ORIGINAL ARTICLE

Comparing the effects of Ketorolac and Ibuprofen on post-operative pain relief after para umbilical hernia repair. A randomized clinical trial

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Abstract:

Objective: To compare the effects of Ketorolac and Ibuprofen on post-operative pain relief after Para umbilical hernia repair.

Study design: Randomized clinical trial.

Place and duration of study: General Surgery Department of Hamdard University Hospital (HUH) Karachi, Pakistan from September 2016–December 2019.

Material and Methods: Patients were selected by non-purposive convenience sampling. 60-patients under went Mesh repair for para-umbilical hernia under general anesthesia are included and divided into two equal groups. Patient with ASA 1 and 2 are included. Age range is 18 years and above. Patients received either 30 mg ketorolac or 800 mg ibuprofen diluted in 200 mL normal saline in a double-blind, randomized fashion, administered over 30 min, in the post-anesthesia recovery unit started within 30 min of skin closure, followed by three additional doses every six hours.

Results: There was no significant difference found between the two groups with mean VAS scores of 33.83±9.06 and 33.00±7.61 after six hours of surgery in the Ibuprofen and Ketorolac groups respectively. Both drugs were found to be effective since the mean pain intensity scores were 5.67±4.49 and 6.83±5.17 respectively. Rescue analgesia (Intravenous Tramadol 50mg) was opted for 17 patients in the Ibuprofen group and 25 in the Ketorolac group, where the difference was statistically significant (p=0.024)

Conclusion: We concluded that there is no difference in post-operative analgesia provided by both drugs. Ibuprofen showed decrease requirement of rescue analgesia as compared to Ketorolac.

Keywords: Para-umbilical hernia, post-operative analgesia, Ketorolac, Ibuprofen, rescue analgesia

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Introduction:

Analgesics play a key role in recovery after special abdominal surgery involving para-umbilical hernioplasty.[1] Improper management of post-operative pain can trigger catecholamine surgery, triggering myocardial ischemia, stroke, and other bleeding problems. Patient immobility increases the risk of severe venous thrombosis and pulmonary embolism, which is associated with serious psychological side effects such as insomnia, depression, and anxiety.[2] Many drugs have been used traditionally after abdominal surgeries such as intravenous (IV) and oral Non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and weak opioids.[3] They all carry their potential side effects as well as excellent efficacy. The potential side effects of NSAIDs include bleeding, gastrointestinal ulceration, renal dysfunction, and poor post-operative bone healing. When properly administered for a short period of time in properly selected patients in the prescribed doses, the incidence rate is considered very low.[4]

Ibuprofen is a non-selective inhibitor of cyclo-

oxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and one of the popularly utilized over-the-counter and prescribed NSAIDs in the world.[5] Oral ibuprofen has analgesic, antipyretic, and anti-inflammatory properties and it is tolerated by most patients. It has a reduced risk of bleeding or gastro-intestinal problem with excellent anti-inflammatory effects because the inhibition ratio of COX-1 to COX-2 of ibuprofen is 2.5:1.[6] Ibuprofen doesn't have respiratory depression, constipation, or other opioid-related side effects but provides pain control that is almost equivalent to narcotics.[7] The half-life of IV Ibuprofen is ~2–3 hours and the maximum recommended dose is 3,200 milligrams (mg).[8] IV Ibuprofen QID (every six hours) in a dose of 800 mg is well tolerated, results in fewer tolerable side effects, reduction in pain score, and decreases added morphine consumption according to different studies when compared to placebo.[9]

Ketorolac is another well-known analgesic drug that has been used all over the world for post-operative pain control in adjunct with paracetamol or opioids for a long time.[10] It is found to be as effective as opioids for analgesia after a variety of abdominal surgical procedures and its efficacy has been proven by many researchers. The bio-availability of IV ketorolac is similar to its oral counterpart, which is about 80–100%, and the peak plasma concentration of 30–60 min is achieved after administration that results in fast analgesia and a half-life of approximately 5–6 hours.[11] Ketorolac carries a comparatively high risk of side effects because it has a ratio of COX-1 to COX-2 inhibition of 330:1 that makes its use controversial in most post-operative settings, including coagulopathy, gastro-intestinal problems, and neurotoxicity.[8,12] This increases surgeons' interest in the use of other groups of non-opioid analgesics.

Post-operative pain management is not only a major concern for surgeons but also for anesthesiologists and patients undergoing abdominal surgery. Therefore, we have designed a randomized, placebo-controlled and double-blind trial to evaluate the efficacy of IV ibuprofen compared with IV ketorolac and the need for tramadol supplementation in post-operative pain, as measured by the visual analog scale. (VAS) in patients undergoing para-umbilical Hernioplasty. Our study aimed to find a suitable analgesic agent for post-operative pain with minimal use of another adjunct analgesic.

Materials and Methods:

This double-blind clinical trial study was conducted at Hamdard University Hospital, Karachi, Pakistan from September 2016 – December 2019. Approval from the Ethical Review Board (ERB) was obtained prior to the evaluation. 60 patients were enrolled in the study and assigned in to 2-groups of Ibuprofen and Ketorolac. Each groups has 30 patients. After clearly defining the purpose and potential risks and benefits of the study, an informed consent form for participating in the study was obtained from all patients.

