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Evaluation of efficacy of pain relief by transdermal diclofenac versus transdermal ketoprofen in patients undergoing hip fracture surgeries

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Abstract

Introduction: Transdermal patches are simple and painless method for providing postoperative analgesia while avoiding risks associated with parenteral administration. The aim of the study was to evaluate the efficacy and safety of transdermal patch of ketoprofen in comparison to diclofenac patch for postoperative analgesia in patients undergoing orthopedic hip fracture surgeries. It is a randomized single blind study.

Methods: Seventy patients were randomly allocated to receive either ketoprofen or diclofenac patch at the end of surgery under spinal anaesthesia. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software.

Results: In group D the VAS score immediately after the operation was 1.51 ± 0.41 and in group K it was 1.58 ± 0.41 , which was significantly nonsignificant ($p > 0.05$ value). We also observed that VAS score remained significantly low in ketoprofen group at 2 hour, 12 hour and 24 hour after the operation ($p < 0.05$).

Only 4 patients in ketoprofen group required rescue analgesia in the first 24 hours but in diclofenac group 7 patients required rescue analgesia but none of the patients in any group required another dose of rescue analgesic in first 24 hours. ($p > 0.05$)

Conclusions: Both ketoprofen and diclofenac transdermal patch are effective for postoperative analgesia but less number of patients required rescue analgesic in ketoprofen group.

Keywords: Pain, transdermal patch, ketoprofen, diclofenac, hip fracture

Introduction

Hip fractures remain one of the most terrible sequelae of osteoporosis in geriatric patients [1]. The once-a-year number of hip fractures worldwide is anticipated to exceed 6 million by 2050. Currently, nearly 50% of hip fracture patients will develop at least one short-term complication which includes infection, delirium, Venous Thromboembolism (VTE), pressure ulcers or cardiovascular events. More than half will experience an adverse long-term outcome including worsened ambulation or functional status, additional fractures and increased mortality.

International Association for the study of Pain defines pain as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such damage" [2]. Pain is a protective mechanism of the body and happens whenever tissue is being damaged and it causes the individual to react and take away the pain stimulus. Severe pain has the potential to "force people to close their eyes to the world, and reduce them to a single experience dominated by a single desire: for it to stop". Therefore, it is no surprise that pain is one of the concerns most frequently raised by patients prior to surgery [3]. Post-operative pain after any type of surgery can have serious detrimental effects and if appropriate analgesia is not given, it can affect respiratory, cardiovascular, gastrointestinal, urinary, and endocrinological systems as well as have chronic effects like delayed recovery and chronic pain [4].

Postoperative pain management is one of the most important components of adequate post-surgical patient's care [5].

Postoperatively, optimizing analgesia aids early mobilization and reduces length of hospital stay, thus reducing costs and preventing patients exposure to the threats of the health-care environment [6]. Therefore post-operative pain management is critical for optimal care of orthopaedic surgery patients. Although ample evidence indicates that an efficacious post-operative pain treatment reduces patient morbidity and improves patient outcome, recent studies demonstrate that about 50-70% of patients experience moderate to severe pain after surgery indicating that post-operative pain remains poorly treated.

Opioids have been administered for hundreds of years to allay anxiety and to reduce the pain associated with surgery. Opioids, administered intramuscularly, as epidural or via intra-vascular route as patient-controlled analgesia, are effective for severe pain. Adjunctive therapy and preemptive analgesia such as nerve blocks, and other methods of delivery such as infusion pumps, have also been used after total knee arthroplasty and anterior cruciate ligament (ACL) reconstruction. Oral Opioids (Tramadol) are effective for moderate to severe pain, have efficacy comparable to morphine but with fewer side effects. Though they are very useful in relieving post-operative pain, they are associated with many severe side effects. Thus there is a need to reduce perioperative opioid consumption.

