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Original Research Article

The effects of nefopam hydrochloride and tramadol hydrochloride on postoperative pain in patients undergoing long bone fracture fixations: A randomised triple blinded study

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ABSTRACT

Background: Orthopaedic surgery has one of the most painful post-operative periods. Pain management is an important consideration in Orthopaedic department. The purpose of this study was to assess the effect of Nefopam hydrochloride and Tramadol hydrochloride in postoperative analgesia in patients undergoing long bone fracture fixations.

Settings and Design: Triple blinded Randomization and allocation to study groups were carried out by odd and even number method. The study was conducted in tertiary care center from May 2019 till March 2020.

Materials and Methods: 184 patients who underwent Orthopaedic surgery were included in this randomized study. 92 patients were placed each in group-A and B. Patients in group-A received Tramadol hydrochloride and in group-B received Nefopam hydrochloride. The primary outcome measures were pain intensity assessed by using a Visual Analogue Scale (VAS) Score, Verbal Rating Scale (VRS) score whereas the secondary outcome measures included side effects related to the drugs and number of patients who required rescue analgesia.

Statistical Analysis: Unpaired t-test and Chi-square test was used to carry out all the data analysis.

Results: The pain intensity assessed on VAS score was significantly better for Tramadol group compared to Nefopam group at all time periods except at 15 minutes and a significant difference was present in verbal rating scale score between the groups only at 24 hours. Side effect profile and requirement of rescue analgesia were more in Nefopam hydrochloride group.

Conclusions: Tramadol hydrochloride was more effective in providing post-operative pain relief in patients compared to Nefopam hydrochloride.

1. Introduction

The incidence of pain following a surgery is just like an alarm system. The reaction to post-operative pain leads to maladaptive behaviour, which cause more harm to patient's body than benefit.[1]

Orthopaedic surgeries produce a higher intensity of pain compared to any other procedure as trauma to bone results in greater pain than that to soft tissues because of the highly sensitive periosteal layer of the bone.[2] Poorly controlled postoperative pain leads to discomfort, readmission, metabolic complications, non-

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planned hospitalization, delayed functional recovery and patient's dissatisfaction.[3] Therefore, even though pain is mostly considered a positive reaction of body, its control post-surgery is critical. Effective post-operative pain relief can result in psychological benefits, early mobilization and return to work and improves patient comfort.[4]

According to recent advances in the mechanisms for the development of pain, sensitization of both the Central nervous system (CNS) and Peripheral nervous system (PNS) due to acute pain leads to development of chronic pain.[4] Every possible attempt to decrease or eliminate the post-operative pain must be done by anesthesiologist or operative surgeon without causing any further problems like hypoventilation due to respiratory depression, coagulation anomalies, drug dependence or tolerance and gastro-intestinal motility problems.[5] Analgesics acts by affecting all these components at different levels in the pain pathway.[6]

Different analgesics are used to control pain in post-operative period by different mechanisms. The most common classes of the drugs used for the treatment of post-orthopedic surgery pain are opiates and/or nonsteroidal anti-inflammatory drugs (NSAIDS). Both of these classes have significant undesired side effects[7] and some of them may directly/indirectly inhibit the bone healing and functional recovery.[8]

Tramadol is a synthetic analgesic that acts centrally via opioid receptors which have higher affinity and cause inhibition of the reuptake of norepinephrine and 5-hydroxytrypatmine (serotonin). It has the advantage of less respiratory depression compared to other opioids. There is higher incidence of side effects like nausea and vomiting and therefore it is a concern to use in postoperative patients.[9]

Nefopam is a nonnarcotic centrally acting drug like tramadol which acts by inhibiting reuptake of norepinephrine and serotonin.[10] It produces a morphine-sparing effect and hence a reduction in the incidence of adverse effects like that of morphine.[11] It has no effect on platelet aggregation and CNS depression.[12] It has been noted to have 15% to 30% minor adverse effects like nausea, vomiting, sweating and sedation.[11]

After extensive literature search, we did not find a more studies that compared the analgesic effect of these two drugs, so we undertook this study, to compare the effects of nefopam hydrochloride and tramadol hydrochloride for post-surgical pain relief in patients who underwent long bone fracture fixation by close reduction with nailing.

