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Original Research Article

The Effectiveness of Tapentadol in Perioperative Analgesia: A Prospective Comparative Study of Nasal versus Oral Preparations

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Conflict of interest: Nil

Abstract

Background: Tapentadol is a relatively new analgesic. The comparison between nasal versus oral formulations was done for their various effects in the perioperative period.

Setting: A study conducted in a tertiary care hospital.

Materials and Methods: Sixty adults, of the American Society of Anaesthesiologists Classes I or II of either sex and age 20–60 years of age undergoing elective laparoscopic cholecystectomies done under general anaesthesia of minimum 90 minutes to less than or equal to 120 minutes duration were divided into 2 groups of 30 each by computerized random allotment (Group –N: Nasal Tapentadol, Group –T: Oral Tapentadol). Group N received two puffs of nasal Tapentadol (Nearly 25mg per puff), 5mins before induction of anaesthesia. Group T received one oral Tapentadol tablet 100mg, 60 minutes before induction of anaesthesia. Statistics: Randomized Control trial, Proportion tests, Correlation, ANOVA, Kruskal Walis test, Regression analysis, Paired t-test, Chi-square test, F test, and, any other analysis found suitable, P-value for analytical purposes: 0.05 [95% Confidence Interval], Software for Statistical Analysis: MS-Excel/ STATA 14 were used for statistics.

Results: Nasal Tapentadol group patients had significantly better analgesia 3 h postoperatively than the oral tapentadol group.

Conclusions: From the Result and Analysis it was concluded that nasal Tapentadol had better analgesic efficacy and hemodynamic stability as compared to oral formulations.

Keywords: Analgesia; Nasal Tapentadol; Oral Tapentadol.

Introduction

The International Association for The Study Of Pain (IASP) has aptly defined pain as ‘’An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.’’ Acute pain following surgery is common and

associated with important clinical sequelae. Between one and three of every four patients report poorly controlled, moderate to severe pain following surgery [1-6]. Ineffective perioperative pain management can increase the risk of a diverse array of complications (e.g., deep vein thrombosis, pulmonary embolism, pneumonia, coronary ischemia, ileus, poor wound healing, insomnia, chronic pain and associated disabilities) [7-9], delay discharge from hospital or ambulatory surgery centre, result in unscheduled hospital admission/readmission, and prolong postoperative recovery [10-13]. In addition to a humanitarian desire to reduce suffering, poorly controlled pain can increase morbidity, delay recovery, impair quality of life, and result in prolonged disability.

Opiates are the standard of care for moderate to severe postoperative pain [14]. Most opioids used in clinical practice produce analgesia by activating m-opioid receptors on neurons within the pain transmission pathway [15]. However, these treatments are commonly associated with adverse effects, including nausea, vomiting, constipation, dizziness, and somnolence [16], which can lead to under treatment of the pain, in an attempt to minimize these events. Tapentadol is a novel, centrally acting analgesic drug. It is the first representative of a new class of drugs, which can be referred to as MOR-NRI drugs, and it displays an analgesic efficacy comparable or superior to that of strong classical opioids such as oxycodone and morphine [17-20]. Tapentadol, despite having lower affinity, provides highly effective analgesia with the ratio of the tapentadol to morphine-equivalent analgesic dose being 2.5:1. For example, the equianalgesic dose of oral morphine for a patient taking 100 mg of oral tapentadol would be 40 mg [21].

The mechanisms responsible for this overall gain in analgesic potency are related to the fact that tapentadol is a fairly selective, rapid-acting norepinephrine (NE) reuptake inhibitor. It provides additional pain suppression by increasing NE and activating alpha-2-adrenergic receptors in the spinal cord and brain. This dual analgesic effect of MOR activation and NE-reuptake inhibition provides analgesic effects equivalent to equipotent doses of oxycodone. Tapentadol has no active metabolites. Many opioids are metabolized into active substances, which increase tapentadol's adverse effects and make its actions unpredictable. Morphine for example, is conjugated into morphine-3-glucoronide and morphine-6-glucoronide. Morphine-6-glucoronide is 100 times more potent than morphine on the MOR, and if accumulated (ie, in renal failure) contributes to prolonged respiratory depression [22].