Most commonly used drugs for postoperative analgesia are Non-steroidal Anti-inflammatory Drugs (NSAIDs) worldwide. NSAID acts by inhibition of cyclooxygenase, leading to a reduction in prostaglandin mediated sensitization of the nociceptors to mechanical or chemical stimulation at the site of surgical trauma [7]. Nonopioid analgesics are favored world-wide as they are devoid of opioid induced side effects requiring less post-operative monitoring. Opioid-sparing NSAIDs, such as Ketorolac, and COX-2-specific NSAIDs have been used in post-operative pain management post hip, knee, and ACL procedures. The oral route is most commonly used route of delivery for NSAIDs however it is associated with certain adverse effects like gastrointestinal bleeding, peptic ulcers, hypertension, oedema and renal disease. This mandates the need for a different choice of route of administration for such drugs.

A medicated adhesive placed on the skin to deliver a sustained release of the drug through the cutaneous route into the bloodstream is known as a transdermal delivery system (TDDS) [8]. Transdermal delivery drug system avoids the pain connected with intravascular and intramuscular routes and is an option for patients who don't tolerate oral formulations in the postoperative period [9]. The advantage of transdermal patch is that it maintains a constant and prolonged drug level, reduces the frequency of dosing, can be self-administered and easily terminated which leads to increased patient compliance and also reduces the incidence of systemic adverse effects due to lower plasma concentrations [10].

The advantages of transdermal Ketoprofen patch over the oral Diclofenac have been evaluated in acute blunt injuries, sports injuries [11], osteoarthritis [12] etc, but the use of transdermal ketoprofen patch in reducing postoperative pain has not been studied extensively. Hence the present study is being undertaken in patients undergoing elective orthopaedic hip fracture surgeries with an objective to evaluate the efficiency of transdermal ketoprofen patch against transdermal diclofenac patch for post-operative pain relief.

Materials and methods

The study was conducted in a tertiary care centre with the approval of ethical committee of the institution. A written and informed consent was obtained from all patients. The patients

were adults of either sex between 20-80 years admitted for Orthopaedic hip surgeries. The Exclusion Criteria included Pregnant females, Patients with prior history Bronchial Asthma, Peptic Ulcer Disease, Patients with skin lesions at patch site, Patients with history of sensitivity to Diclofenac or Ketoprofen.

Method of data collection

Cases were admitted from Orthopaedics OPD/Emergency after history taking, physical examination and X-ray of Pelvis with bilateral hip joint for confirmation of the diagnosis. The recruited cases were explained the purpose and relevance of the study. Those willing to volunteer were included in the study after informed and written consent. After the patient was admitted to the Department of Orthopaedics, Era's Lucknow Medical College, Age, gender, relevant history, past history, personal history, family history were recorded. Detailed examination including general physical signs, local examination and systemic examination was conducted on every patient. Preoperatively the patients were assigned into two groups (Group D and Group K) after drawing chits numbered from 1 to 70 which had been randomized using Excel to receive Transdermal Diclofenac or Transdermal Ketoprofen patch immediately after spinal anaesthesia. The patients were monitored for pain immediately postoperatively (0 hours) and at 2, 4, 8, 12 and 24 hours postoperatively using Visual Analogue Scale (VAS). Request for rescue analgesic (Tramadol 2mg/kg) were noted in both the groups. The study ends when patients have a VAS > 4 or at first request for rescue analgesic.

Statistical Analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

Results

We included total of 70 patients undergoing Orthopaedic Hip fracture surgeries managed by Transdermal Diclofenac versus Transdermal Ketoprofen in this study and these patients were further divided into two groups i.e. Group D (Diclofenac patch) and Group K (Ketoprofen Patch) with 35 patients in each group.

Demographic details

The below table shows the demographic profile of the studied patients where the mean age of group D patients was 56.5±15.32 years and that of group K was 53.63±16.9 years. The male and the female distribution was similar in both group and male patients were in majority in both the groups and the association was statistically insignificant ($p>0.05$). The mean duration of surgery was 98.29±12.8 min in Group D and 96.43±12.58 min in Group K respectively which was statistically insignificant ($P>0.05$).