2. Materials and Methods

2.1. Study design and participants

This prospective triple blinded study was conducted in the Orthopaedic department of a tertiary care center from May 2019 till March 2020 after getting the approval from institutional ethical committee. Patients were recruited in the study after proper written and informed consent. Patients in belonging to the American Society of Anaesthesiologists class I and II and age group of 18-60 years undergoing close reduction and internal fixation with nailing of single long bone fracture in lower limb were included in the study. Patients with any cardiac disease, renal or hepatic insufficiency, glaucoma, mentally unstable, drug addicts and on epidural analgesia during/after surgery were excluded from the study.

2.2. Procedure

On admission to the hospital, a detailed patient history with emphasis on the medical illnesses and mode of injury was taken and a thorough work-up of all the systems was done before surgery. All required pre-operative investigations like complete blood count, Coagulation profile (Bleeding time/Clotting time), Blood grouping, kidney function test, liver function test if indicated, chest x-ray, electrocardiogram (ECG) were advised. All the surgeries were done under spinal anaesthesia.

2.3. Randomization

The enrolled 184 patients satisfying the inclusion criteria were assigned into two groups according to randomized odd & even numbers method. The principal investigator prepared the study drugs and co-investigators were blinded to study drugs being administered to the patients and also outcome evaluators by co-investigators. Both the patients and co-investigators were blinded to group allocations. The data analyser, who was not involved in the study, analysed the outcome data statistically. Group-A included all odd numbered patients who received Tramadol hydrochloride and group-B included all even numbered patients who received Nefopam hydrochloride as per Table 1. Both the drugs were administered intravenously starting one hour post-operatively in post analgesia care unit (PACU) for initial 24 hours.

Table 1: Dose and duration of the drugs

Group	Drug	Dose and Duration
A	Tramadol hydrochloride	"100 mg in 100 ml normal saline intravenous infusion over a 15 minutes period, every 6^{th} hourly."
B	Nefopam hydrochloride	"20 mg in 100 ml normal saline intravenous infusion over a 15 minutes period, every 6^{th} hourly."

2.4. Outcome assessment

Outcome was measured by Visual Analogue Scale (VAS) Score (where 0=no pain and 10= worst pain), Verbal Rating Scale (VRS) score (none, mild, moderate and severe) at 15 minutes, 30 minutes, 1 hour, 4 hours, 6 hours, 12 hours and 24 hours after 1^{st} dose of drug administration.

After 30 minutes of receiving the dose of analgesia, if the patient complained of severe pain and the VAS score was >8, then rescue analgesia was given in the form of diclofenac sodium 75 mg (administered parenterally). The frequency of administration of rescue analgesic drug was also recorded.

Side effects including nausea, vomiting, headache, constipation, itching if any were also documented.

2.5. Statistical analysis

The results were presented in percentages, mean ± SD and frequencies. The continuous variables present between the groups were evaluated using unpaired t-test. Categorical variables were evaluated using Chi-square test and p-value <0.05 was considered to be significant.

3. Results

A total of 184 patients were enrolled in this study. After allocation 92 patients in each group were included in the study. A CONSORT (Consolidated Standards of Reporting Trials) diagram explaining the flow of participants is shown in Diagram 1.

There was no significant difference in age and sex between the groups (p>0.05). The mean patient age was 37.37±12.80 and 36.92±14.14 in group-A and group-B, respectively. About one third of patients in group-A (33.7%) and group-B (35.9%) were below 30 years of age. 72.9% (n=67) Patients in group-A and 75% (n=69) patients in group-B were males. (Table 2) Femur fracture was seen in 40 and 32 patients of group-A and group-B respectively. Tibia fracture was present in 52 patients of group-A and 60 patients of group-B.

Table 2: Patient data description

Characteristic	Group A (n=92) % (n)	Group B (n=92) % (n)
Age		
<30	33.7 (31)	35.9 (33)
30-40	32.6 (30)	26.1 (24)
41-50	18.5 (17)	17.3 (16)
>50	15.2 (14)	20.7 (19)
Sex		
Male	72.9 (67)	75.0 (69)
Female	27.1 (25)	25.0 (23)

Figure 1 shows the comparison of VAS score over time between the groups. VAS score between both the groups has p<0.05 at all the time periods except at 15 minutes. Group-A had lower VAS score than group-B. The decrease in VAS score was more in group-A than group-B.