Tapentadol has fast oral absorption, reaching its maximum serum concentration in less than 2 hours and can be taken irrespective of meals. The bioavailability is 32% due to first pass effect.

The rate and extent of absorption with 22.5 mg and 45mg Tapentadol intranasal route shows higher bioavailability at half the dosage of 22.5mg, quicker absorption as compared to the oral route and similar exposure to 50mg and 100mg respectively of oral Tapentadol HCL, better tolerance and reduced incidence of gastrointestinal and central side effects as compared to oral preparations.

The main metabolic pathway occurs through glucuronic acid binding and 97% due to phase 2 reactions. The main metabolite is tapentadol –O- glucuronide, which does not exercise any activity on opioid receptorsor reuptake systems of synapses or other junctions. Nearly 97% of the drug delivered is transformed into inactive metabolites.

Tapentadol nasal spray is specially formulated as a hydrophilic mucoadherent formulation that offers quick delivery, with adsorption on the nasal concha, that is innervated with nerves and blood vessels, offering quick onset of clinical analgesia that is comparable to parenteral formulations without the complementary set of gastrointestinal side

effects. This study was conducted to compare the analgesic effects of nasal Tapentadol versus oral Tapentadol as premedication for perioperative analgesia, Intraoperative haemodynamic stability and Intra and postoperative requirement of rescue analgesic.

Materials and Methods

This comparative, prospective and randomized controlled study was carried out, after obtaining approval from the Hospital Ethics Committee and written informed consent from the patients. Sixty adults, of the American Society of Anaesthesiologists Classes I or II of either sex and age 20–60 years of age undergoing elective laparoscopic cholecystectomies done under general anaesthesia of minimum 90 minutes to less than or equal to 120 minutes duration were divided into 2 groups of 30 each by computerized random number table. (Group – N: Nasal Tapentadol, Group –T:Oral Tapentadol).Group N received two puffs of nasal Tapentadol (Nearly 25mg per puff) 5mins before induction of anaesthesia. Group T received one oral Tapentadol tablet 100mg, 60 minutes before induction of anaesthesia. Pre-anesthetic evaluation was done day before OT. All patients were fasted for solid food for 8 hours, for light meal for up to 6 hours, for non-clear fluid for up to 4 hours and for clear fluids up to 2 hours before the surgery.

In the operation theater, the patient's body weight, fasting status, and consent was checked, i.v cannula was established. Standard monitors like ECG, Pulse oximeter, NIBP were connected to the patients and baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), Rate Pressure Product (RPP) were noted. Rate pressure product were calculated from recordings of SBP and HR, at various time intervals. General anaesthesia will be induced by IV Fentanyl 1-1.5 μg/kg, Propofol 1-2 mg/kg. After achieving proper mask ventilation Atracurium 0.5 mg/kg will be given to facilitate tracheal intubation. Then the patient will be mask ventilated for 3 minutes followed by laryngoscopy and endotracheal intubation; then Atracurium 0.1 mg/kg will be given as maintenance at regular intervals. According to patient haemodynamics, anaesthesia will be maintained with Nitrous oxide 60%, Isoflurane 0.6-1.0% in 40% oxygen. The lungs will be mechanically ventilated and the end-tidal carbon dioxide concentration will be maintained at 30-40 mm Hg. At the end of the surgery, neuromuscular block will be reversed with Neostigmine at a dosage 0.05 mg/kg iv and Glycopyrrolate at a dose of 0.004 mg/kg/iv dose. Hemodynamic parameters including HR, SBP, DBP, MAP, RPP and any adverse effect will be recorded 1 min after intubation. Then the parameters will be recorded at 15-minute interval till the end of surgery. In the post operative period, parameters will be recorded at 5mins, 120 mins, 240 mins after extubation.

In addition, VAS score (Scale 1-10) was recorded in the post operative period at the same intervals. Any patient who complained of pain with VAS > 5 in the post operative period, was given IV Paracetamol 15 mg/kg body weight over 15 minutes and the time was noted. Any patient complaining of any side effects like nausea, vomiting, headache dizziness was recorded and managed accordingly.

