Pre-emptive Analgesic Efficacy of Intravenous Diclofenac versus Paracetamol in Orthopedic Surgery

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Background: Different treatment modalities have been proposed to relieve pain after orthopedic surgeries, however, despite significant advances in pain management, it is still inadequately relieved.

Objective: To evaluate the pre-emptive analgesic efficacy of diclofenac and paracetamol in patients undergoing orthopedic surgery of the upper limbs.

Design: A Prospective Randomized, Double-Blind, Controlled Study.

Setting: St. Stephen's Hospital, New Delhi, India.

Method: This prospective randomized, double-blind, controlled study was performed on 100 patients of the American Society of Anesthesiologists (ASA) physical status classes 1 and 2 with an age group of 18-65 years of either sex undergoing upper limb orthopedic surgery. Group P (paracetamol) patients have been given 1g paracetamol intravenously 30 minutes before surgery. Group D (diclofenac) have been given intravenous 75 mg diclofenac sodium (in 100 ml 0.9% saline) 30 minutes before surgery.

Result: Personal and clinical characteristics were comparable between the two groups. The mean time between extubation and the need for the first analgesic dose was 75.46±15.72 **minutes in Group P and** 137.12±12.5 **minutes for Group D (p-value =0.002). The number of IV fentanyl (1 mcg kg-1) doses following extubation in the first 6 hours was 1.83±0.21in Group P and 1.20±0.24 for Group D (p-value =0.03). Nausea/vomiting was reported 2 (6.67%) patients in Group D, and 3 (10%) in Group P.**

Conclusion: Pre-emptive administration of diclofenac and paracetamol is cost-effective, and safe method of providing postoperative analgesia for patients undergoing orthopedic surgery of the upper limbs.

INTRODUCTION

The relief of postoperative pain represents one of the clinical areas on which precise standardization does not exist despite the published data. It is still inadequately relieved despite substantial improvements in the knowledge of mechanisms and treatment of pain. Different treatments have been proposed to relieve pain after orthopedic surgery. The administration of analgesics before surgery is used by many as a method of reducing postoperative pain. Pre-emptive analgesia is an antinociceptive procedure that prevents the production of afferent feedback lateral processing that amplifies postoperative pain[1]. Therefore, it is important to start analgesia before surgery, which would cover the surgery and the initial postoperative period. Studies have shown that besides relieving the pain, this also decreases the length of intensive care or hospital stay and morbidity[2,3].

A multimodal analgesic regimen including opioids, acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthetics can be administered either alone or in combination to achieve adequate analgesia without untoward side effects[4]. The American society of anesthesiologists (ASA) acute pain management practice guidelines state that clinicians should use multimodal analgesia whenever possible in the perioperative setting. The ASA recommends that all surgical patients receive around-the-clock regimen of acetaminophen and NSAID unless contraindicated and the dosages and duration of therapy should be individualized, considering efficacy with the risk of adverse events[5,6].

The aim of this study is to compare the efficacy of preemptively intravenous (IV) diclofenac with IV paracetamol for postoperative pain relief in patients undergoing orthopedic surgery.

METHOD

One hundred ASA Grade I and Grade II physical status patients aged 18-65 years, of both genders were selected for elective upper limb orthopedic surgical procedure under general anesthesia (GA). The trial has been registered prospectively with the clinical trial registry of India (CTRI/2017/07/009049). This study was conducted between 1 January 2016 to 31 July 2016. Written informed consent was obtained from all patients.

Complete blood count, renal/liver function tests, coagulation profile, X-ray chest, and electrocardiogram (ECG) were normal. Patients were admitted for either unilateral or bilateral upper limb (shoulder, humerus and elbow) surgical procedures. Patients having allergic reactions to study medications, gastric ulcer complaints, coagulopathy, major organ disease, psychiatric or neurological disorders, drug or alcohol addiction were excluded. Alprazolam 0.25 mg and pantoprazole 40 mg tablets perorally were provided at bedtime as premedication. Intravenous infusion line was started with ringer lactate 60 minutes

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before the commencement of anesthesia. In the preoperative holding area, patients were randomly assigned to one study group using a random number (n=50 in each). The involved anesthesiologist kept unaware of the group allocated and medication administered to them as per the study protocol. Group P patients were given intravenous 1g paracetamol diluted in 100ml of 0.9% normal saline (NS) covered with an opaque sheet, half an hour before the surgical procedure. In Group D patients, 75 mg diclofenac (injection Dynapar AQTM) diluted in 100 ml of 0.9% NS wrapped with an opaque sheet, was administered intravenously 30 minutes before surgery.

All patients were induced with fentanyl 2 mcg/kg, sodium thiopentone 5 mg/kg and succinylcholine 2 mg/kg intravenously. Neuromuscular relaxation was achieved with non-depolarizing muscle relaxant atracurium besylate 0.5 mg/kg and the top-up dose was 1/4th of the loading dose at the intermittent interval. Anesthesia was maintained with oxygen and nitrous oxide mixture (40:60) and isoflurane (0.5-1%) delivered by IPPV using a circle absorber system. Residual neuromuscular block was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. The intraoperative pain was evaluated by assessing various hemodynamic variables (involuntary increase in heart rate and blood pressure). Postoperative pain assessment was done at different time intervals; 15 minutes, 30 minutes, 1 hour, 2 hours, 4hours, and 6hours using the Visual Analogue Scale (VAS) that range from 0 to 100 mm. The rescue analgesia was given as fentanyl 1 mcg/kg or 50 mcg IV if the VAS score was >3. The postoperative complication was documented and treated accordingly.