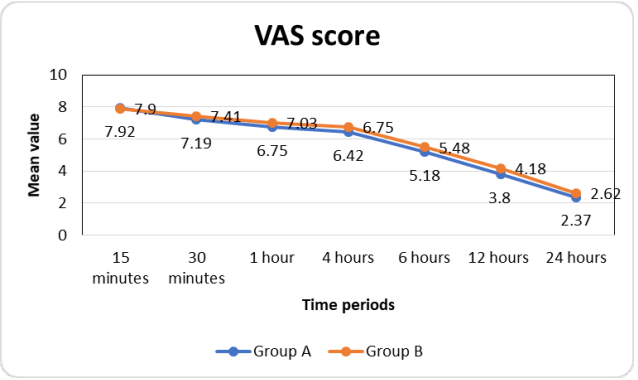

Fig. 1: Comparison of VAS over time periods between the groups

Table 3 shows the comparison of VRS score over time periods between the two groups. Difference in VRS score between the groups was significant only at 24 hours with a p=0.01. The decrease in VRS score over the time was higher in group-A compared to group-B.

Table 3: Comparison of verbal rating scale score over time periods between the groups

Time periods	Group A (n=92) Mean score±SD	Group B (n=92) Mean score±SD	p-value*
15 minutes	3.00±0.00	3.00±0.00	-
30 minutes	3.00±0.00	3.00±0.00	-
1 hour	2.98±0.12	2.97±0.17	0.64
4 hours	2.45±0.70	2.59±0.39	0.09
6 hours	2.03±0.17	2.08±0.27	0.13
12 hours	1.97±0.17	2.00±0.00	-
24 hours	1.31±0.46	1.58±0.89	0.01*

* Significant relationship (p<0.05)

Nausea was found in 1.1% and 1.1% patients of group-A and group-B, respectively. Vomiting was only 1.1% in group-B and absent in group-A. Side effects between both the groups had p>0.05. Injection Ondansetron 1 amp was given in 1 (1.1%) patient of group-A and in 2 (2.1%) patients of group-B.

Rescue analgesic Diclofenac sodium 75 mg was given in 4.3% of group-A and in 18.5% of group-B. Rescue analgesia (Diclofenac sodium 75 mg) between the two groups had a p<0.05.