Table 1: Demographic profile

Parameters	Group D (n=35)	Group K (n=35)	p-value
Mean Age (years)	56.5±15.32	53.63±16.9	0.458
Gender	Male	20 (57.1%)	1.00
	Female	15 (42.9%)	
Duration of Surgery (min)	98.29±12.8	96.43±12.58	0.532

The following table shows the mean BMI of the studied patients where the mean BMI of group D patients was 24.13±5.13 kg/m² while 23.86±5.03 kg/m² in group K and the association was statistically insignificant ($p>0.05$)

Table 2: BMI of the studied patients

Parameters	Group D (n=35)	Group K (n=35)	p-value
Height (m)	1.56±0.12	1.53±0.10	0.332
Weight (Kg)	58.11±10.1	55.6±9.4	0.296
BMI (kg/m ²)	24.13±5.13	23.86±5.03	0.826

The below table shows the diagnosis of the studied patients where the majority of patient were found to be having Intertrochanteric fracture right (31.4%) in group D and Intertrochanteric fracture right (37.1%) in group K. ($p>0.05$)

Table 3: Diagnosis of the study patient

Diagnosis	Group D (n=35)	Group K (n=35)	P value
Fracture neck of femur Right	9 (25.7%)	4 (11.4%)	0.297
Fracture neck of femur Left	8 (22.9%)	6 (17.1%)	
Intertrochanteric fracture right	11(31.4%)	13 (37.1%)	
Intertrochanteric fracture Left	7 (20.0%)	12 (34.3%)	

Table 5: VAS immediately post-operative and required rescue analgesic of the study patient

Parameters	Group D (n=35)	Group K (n=35)	P value
VAS immediately postop	1.51±0.41	1.58±0.41	0.477
No. of patient who required rescue analgesic in first 24 hours	7 (20.0%)	4 (11.4%)	0.324

The below table shows the VAS score of patients in both the groups after 2, 4, 8, 12 and 24 hours postoperatively and it was

The below table show the surgery procedures in the studied groups where the majority of patients underwent PFN Right with 25.7% and 28.6% in group D and group K respectively ($p>0.05$)

Table 4: Surgery of the study patient

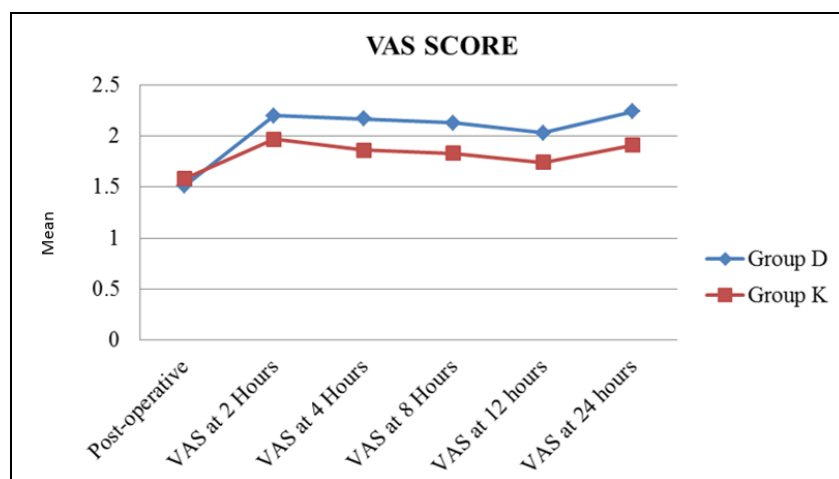
Surgery	Group D (n=35)	Group K (n=35)	P value
DHS Left	2 (5.7%)	1 (2.9%)	0.663
DHS Right	3 (8.6%)	1 (2.9%)	
HRA Left	7 (20.0%)	7 (20.0%)	
HRA Right	8 (22.9%)	4 (11.4%)	
PFN Left	4 (11.4%)	9 (25.7%)	
PFN Right	9 (25.7)	10 (28.6%)	
THR Left	1 (2.9%)	1 (2.9%)	
THR Right	1 (2.9%)	2 (5.7%)	

The following table shows the VAS score immediately after the operation which was found to be 1.51±0.41 for group D and 1.58±0.41 for group K respectively ($p>0.05$) and the number of patients who required rescue analgesic were more in group D (20.0%) than that in group K (11.4%)

significantly lower at 2 hours, 12 hours and 24 hours postoperatively in Group K.