Results

All the statistical analysis was carried out using Microsoft Excel, 2013, and STATA 14 software.

The student’s t-test was used to test the null hypothesis that the mean of the two groups is the same at a 5% level of significance.

Both groups were comparable concerning their demographic profile, baseline hemodynamic parameters, and perioperative pain relief. This has also been statistically verified since the mean differences between them among the groups are insignificant at a 5% level of significance.

Table 1

	Nasal Tapentadol		Oral Tapentadol	
	Mean	**SD**	**Mean**	**SD**
Age	40.33333	11.76885	43.56	11.64
Male: Female	16:14		16:14	
Height	64.33333	2.495974	61.8	2.82
Weight	61.13333	6.668161	61.7	5.89

The table are reported as Mean ± S.D .p-value < 0.05 is considered significant

Table 2

	Nasal Tapentadol	Oral Tapentadol	p-value
	Mean	**Mean**	
SBP 0	111.6957	116.2727	0.06
SBP 15	108.4348	119.4545	0.00
SBP 30	107.3043	115.7273	0.00
SBP 45	104.6087	113.1364	0.00
SBP 60	101.3913	110.5909	0.00
SBP 75	100	108.2667	0.00
SBP 90	98.83333	107.1429	0.00
SBP 105	99.66667	111.1429	0.00
SBP 120	95.28571	111.7143	0.01

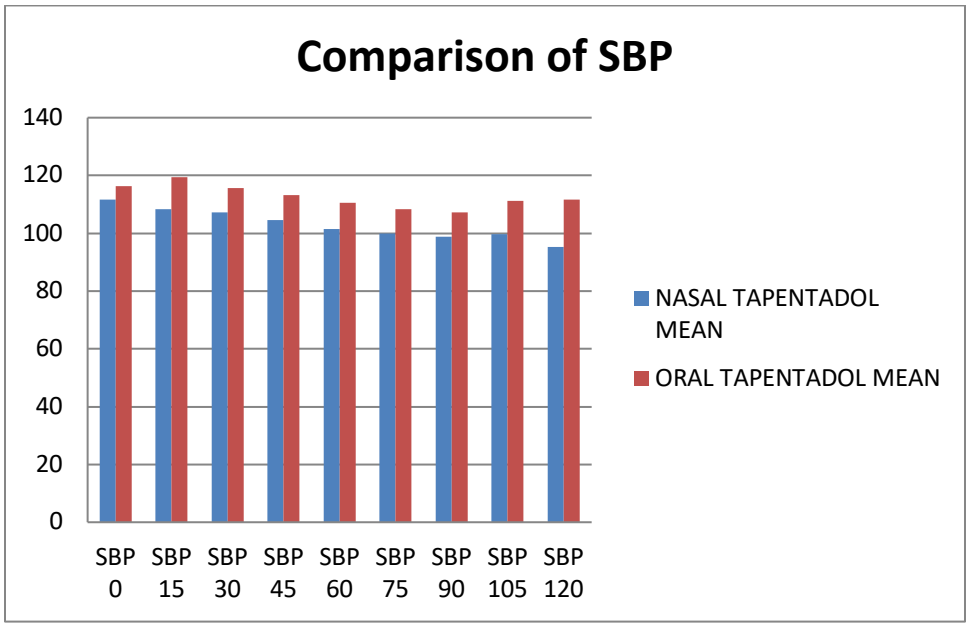

Figure 1

As the p-values of all the groups are 0.00, we conclude that the Null hypothesis is rejected at 5% level of significance and the SBP is higher for the group Oral Tapentadol as can be observed from the mean values.