Statistical data were analyzed using GraphPad Software and presented in mean (SD), frequency, percentage and median (range) as appropriate. The comparative evaluation between groups D and P was done using 2x2 contingency table with student t-test, Chi-square test, or Fisher's exact test by GraphPad Prism version 7.00 for Windows, 2016. P-value < 0.05 and confidence interval of 95% was considered significant.

RESULT

Age, BMI, male/female ratio, and duration of surgery were comparable and non-significant (p=0.44, 1.0, 0.17, 1.0, and 0.90) between the two groups, see table 1. Intraoperative hemodynamics and pain score were comparable in both groups. The mean time between extubation and the first analgesic dose required was 75 minutes for groups P and 137 minutes for group D, P-value =0.0001), see table 2. The mean number of IV fentanyl (1mcg/kg) doses following extubation in the first 6 hours was 1.83 in Group P and 1.20 for Group D, P-value=0.0001. Nausea and vomiting were reported in 2 (6.67%) patients in Group D and 3 (10%) in Group P; the difference was not significant (P-value =1.00). None of the patients had renal profile dysfunction in the postoperative period.

Table 1: Patients' Characteristics, Duration and Type of Surgeries Performed

	Group D	**Group P**	P-value
Age	40.15±4.6	39.31 ±5.8	0.44
BMI	22.4± 1.4	22.8.0± 1.39	0.17
Sex ratio (M/F)	12/18	13/17	1.0
Surgical duration (min.)	75 (50-90)	77 (55-85)	0.90
Types of surgeries:			
1. Brachial plexus repair	8	7	0.92
2. Elbow fracture repair	11	13	0.71
3. Both bone forearm reduction and internal fixation	27	24	0.85

BMI: body mass index; VAS: visual analog score; M/F: male/female

Table 2: VAS Scores Postoperatively, Time between Extubation and First Analgesic Dose and Rescue Analgesic in the First 6 Hours Following Extubation

		Group D	**Group P**	**P-value [95% confidence interval]**
First 0-2 hours:	VAS<3	35	14	<0.001
	VAS>3	11	30	
Next 2-6 hours:	VAS<3	29	13	0.0017
	VAS>3	17	31	
Mean duration between extubation and first analgesic dose (minutes)		137.12±12.5	75.46±15.72	0.002 [55.7, 67.6]
Mean number of rescue analgesic in 6 hours		1.20±0.24	1.83±0.21	0.03 [0.54, 0.72]
Side effect:	Nausea and vomiting	2	3	1.0
	Oliguria or deranged renal functions	0	0	----

DISCUSSION

Experimental studies conducted on nociception have suggested that tissue injury and trauma can cause processing of pain stimulus that has high intensity and increased duration[7,8.]

Studies on human beings related to pain perception show the changes in the function of the central nervous system. Nociception has been demonstrated to be unequivocally attenuated by pre-emptive analgesia; however, similar studies have yielded conflicting results[9,10]. Pre-emptive analgesia not only controls postoperative pain effectively but also has been found useful in the prevention of chronic pain of neuropathic origin[11].

Gillberg et al found that postoperative pain is significantly reduced when a non-steroidal anti-inflammatory drug was given before anesthesia[12]. Campbell et al found that patients who received intravenous diclofenac sodium had significantly less pain 30 minutes postoperatively[13]. Our study demonstrated that Group D had a long duration before the first rescue analgesic and overall, less total opioid (fentanyl) consumption. Furthermore, group D showed a significant decrease in pain at any given time during the postoperative period. Moreover, no significant side-effects were seen in both groups.

Desjardins et al have found that in the immediate postoperative period, the intensity of pain was reduced with a single dosage of diclofenac sodium (with a half-life of 2 hours). The reduction of pain peaked within 2-4 hours after orthopedic surgery[14]. In our study, the mean duration between extubation and first analgesic dose in group D was 137 minutes, almost double than Group P. Our result is similar to a study by Gazal et al[15].

The incidence of nausea and vomiting was low and comparable in each group. This could be attributed to the prophylactic administration of ondansetron to all the patients at the end of surgery[16]. In a study conducted by Joshi et al, it has been observed that preoperative dosage of analgesics produced a significant reduction in postoperative pain

within 2-4hours of treatment[17]. Preoperative analgesics significantly reduced opioid consumption in orthopedic surgeries. Our result was similar to other studies[18-20]. Diclofenac has an opioid-sparing effect but with adverse effects, such as acid peptic disease, nausea, and gastric discomfort. No excessive bleeding or blood soiling of the dressing were reported in the early postoperative period. Diclofenac sodium is a potent cyclo-oxygenase enzyme inhibitor found in platelets that is important for the formation of thromboxane A2, which is necessary for platelet aggregation and vasoconstriction, thereby prolonging bleeding[21,22]. It inhibits cyclooxygenase (COX-1 and 2) enzyme, and a recent finding suggests that it also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis[23].

In our study, we found that diclofenac provided better postoperative analgesia than paracetamol in terms of efficacy and duration. However, being cost-effective compared to IV paracetamol, it could be used for pain relief after orthopedic surgery.

The limitations of this study were: rescue analgesic was administered based on a particular VAS score that may vary according to the subjective observer and patient's interpretation. Additionally, because of the limited sample size of the study, it might be difficult to generalize the result.

CONCLUSION

Diclofenac is a safe, potent, and cost-effective pre-emptive analgesic which can be easily incorporated for pain relief in upper limb orthopedic surgery compared to paracetamol.

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