[17,22]The most consistently cited effects of gabapentin are somnolence and dizziness, postoperative nausea and vomiting,sedation.[25] This study is an effort to compare the effects of tapentadol and gabapentin for postoperative analgesia in patients undergoing abdominal surgeries.

AIMS AND OBJECTIVES

To compare the analgesic effect of oral tapentadol versus oral gabapentin as premedication for postoperative analgesia in terms of

1. Total duration of analgesia
2. Anaesthesia sparing effect in terms of anaesthetic consumption
3. Intraoperative haemodynamic stability
4. Postoperative nausea and vomiting
5. Post operative sedation
6. complications or side effects if any

MATERIALS AND METHODS

A randomised prospective study of total number of 60 cases will be conducted .Patients will be divided into 3 groups of 30 each.

Group A – Patients will receive oral Tapentadol 100 mg 60 minutes before the procedure.

Group B – Patients will receive oral gabapentin 300 mg 90 minutes before the procedure.

Preanaesthetic check up will be done.

Inclusion and Exclusion criteria will be as follows:

Inclusion Criteria:

1. Age – 16-60 years
2. ASA – grade I and II
3. Sex: Male or female
4. Patients undergoing abdominal surgeries
5. Duration of surgery: minimum 30 minutes to maximum120 minutes

Exclusion criteria:

1. Known allergy to any of the study medication
2. Opioid dependence
3. History of renal or liver disorder
4. Patient already taking MAO inhibitor or SSRIs
5. Known case of diabetes
6. Known case of hypertension
7. Known case of ischemic heart disease, arrhythmias

Preoperative Investigations:

1. Hb
2. BT/CT/PT
3. Urine routine and microscopy
4. Blood sugar level
5. Blood urea level
6. Serum Creatinine
7. LFTs
8. S. Proteins
9. Platelet count
10. ECG
11. CXR

A written informed consent will be obtained in each case in their vernacular language.All patients are explained the concept of scores used in the study and their scores are

assessed accordingly. After thorough preanaesthetic assessment and obtaining consent patient satisfying inclusion criteria undergoing abdominal surgeries will be randomly assigned into one of the following groups.

Group T: patients will receive oral tapentadol 100 mg 60 minutes before the procedure

Group G: Patients will receive oral gabapentin 300 mg 90 minutes before the procedure.

Intraoperative monitoring of patient with ECG, Heart rate and blood pressure will be done.

Premedication with injection glycopyrrolate 0.2 mg, injection ondansetron 4 mg iv,injection midazolam 0.5 mg, injection fentanyl 1 ug/kg will be given. Induction of general anaesthesia will be done with injection propofol 4mg/kg, injection succinylcholine 2 mg/kg and intubation will be done with appropriate sized portex endotracheal tube and will be maintained by oxygen 50%, nitrousoxide 50% and isoflurane 0.4 -0.6% with vecuronium 0.08 mg/kg as muscle relaxant. Respiratory frequency and tidal volume were adjusted to maintain the end tidal carbon dioxide level at 35-40 mm Hg. End tidal isoflurane concentrations were monitored continuously and recorded at 10 minutes.(Time 1),30 minutes after induction of anaesthesia(time 2),30 minutes after skin incision(Time 3) and at the end of the procedure(.Time 4) Isoflurane was titrated guided by bispectral index BIS =40-50 and haemodynamic end points.(Mean arterial pressure and heart rate within 20% of the preinduction value.) Isoflurane titrated using BIS alone might provide insufficient analgesia, the protocol allowed to increase the inspired isoflurane concentration if BIS exceeded 5,if this did not achieve the targeted values of blood pressure and heart rate, analgesia in the form of 0.5-1 ug/kg boluses of fentanyl was used and those cases were considered as failed cases and were excluded from the study. All the parameters were recorded at 15 minutes intervals. After completion of surgery, neuromuscular blockade was reversed with glycopyrrolate 5ug/kg and neostigmine 0.04 mg/kg. Patients were extubated when adequate spontaneous ventilation was established. Patients were first transferred to recovery room and then to surgical ward. Postoperative pain assessment was monitored by anaesthetist who was blinded to the drug used- Time 1 – on arrival to PACU. Duration of analgesia was assessed using visual analogue scale. Patients were asked to rate their pain on a scale marked from 0 to 10 where o is no pain and 10 is worst pain imaginable. The time from extubation till NRS score >=4 will be defined as the duration of analgesia. Mean VAS Score in group G was --- and Group T was --.Patients were supplemented with analgesic diclofenac 1-1.5mg/kg if NRS.>= 4 and monitored for the time to first analgesic usage. Illiterate patients were assessed using coin assessment scale. If VAS>=5 tramadol 1mg/kg was administered. The time to first postoperative analgesic dose and total amount of analgesic used mg/24 hours by each group were recorded. The amount of inhalational agent consumed was calculated from the Dion's formula.[27] Amount of volatile inhalational agent used (ml) = molecular Weight*Fresh gas flow*Dial concentration*duration / 2412 *density Vital parameters were measured intra operatively in terms of mean pulse rate and mean arterial pressure starting from the start till end of surgery. Sedation of the patient was checked by Ramsay Sedation Scale. Mean Sedation Score in Group G was --and in group T was--All side effects such as dizziness, nausea, vomiting, diarrhoea ,epigastric discomfort, peripheral edema or headache were recorded if present. Postoperative nausea and vomiting will be evaluated for 3 hours half hourly and hourly till 6 hours,2 hourly till 12 hours and then 4 hourly till 24 hours. The number of vomiting episodes will be registered as 0 or no episodes scored as none=0,1 episode as mild =1,2or3 episodes as moderate =2,more than 3 episodes as severe=3. Ondansetron 4 mg intravenously was given for vomiting. Statistical analysis will be done by applying appropriate statistical test. Statistical significance will be assumed at $p< 0.05$.