Table 3

	Nasal Tapentadol Mean	Oral Tapentadol Mean	p-value
DBP 0	70.22727	77.90909	0.00
DBP 15	67.72727	75.27273	0.00
DBP 30	65.86364	74	0.00
DBP 45	64.31818	72.13636	0.00
DBP 60	62.86364	71.95455	0.00
DBP 75	61.17647	71.73333	0.00
DBP 90	61.88235	72	0.00
DBP 105	62.83333	73.42857	0.01
DBP 120	65.28571	70.6	0.18

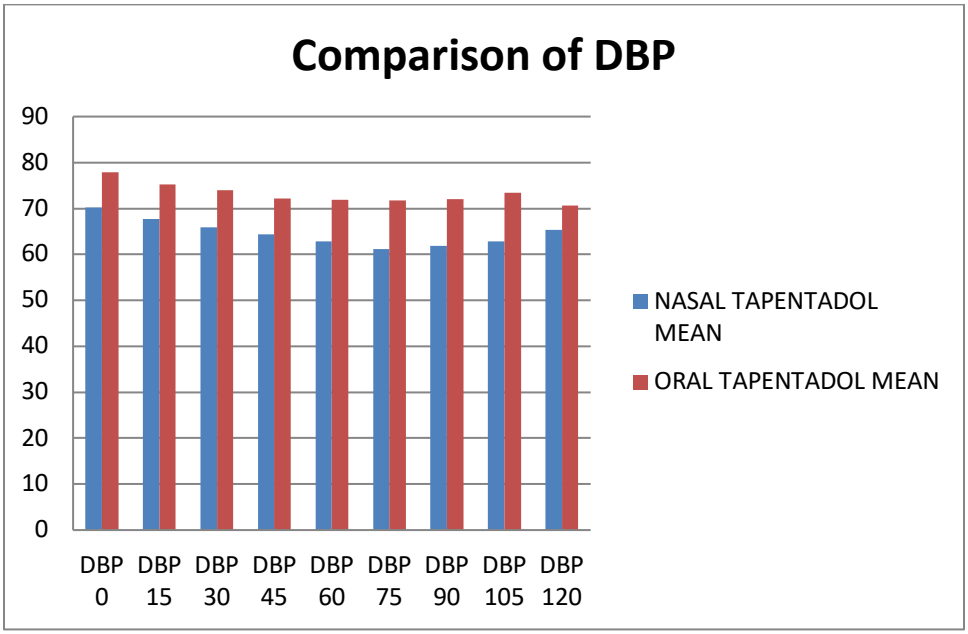

Figure 2

As the p-values of all the groups are 0.00, we conclude that the Null hypothesis is rejected at 5% level of significance and the DBP is higher for the group Oral Tapentadol as can be observed from the mean values.

Table 4

	Nasal Tapentadol Mean	Oral Tapentadol Mean	p-value
MAP 0	126.5362	129.0606	0.39
MAP 15	122.9855	134.1818	0.00
MAP 30	122.0725	129.6364	0.01
MAP 45	118.971	126.803	0.01
MAP 60	115.1449	123.4697	0.00
MAP 75	83.47826	82.12121	0.93
MAP 90	87.88406	75.63636	0.45
MAP 105	29.2029	39.36364	0.54
MAP 120	32.04348	42.04545	0.56