Table 6: VAS Score of the study patient

Parameters	Group D (n=35)	Group K (n=35)	P value
VAS at 2 Hours	2.2±0.58	1.97±0.58	0.101
VAS at 4 Hours	2.17±0.54	1.86±0.55	0.020
VAS at 8 Hours	2.13±0.69	1.83±0.68	0.071
VAS at 12 hours	2.03±0.59	1.74±0.58	0.041
VAS at 24 hours	2.24±0.59	1.91±0.58	0.021

**Fig 1:** VAS Score of the study patient

Discussion

The present study was a randomised comparative study on 70 patients to evaluate the efficacy of transdermal Ketoprofen patch as post-operative analgesia in Orthopaedic hip fracture surgeries compared to Transdermal Diclofenac. Patients were randomly allotted into two equal groups consisting of 35 patients each. Demographic details, medical history and clinical evaluation of the patients was carried out. Radiographs were taken to confirm the diagnosis. Patients included for the study were all ASA

physical status I or II, of healthy adult subjects of either sex undergoing Orthopaedic hip fracture surgeries. The patients were applied a patch of transdermal diclofenac or transdermal ketoprofen immediately after spinal anaesthesia and pain was assessed postoperatively at the end of surgery (0 hr), 2, 4, 8, 12, and 24 hours using a VAS. At any time during the study, if the VAS was more than, or equal to, four, an injection of tramadol 100 mg was administered intravenously as rescue analgesia.

Findings in comparison to other studies

Mean Age

In the present study the mean age of the studied patients of group D was 56.5 ± 15.32 years and that of group K was 53.63 ± 16.9 years and the association was found to be statistically insignificant ($p > 0.05$). Verma R *et al.* [13] (2016) quoted the average age of patients in group D was 41.27 ± 5.64 years and 40.4 ± 4.74 years in group K ($p > 0.05$). Jadhav P *et al.* [14] (2018) reported the insignificant association between the age of both the groups studied. This shows that hip fractures or surgeries usually performed in 5th and above decades of human life.

Gender distribution

In our study the male patients were in majority in both the groups (D and K) and the association was statistically insignificant ($p > 0.05$). Our results were similar to the study performed by Verma R *et al.* [13] who reported 6:2 male: female ratio in group D and 11:4 in group K ($p > 0.05$).

VAS immediately post-operative and required rescue analgesic of the study patient

We found the VAS score immediately after the operation which was found to be 1.51 ± 0.41 for group D and 1.58 ± 0.41 for group K respectively ($p > 0.05$) and the number of required rescue analgesic were more in group D (20.0%) than that in group K (11.4%). The efficacy and tolerability of diclofenac patch in comparison to its other formulations for postoperative analgesia has previously been observed. Funk L *et al.* [15] observed that transdermal diclofenac patches provides significantly better pain relief as compared to diclofenac tablets in the early postoperative period following arthroscopic shoulder surgery. Krishnan R *et al.* [16] also observed that intra-operative application of a single dose of 100 mg transdermal diclofenac patch is as effective as a single dose of intramuscular diclofenac (75 mg).

Ketoprofen in oral, i.v., i.m. preparations has been used by various authors for postoperative analgesia and they observed that ketoprofen is an effective analgesic for moderate to severe acute postoperative pain. [17], [18] In a study done by Sarzi Puttini P *et al.* [19] (2013) also observed in their meta analyses that orally administered ketoprofen (50-200 mg/day) relieves moderate to severe pain and improves functional status and general condition better than of diclofenac (75-150 mg/day).