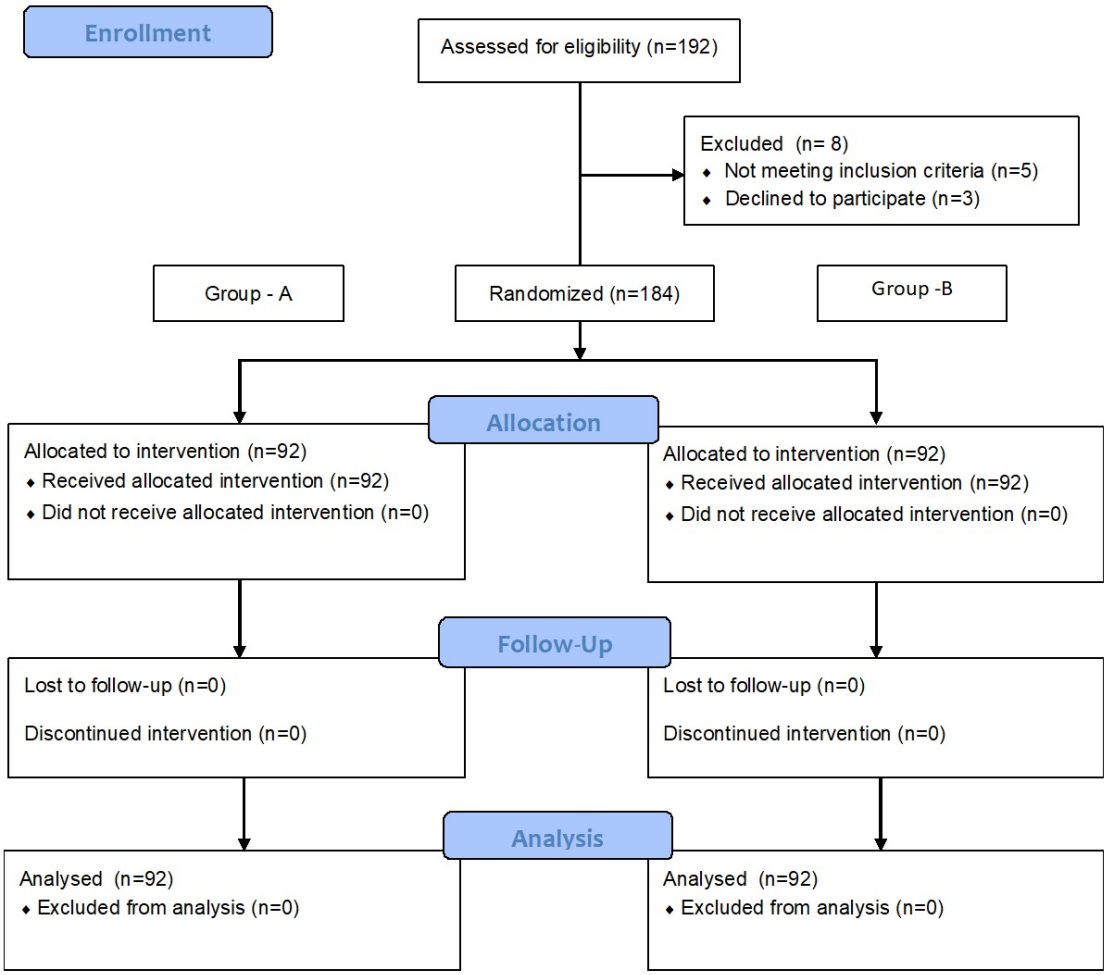

Diagram 1: Flow diagram

4. Discussion

Acute postoperative pain is the most common morbidity following any surgical procedure. In these patients, insufficient pain management commonly affects their quality of life and to alleviate this and achieve postoperative rehabilitation and comfort analgesics are given.[11,13] Tramadol and Nalbuphine are the widely used opioid analgesics for postoperative pain management.[14]

In the present study, the patients were administered with Tramadol hydrochloride or Nefopam hydrochloride to assess the analgesic efficacy by using VAS score, VRS score and side effects. Even though in studies of analgesic efficacy the need for placebo has been illustrated, we didn't include a placebo in our study since both drugs used are well-established. Even after extensive literature search, we did not find more studies that compared the analgesic effect of these two drugs.

In the current study, the mean age was 37.37±12.80 years and 36.92±14.14 years for group-A and group-B, respectively whereas majority of the patients in both groups were males. Age and gender were both found to be statistically insignificant (p>0.05). Lanzetta et al (1998) compared Tramadol and Ketorolac given after orthopaedic surgery and concluded that there was no difference with respect to age and gender between the two groups as per their findings.[5] Remerand et al (2013) compared Nefopam and placebo groups and recorded no significant difference between the two groups.[15] Koh et al (2019) found no significant difference in demographic data.[16] Du Manoir et al (2003) also found comparable data with respect to the characteristics of the two groups of Nefopam and placebo group.[11] As per Paudel R et al (2017), there was no difference between Tramadol and Diclofenac groups in gender wise distribution of patients and majority were males.[17]

In this study, VAS score between the two groups was statistically significant at all the time periods except at 15 minutes suggesting better pain control with tramadol

than nefopam. The decrease in VAS score was higher in group-A than group-B from 15 minutes after administration to 24 hours. As per Hopkins et al (1998), after major orthopaedic surgery that VAS score was insignificant comparison between tramadol and morphine administered via subcutaneous patient controlled analgesia.[18] Du Manoir et al (2003), found that pain VAS score for Nefopam was found to be significantly lower than the placebo group (p=0.002 and p=0.04, respectively) at PACU arrival and during the entire complete PACU period.[11] In assessment by Evans et al (2008), the intensity of pain was decreased on VAS score at 24 hours with Nefopam.[19] In a study by Paudel R et al (2017), VAS score assessed mean pain intensity was higher in Tramadol group which was significant than the Diclofenac group in the entire study period (120 hours) except at 88 hours.[17] YN OH et al (2018) reported that there was insignificant difference (p = 0.48) in the VAS scores at 10 and 30 minute, and 1, 4, 8, 12, 24, and 48 hour between the nefopam and ketorolac group after surgery.[20] Koh et al (2019) documented no significant VAS score difference between the Nefopam and Control group.[16]

