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 sequele 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 than 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 Nonsteroidal 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 problems associated with systemic administration.

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 significant (P < 0.05).

| 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%)     | 20 (57.1%)     | 1.00    |
| Female                      | 15 (42.9%)     | 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/m²)    | 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 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%)      |         |
| DHS Right       | 3 (8.6%)      | 2 (5.7%)      |         |
| 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%)      |         |

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 following table shows the VAS score of patients in both the groups after 2, 4, 8, 12 and 24 hours postoperatively and it was 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 | 2.24±0.59     | 2.47±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 to150 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.

References

1. Cooper C. Campion, Melton Lr. Hip Fractures in the Elderly: A World-Wide Projection. Osteoporosis Int. 1992; 2:286-289.
2. Hosseini Jahromi SA, Hosseini Valami SM, Hatamian S. Comparison between Effect of Lidocaine, Morphine and Ketamine Spray on Post-Tonsillectomy Pain in Children. Anesth Pain. 2012; 2(1):17-22.

3. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2004; 100(6):1573-1581.

4. Hurley RW, Murphy JD, Wu CL. Acute Postoperative Pain. In: Miller RD, Editor. Miller’s Anesthesia 8th ed. Churchill Livingstone: The Elsevier Publisher, 2015, 2976-7.

5. Imani F. Postoperative pain management. Anesth Pain. 2011; 1(1):6-7.

6. Ján Dixon, Fiona Ashton, Paul Baker, Karl Charlton, Charlotte Bates, William Eardley. Assessment and Early Management of Pain in Hip Fractures: The Impact of Paracetamol. Geriatr Orthop Surg Rehabil. 2018; 9:2151459318806443.

7. Raja SA, Meyer RA, Campbell JN. Peripheral mechanisms of somatic pain. Anesthesiology. 1988; 68:571-590.

8. Ng P, Kam CW, Yau HH. A comparison of Ketoprofen and Diclofenac for acute musculoskeletal pain relief: a prospective randomised clinical trial. Hong Kong. J Emerg Med. 2001; 8:73-77.

9. Naedal J, Brown K. NSAID-associated adverse effects and acid control aids to prevent them: A review of current treatment options. Drug Safety. 2006; 29(2):119-32.

10. Singh SP, Jain DK, Das S, Jain S. Prospective Case-control Study on the Comparison of Postoperative Pain Relief with Transdermal Diclofenac Patch and Injection Diclofenac. International Journal of Head and Neck Surgery, October-December. 2015; 6(4):129-133.

11. Predel HG et al. Diclofenac patch for topical treatment of acute impact injuries; a randomized, double-blind, placebo-controlled, multicenter study. Br J Sports Med. 2004; 38:318-323.

12. Arthur AM, Bookman Kate SA, Williams J. Zev Shainhouse Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. Can Med Assoc J. 2004; 171(4):333-8.

13. Verma R, Kumar S, Goyal A, Chaudhary A. Comparison of single dose transdermal patches of diclofenac and ketoprofen for postoperative analgesia in lower limb orthopaedic surgery. International Journal of Research in Medical Sciences Verma R et al. Int J Res Med Sci. 2016; 4(3):718-721.

14. Jadhav P, Sinha R, Uppada UK, Tiwari PK, Subramanya Kumar AVSS. Pre-emptive Diclofenac Versus Ketoprofen as a Transdermal Drug Delivery System: How They Face. Journal of maxillofacial and oral surgery. 2018; 17:4:488-494.

15. Funk LM, Weiser TG, Berry WR et al. Global operating theatre distribution and pulse oximetry supply: an estimation from reported data. Lancet. 2010; 376:1055-1061.

16. Krishna R, Nataraj MS. Efficacy of a single dose of a transdermal diclofenac patch as pre-emptive postoperative analgesia: a comparison with intramuscular diclofenac. South Afr J Anaesth Analg. 2012; 18(4):194-97.

17. Barden J, Derry S, McQuay HJ, Moore RA. Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. The Cochrane database of systematic reviews. 2009; (4):CD007355.

18. Berti M, Albertin A, Casati A, Palmisano S, Municino G, da Gama Malcher M et al. A prospective, randomized comparison of dexketoprofen, ketoprofen or paracetamol for postoperative analgesia after outpatient knee arthroscopy. Minerva Anestesioligica. 2000; 66(7-8):549-54.

19. Sarzi-Puttini P, Atzeni F, Lanata L, Bagnasco M. Efficacy of Ketoprofen Vs Ibuprofen and Diclofenac: A Systematic Review of the Literature and Meta-Analysis. Clin Exp Rheumatol. 2013; 31(5):731-8.

20. Elhakim M. A comparison of intravenous Ketoprofen with pethidine for postoperative pain relief following nasal surgery. Acta Anaesthesiol Scand. 1991; 35:279-282.

21. Adachi H, Ioppolo F, Puloni M, Santilli V. Physical characteristics, pharmacological properties and clinical efficacy of the Ketoprofen patch: a new patch formulation. Eur Rev Med Pharmacol Sci. 2011; 15:823-830.

22. Raichurkar A, Ramachandra KKB. Placebo Controlled Comparative Study of Efficacy of Diclofenac and Ketoprofen Transdermal Patches In Attenuating Intravenous Cannulation Pain. J Dent and Med Sci. 2015; 14(3):111-4.

23. Bachalli PS, Nandakumar H, Srinath N. A comparative study of diclofenac transdermal patch against oral diclofenac for pain control following removal of mandibular impacted third molars. J Maxillofac Oral Surg. 2009; 8(2):167-172.

24. Adachi H, Ioppolo F, Paoloni M, Santilli V. Physical characteristics, pharmacological properties and clinical efficacy of the ketoprofen patch: A new patch formulation. Eur Rev Med Pharmacol Sci. 2011; 15:823-830.