Use of Diclofenac patches in sports injuries has also shown a statistically significant difference in pain relief over a period of 2 weeks in placebo-controlled studies. [20] Ketoprofen in TDDS has been shown to be better absorbed than Diclofenac, which can be attributed to the difference in their molecular weights, i.e. 260 and 325 Da, respectively. [21]

In a study by Jadhav P *et al.* [14] reported 12% of subjects in the Diclofenac group required rescue analgesic in the form of tramadol given parenterally compared to 4% in Ketoprofen group. Tramadol being an opioid and possessing a higher analgesic efficacy was advocated for relieving pain in these patients. Verma R *et al.* [13] depicted that only 3 patients in ketoprofen group required rescue analgesia in the first 24 hours but in diclofenac 11 patients required rescue analgesia. Although the usual dose of ketoprofen used in various studies through various routes varied from 20 to 150 mg for postoperative analgesia and they could not find any study suggesting transdermal dose for ketoprofen, they used commercially available 20 mg ketoprofen patch. When they compared this dose of ketoprofen with 100 mg diclofenac patch, they found

this to be better.

Bhargav *et al.* reported that there was a significant difference in the intake of number of rescue analgesics in the initial 24 hours postoperatively between both the treatment groups with increased requirement of rescue analgesia following diclofenac patch application in the study population. Eight patients (n=8, 20%) consumed rescue medication after application of diclofenac patch. When the patients received ketoprofen patch for the contralateral extractions, the need for rescue analgesic medication was eliminated.

VAS Score of the study patient

We found that VAS score remain significantly low in ketoprofen group at 2 hours, 12 hours and 24 hours post-surgery ($p < 0.05$). The evidence based on literature search comparing the analgesic efficiency of ketoprofen to that of diclofenac suggests that the ketoprofen is a superior alternative to achieve analgesia in post-operative pain management. Verma R *et al.* [13] compared the efficacy of single dose transdermal patches of diclofenac and ketoprofen to achieve post-operative analgesia in patients undergoing lower limb orthopaedic surgery. Through this observation they concluded that both ketoprofen and diclofenac transdermal patches provided post-operative analgesia with reduced rescue analgesic consumption when ketoprofen was applied as compared to subjects in diclofenac patch group.

The mean VAS score was significantly reduced in the ketoprofen patch group in their study. The results from the present study are in consistency showing a decreased mean VAS score when ketoprofen patch was applied when compared to diclofenac. The consumption of rescue analgesic was more in patients where diclofenac patch was used. Similar observations were also proposed by Jadhav P *et al.* [14] comparing post-operative analgesia in patients receiving transdermal diclofenac and ketoprofen patch used for orthognathic surgery. In another placebo controlled comparative study between transdermal diclofenac and ketoprofen patch in assessing the pain severity during venous cannulation, it was concluded that both the patches were effective in reducing the VAS score during venous cannulation, with reduced pain scores in patients where ketoprofen was used. [22] However, Bachali PS *et al.* [23] concluded that analgesic potency of transdermal diclofenac patch might be inadequate in the immediate postoperative period and it may be prudent to use oral diclofenac for pain relief following which transdermal patch may be initiated for pain control.

Ketoprofen, moreover, is one of the NSAIDs with the highest cutaneous permeability. Therefore, it penetrates the skin more rapidly when compared to other NSAIDs like diclofenac or indomethacin. Also in animal models, the ketoprofen patch preparation showed superior skin permeability compared to diclofenac, flurbiprofen and piroxicam [24].

Conclusion

To conclude, transdermal patch of ketoprofen and diclofenac both are effective for postoperative analgesia in lower limb orthopaedic surgery under spinal anaesthesia but in diclofenac group more patients required rescue analgesic as compared to ketoprofen group. Furthermore studies are required to prove its efficacy and safety in various other types of surgeries.

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