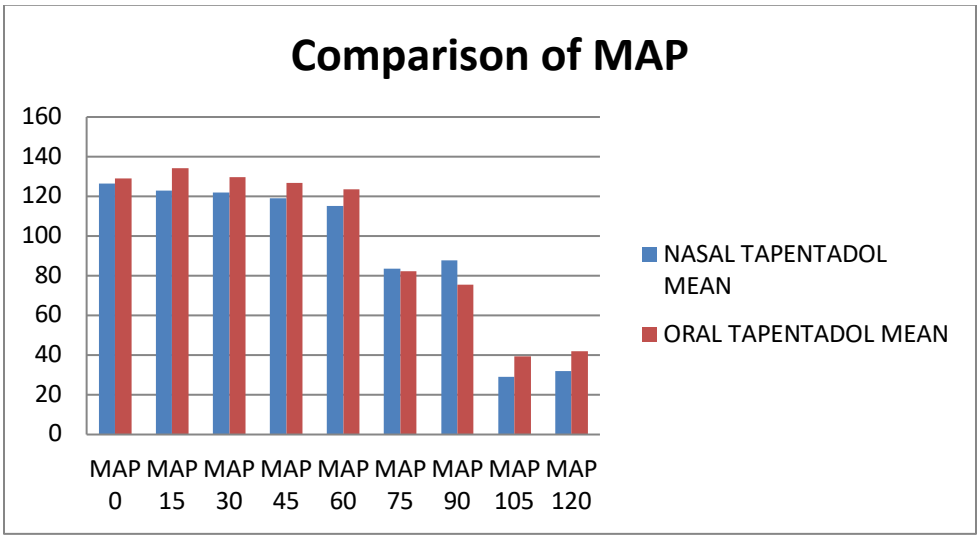

Figure 3

As the p-values of all the groups are 0.00, we conclude that the Null hypothesis is rejected at 5% level of significance and the MAP is higher for the group Oral Tapentadol in majority patients as can be observed from the mean values.

Table 5

	Nasal Tapentadol Mean	Oral Tapentadol Mean	p-value
HR 0	74.08696	101.8182	0.00
HR 15	74.47826	101.7727	0.00
HR 30	73.43478	103.4091	0.00
HR 45	72.86957	100.7727	0.00
HR 60	70.91304	100.0952	0.00
HR 75	70.17647	99	0.00
HR 90	68.35294	101.6429	0.00
HR 105	75	105.1429	0.00
HR 120	73.85714	103	0.00

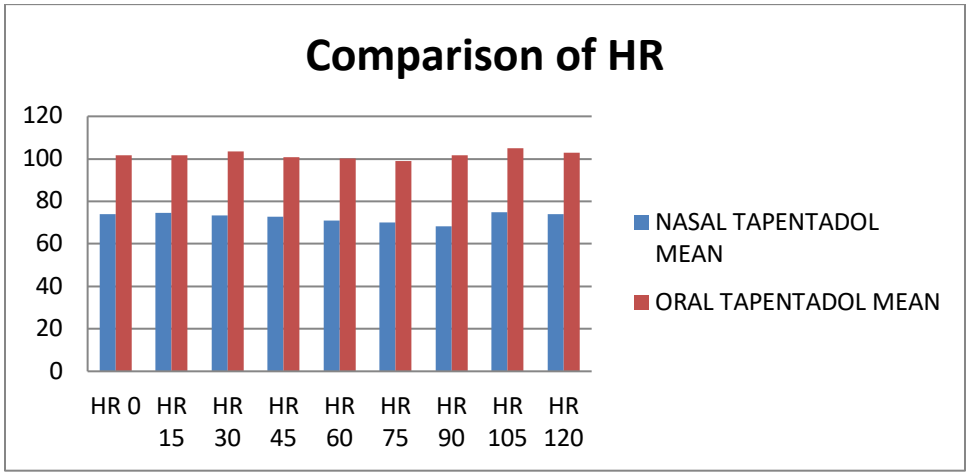

Figure 4

As the p-values of all the groups are 0.00, we conclude that the Null hypothesis is rejected at 5% level of significance and the HR is higher for the group Oral Tapentadol as can be observed from the mean values.

Table 6

	Nasal Tapentadol Mean	Oral Tapentadol Mean	p-value
SPO2 0	99.81818	99.95455	0.31
SPO2 15	99.68182	99.86364	0.21
SPO2 30	99.77273	99.36364	0.05
SPO2 45	99.5	99.22727	0.39
SPO2 60	99.63636	99.31818	0.13
SPO2 75	99.8125	99.41176	0.13
SPO2 90	99.75	99.75	1.00
SPO2 105	100	99.66667	0.27
SPO2 120	100	99.57143	0.21