Our study showed significant (p=0.002) difference between the groups in Verbal Rating Scale (VRS) score only at 24 hours. The score being lower at 24 hours in group-A than group-B. Du Manoir et al (2003) showed no difference between Nefopam group and placebo group in verbal pain score after orthopaedic surgery.[11] Akinci SB et al (2005), found that after Arthroscopic Knee Surgery, there was insignificant difference between groups morphine and tramadol in verbal pain score.[21] After comparing the Ketamine and Nefopam groups with the control group it was found by Li M et al (2017) that VRS and VAS scores were notably higher postoperatively at 1, 2, 6 and 12 hours in the control group than the group Ketamine and group Nefopam. 1, 2, 6 and 12 hours after surgery, the mean Ketamine VAS score and VRS score were lower than the Nefopam group.[22]

Our study observed that nausea was present in 1.1% of group-A and in 1.1% of group-B. Vomiting was only 1.1% in group-B and absent in group-A. The incidence of nausea and vomiting were statistically insignificant between both the groups. They were more frequently observed in group-B than group-A. Heel RC et al (1980) documented that the most commonly reported side effects during the administration of Nefopam are nausea, vomiting and sweating.[10] Evans et al (2008) reported that with Nefopam there was an increased incidence of tachycardia and sweating.[19] Du Manoir et al (2003) made the observation that unnecessary effects were present worldwide, in both Nefopam and placebo groups. These included nausea (40.5%), retention of urine (24%), vomiting (20%) and drowsiness (58.5%). Sweating was found in Nefopam and placebo groups of five and two patients, respectively.[11] Solanki RN et al (2015) and Kumar et al (2017) noted that compared to the Nalbuphine group, adverse events like nausea and vomiting were higher significantly in the tramadol group.[23,24]

In this study, 1.1% of group-A and 2.1% of group-B were administered an injection of Ondansetron (2ml) for the side effects, nausea and vomiting. Difference was insignificant (p>0.05) with respect to frequency of drug given for these side effects. Lu KZ et al (2013) concluded that nefopam plus ondansetron greatly decreased gastrointestinal adverse events without reducing analgesic efficacy, compared to Nefopam alone.[25] Remerand et al (2013) found that Ondansetron was required significantly less in the nefopam group for nausea and vomiting.[15] Kiran et al (2018) showed that to relieve vomiting, the antiemetic of choice was Ondansetron in Tramadol and Nalbuphine group.[14]

In the present study, there was a significant difference between the two groups with respect to frequency of rescue analgesia given, with group-A requiring less than group-B. Du Manoir et al (2003) and Evans et al (2008) recorded that cumulative 24 hour consumption of Morphine with Nefopam was less compared with control group.[11,24] On comparing Nalbuphine with tramadol, Daina MG et al (2009) reported that rescue analgesia was required more in nalbuphine group than tramadol group.[26] Solanki RN et al (2015) reported that the risk of rescue analgesic administered in the form of an injection of Diclofenac sodium diluted in 10ml Normal Saline in patients after orthopedic surgery, was higher in the group-tramadol than group-nalbuphine when administered eight hourly.[23] Kiran et al. (2018) reported no statistical significance between Tramadol and Nalbuphine group in the requirement of rescue analgesia.[14]

The limitations of this study were its small sample size and short duration of study. Performing research with a larger sample size and longer duration of study period are required to have more significant findings.

5. Conclusion

This comparative study concluded that both Tramadol hydrochloride and Nefopam hydrochloride responded well in providing postoperative pain relief in patients undergoing close reduction and nailing of long bone fractures but Tramadol hydrochloride was more effective compared to Nefopam hydrochloride as was evident by lower VAS, VRS scores and higher frequency of rescue analgesia needed in nefopam hydrochloride group.

6. Source of Funding

None.

7. Conflict of Interest

None.

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