RESULTS

Table 1

Pulse rate at	Group G		Group T		p-value
	Mean	SD	Mean	SD	
Pre operative	83.10	4.8	84.90	3.6	0.095
0 min	79.60	2.85	82.27	3.85	0.004*
15 min	81.40	3.49	82.80	3.55	0.129
30 min	82.00	4.95	84.13	3.48	0.059
45 min	82.67	5.97	83.60	3.38	0.460
60 min	83.60	6.63	83.53	3.35	0.961
75 min	82.87	6.62	84.00	3.28	0.405
90 min	83.87	7.68	83.33	2.70	0.722
105 min	84.93	7.84	84.53	4.70	0.812
120 min	85.07	7.23	83.67	6.17	0.423

*Significant (p-value < 0.05) Unpaired t-test used

Table 2

SBP at	Group G		Group T		p-value
	Mean	SD	Mean	SD	
Pre operative	112.33	6.26	112.67	9.07	0.869
0 min	110.33	3.20	111.67	5.31	0.244
15 min	115.33	7.30	113.00	7.94	0.241
30 min	111.00	6.07	116.33	10.66	0.021*
45 min	112.67	8.68	113.00	8.37	0.880
60 min	111.67	7.91	114.67	8.19	0.155
75 min	112.67	8.68	112.33	7.74	0.876
90 min	111.67	6.48	110.67	8.28	0.604
105 min	109.31	7.04	109.00	8.03	0.875
120 min	113.10	8.50	112.67	7.85	0.838

*Significant (p-value < 0.05) Unpaired t-test used

Table 3

DBP at	Group G		Group T		p-value
	Mean	SD	Mean	SD	
Pre operative	71.9	5.8	75.1	6.9	0.062
0 min	79.00	3.05	90.33	18.47	0.002*
15 min	77.00	5.35	74.33	5.04	0.052
30 min	75.33	6.29	77.00	5.35	0.274
45 min	77.00	5.35	77.67	5.68	0.642
60 min	76.00	6.21	80.00	3.71	0.004*
75 min	77.67	5.68	78.33	4.61	0.620
90 min	75.33	5.07	75.67	5.04	0.799
105 min	77.67	5.04	78.67	4.34	0.414
120 min	75.00	5.72	77.00	4.66	0.143

*Significant (p-value < 0.05) Unpaired t-test used

Table 4:

Group	Number of patients	Consumption of Inhalation anaesthetic		p-value
		Mean	SD	
Group G	30	14.5	1.2	< 0.001
Group T	30	11.3	1	

p-value < 0.05 (Significant) Unpaired t-test used

Table 5:

VAS at	Group G			Group T			p-value
	Min	Max	Median	Min	Max	Median	
Post op 30 min	5	7	5	2	4	3	< 0.001
60 min	4	5	5	1	4	2	< 0.001
90 min	4	5	4	1	4	2	< 0.001
120 min	4	6	4	1	3	2	< 0.001