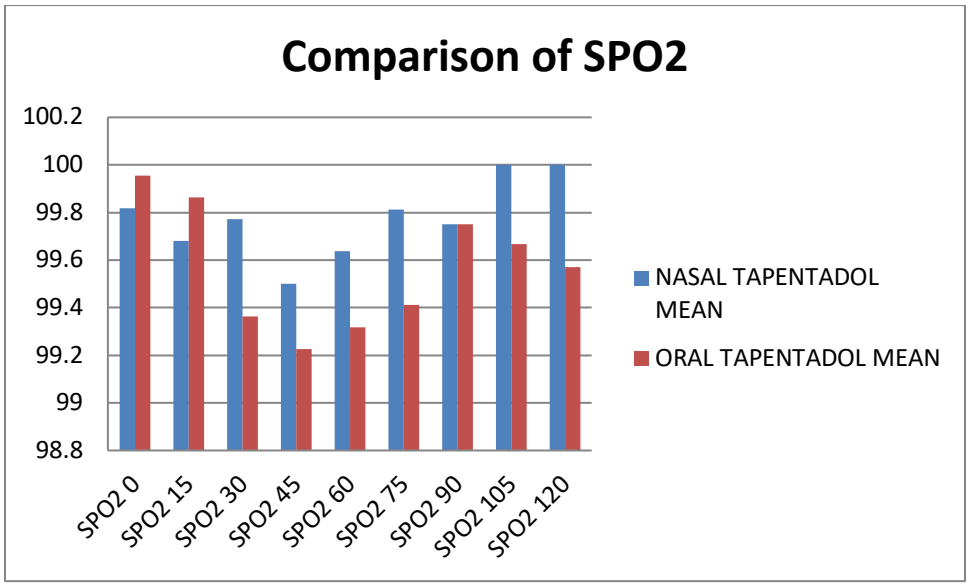

Figure 5

As the p-values of all the groups are higher than 0.00, we conclude that the Null hypothesis is rejected at 5% level of significance and the SPO2 level remains roughly the same for both groups.

Table 7

	Nasal Tapentadol Mean	Oral Tapentadol Mean	p-value
VAS 0	1.285714	3.125	0.00
VAS 1HR	2	3.375	0.00
VAS 2HR	2.285714	4.5	0.00
VAS 03HR	2.666667	4.875	0.00
VAS 4HR	2.666667	4.875	0.00

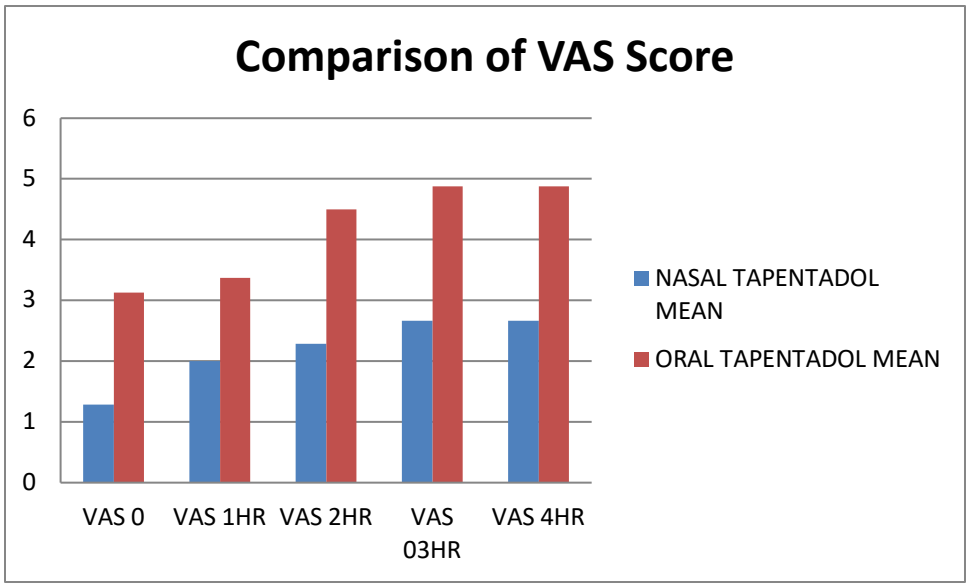

Figure 6

As the p-values of all the groups are 0.00, we conclude that the Null hypothesis is rejected at 5% level of significance and the VAS Score is higher for the group Oral Tapentadol as can be observed from the mean values.

Discussion

In the study when Systolic blood pressure was compared between the nasal and oral Tapentadol group, it was observed that the p-values of all the groups were 0.00, hence the Null hypothesis was rejected at 5% level of significance and the Systolic blood pressure was higher for the group of Oral Tapentadol which was observed from the mean values.