*Significant (p-value < 0.05) Mann-Whitney U test used

Table 6:

Sedation at	Group G			Group T			p-value
	Min	Max	Median	Min	Max	Median	
Post op 30 min	2	3	3	1	2	1	< 0.001
60 min	2	3	2	1	2	1	< 0.001
90 min	2	3	2	0	2	1	< 0.001
120 min	1	3	2	1	2	1	< 0.001

*Significant (P-value < 0.05) Mann-Whitney U test used

DISCUSSION

Postoperative pain is an important factor that affects recovery from anaesthesia and surgery. Multiple mechanisms are involved in postoperative pain, a multimodal analgesia regimen using a combination of opioid and non opioid analgesics has become the treatment of choice1.Perioperative analgesia has been traditionally provided by opioid analgesics. However extensive use of opioids has been associated with well known side effects like respiratory depression, vomiting, pruritus, urinary retention. The upper abdominal incisions cause substantial respiratory disturbance causing hypoxia, hyperventilation and pulmonary shut down due to pain. Hence adequate analgesia in upper abdominal surgeries carries significance than mere patient comfort.[1,2,.3] Gabapentin was introduced in 1994 as antiepileptic drug for partial seizure. It is also used as adjunctive therapy in neuropathic pain states. It alleviates pain and prevent acute nociceptive and inflammatory pain both in animals and volunteers especially when given before trauma.[4,5,6] Tapentadol classified by the US Food and Drug administration as a class 2 opioid is currently marketed in the united states as immediate release for moderate to severe acute pain in the tablets of 50 mg,150 mg, 200 mg and 250 mg. Tapentadol has a low affinity mu opioid receptor agonist and a norepinephrine reuptake inhibitor. It is not a racemic compound. It has no active metabolites and this property makes it useful in patients with hepatic and renal failure. The most common side effects of tapentadol are nausea(30%), vomiting(18%), dizziness(24%), and somnolence(15%) Improved GIT tolerability is the main advantage. The drug is contraindicated with MAOI, CNS depressants.[7,8] Tapentadol exhibits unique analgesic action. It interacts with ascending pathways responsible for pain perception and descending tracts that suppress noxious transmission. The ascending pathway is excitatory. Activation of pre and postsynaptic opioid receptors in the ascending pathway inhibits presynaptic release of noxious transmitters as well as postsynaptic depolarization of second order cells.

The efficacy of tapentadol IR was demonstrated in one phase II and two phase III postsurgical trials. But its effectiveness for provision of postoperative analgesia in upper abdominal surgery was never evaluated or compared with gabapentin till date by any research worker. After written informed consent and approval of instituitional ethical committee, after inclusion and exclusion criteria, 60 patients undergoing upper abdominal surgery were divided after randomisation with coin test into group G(30) and group T(30).Preoperative demographic data was comparable in both the groups. Preoperative vital parameters in both the groups are as per Table 1,2,3. And comparable Group G patients received 300 mg of gabapentin 60 minutes before orally preoperatively and group T patients received 100 mg of tapentadol. The surgeries were performed by the same unit head surgeon. The intraoperative vital parameters were monitored as shown in Table 1,2,3. And were found to be comparable and statistically non significant. The intraoperative consumption of isoflurane was found to be less in gabapentin group as compared to group T.(Table 4)- Postoperative monitoring included vital parameters and postoperative pain score assessment and consumption of rescue analgesia. Table 5 and Table 6. The patient satisfaction score was measured in both the groups. Table 5 It was found that quality and duration of postoperative analgesia was found to be superior in tapentadol group as compared to gabapentin group. The mean sedation score in both the groups was as in table 6 Patients in group G were found sedated postoperatively and less oriented to time, place and person. Tapentadol has proven to be having definite advantage over gabapentin in the postoperative period. The main side effect found in G group was dizziness and sedation9.In group T, only 2 patients complained of vomiting which was managed by injection ondensetron10 .No other major side effects were found in both the groups. Though gabapentin has been used in chronic neuropathic pain settings, it can also be used in perioperative settings as premedication with sparing of inhalational anesthetic agent which is an advantage and with few side effects11.Tapentadol a novel new analgesic agent has been used in chronic pain setting has a definite role as preemptive analgesic when used for upper abdominal surgeries.

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