In the study when Diastolic blood pressure was compared between the nasal and oral Tapentadol group, it was observed that the p-values of all the groups were 0.00, hence the Null hypothesis was rejected at 5% level of significance and the DBP was higher for the group Oral Tapentadol which was observed from the mean values.

In the study when Mean Arterial blood pressure was compared between the nasal and oral Tapentadol group, it was observed that the p-values of all the groups were 0.00, hence the Null hypothesis was rejected at 5% level of significance and the MAP was higher for the group Oral Tapentadol which was observed from the mean values.

In the study when Heart Rate was compared between the nasal and oral Tapentadol group, it was observed that the p-values of all the groups were 0.00, hence the Null hypothesis was rejected at 5% level of significance and the heart rate was higher for the group Oral Tapentadol which was observed from the mean values.

In the study when Visual Analogue Score was compared between the nasal and oral Tapentadol group, it was observed that the p-values of all the groups were 0.00, hence the Null hypothesis was rejected at 5% level of significance and the Visual Analogue Score was higher for the group Oral Tapentadol which was observed from the mean values.

In two separate studies evaluating patients with severe osteoarthritic knee pain and lower back pain, tapentadol ER was found to be more effective than placebo and as effective as oxycodone controlled release (CR) [23]. Tapentadol ER 100–250 mg twice a day (BID) was compared to oxycodone ER 20–50 mg BID. Tapentadol ER was found to effectively relieve moderate to severe chronic low back

pain over 15 weeks (comparable to OxyContin, superior to placebo). Tapentadol ER was associated with better GI tolerability than oxycodone CR. The long-term tolerability and safety profile of tapentadol ER was studied by Wild *et al* [24]. Tapentadol ER was shown to be superior to both placebo and oxycodone CR in improving at-work productivity for patients with osteoarthritic pain. This difference is attributed to the fact that tapentadol ER was able to offer comparable pain control with fewer TEAEs, and therefore exhibiting a lower attrition rate [25]. Tapentadol ER can be used in patients who need pain medication around the clock, and who do not need it as a rescue medication.35 Patients did not appear to become tolerant to tapentadol as they do with other opiates. Studies have shown that patients using tapentadol for 24 months have shown no increase in their tapentadol dose [27]. In the study done by Debashish Paul, Sachin Narayan Kulkarni *et al* in the year 2015 it was found that there was significant reduction of VAS pain score at 0, 2, 6 and 12 hours (p-values 0.0005, 0.003, 0.001, 0.0005 respectively) in laparoscopic cholecystectomy, and which also commented Paracetamol was better than Diclofenac at 6 and 12 hours [26]. In a randomized double-blind study designed by Sarika and Rachna Wadhwa in 2015 to compare preemptive analgesic efficacy of Acetaminophen, Diclofenac and combination of both, administered orally in patients undergoing elective modified radical mastectomy, the Global satisfaction score (GSC) as regard to postoperative pain at 24 hours were significantly better in Diclofenac group as compared to Acetaminophen [27].

In a Phase 1 study, the PK results obtained with nasal and oral Tapentadol showed, higher bioavailability at dosage of 22.5 mg in the nasal route, quicker absorption as compared to the oral route, similar exposure to 50mg and 100mg respectively of oral Tapentadol HCL, well tolerated with reduced incidence of gastrointestinal and central side effects via the nasal route. In the present study, it was observed from the mean values that SBP, DBP, Heart rate and MAP and VAS score was higher for the Oral Tapentadol group as compared to the nasal Tapentadol group.

Conclusion

From Results and Analysis it was concluded that, hemodynamic stability was more significant in the nasal Tapentadol group as compared to the oral tapentadol group, Postoperative VAS score was significantly lower in the nasal Tapentadol group as compared to the oral Tapentadol group, time interval for requirement of rescue analgesia was significantly prolonged in the nasal Tapentadol group as compared to oral Tapentadol group. Hence Tapentadol nasal spray provided better hemodynamic stability and perioperative pain relief

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