All patients aged 18-years and above, of either gender, with an uncomplicated para-umbilical hernia, undergoing hernioplasty, and American Society of Anesthesiologists class I and II were included.

Those with a severe hepatic and renal disease, consumption of anti-inflammatory drugs or anti-pyretic drugs before the study, redo surgery (recurrent, incisional hernia), complicated hernia (strangulated, obstructed), or those with hernia except para-umbilical they were not included.

Randomization: randomization was performed using randomly generated computer-generated randomization to ensure that patients and investigators did not know a treatment allocation before entering the study, and the distribution was done at 1:1 to obtain Ketorolac or Ibuprofen.

Patients received either 30 mg ketorolac or 800 mg ibuprofen diluted in 200 mL normal saline in a double-blind, randomized fashion, administered over 30 min, in the post-anesthesia care unit started within 30 min of skin closure, followed by three additional doses every six hours. Patients received instructions to request rescue

Table 1: Baseline characteristics of patients

	Ibuprofen	Ketorolac	p-Value
Gender:			
Males	11	8	0.405
Females	19	22	
Age:	53.50±12.81	52.20±15.26	0.72
Comorbids:			
Diabetes	9	7	0.540
Hypertension	17	17	
Both	3	6	
Duration of the first onset of hernia (months)	4.12±3.8	6.40±5.3	0.06
Height (inches)	65.60±5.71	65.36±5.58	0.87
Weight (Kg)	62.40±14.51	64.76±17.22	0.56
BMI (kg/m²)	26.09±5.64	25.63±6.62	0.77

Table 2: Visual analog scale score assessment after surgery at different time intervals after surgeries and their comparison between the two groups

VAS Score	Ibuprofen	Ketorolac	p-Value
6 hours	33.83±9.06	33.00±7.61	0.70
12 hours	24.00±8.34	25.50±7.35	0.46
24 hours	12.33±8.97	15.33±7.64	0.17
48 hours	5.67±4.49	6.83±5.17	0.36

Table 3: Number of patients who requested rescue analgesia

VAS Score	Ibuprofen (n=30)	Ketorolac (n=30)	p-Value
Rescue Analgesia	17 (56.66%)	25 (83.33%)	0.024

analgesia, which is 50 mg of intravenous tramadol per delivered dose, with no less than an interval of six hours in between two rescue doses. Study patients received no analgesic medications except the randomized, blinded study drug and rescue tramadol.

Pain intensity levels were subjectively measured using a 100 cm VAS, 0 = no pain to 100 = unbearable pain). The main outcomes were VAS at 6, 12, 24, and 48 hours with their comparison in the two groups. The second effect was the total amount of sedative analgesia (intravenous tramadol) use. Data analysis was done using SPSS version 23.0. Frequency and percentages were used for categorical variables while mean with standard deviations were presented for continuous variables. Chi-square and t-tests were used to check the associations between the two groups based on categorical and continuous variables respectively. P-value <0.05 was considered statistically significant.

Results:

A total of 60 patients with an uncomplicated para-umbilical hernia who were operated on were registered. There were 19 (31.66%) males and 41 (68.33%) females with a mean age of 52.85±13.98 years. Post-operatively 30 were given IV Ketorolac and 30 were given IV Ibuprofen as analgesics. The rest of the demographic characteristics are given in Table 1.

When we assessed the pain intensity by VAS, there was no significant difference found between the two groups with mean VAS scores of 33.83±9.06 and 33.00±7.61 after six hours of surgery in the Ibuprofen and Ketorolac groups respectively. Although both drugs were found to be effective since the mean pain intensity scores were 5.67±4.49 and 6.83±5.17 respectively as shown in Table 2.

Patients were given an option of rescue analgesia which was opted for 17 patients in the Ibuprofen group and 25 in the Ketorolac group, where the difference was statistically significant (p=0.024) (Table 3).

Discussion:

The primary objective of our clinical study was to evaluate and compare the efficacy of IV ibuprofen and IV ketorolac in the treatment of post-operative pain in subjects undergoing para-umbilical hernioplasty. The results of our study showed that the use of IV Ibuprofen, compared with IV ketorolac, had no significant differences in post-operative pain scores. The literature supported the use of both drugs traditionally to control post-operative pain as a single agent or in combination with other drugs (morphine, paracetamol, etc.).

Eftekharian HR et al. studied the effect of ketorolac in post-operative maxillo-facial surgeries where patients who received ketorolac had significantly decreased post-operative pain within 30 minutes as compared to placebo (p<0.001).[13] They also observed minimal unwanted side effects of ketorolac. Thus, supporting the strong

analgesic property of ketorolac with a better safety margin and make it a safe and effective choice for surgeons.

Another study by Uddin et al.[14] in Bangladesh was conducted to compare the analgesic efficacy and safety of ketorolac and pethidine in pain relief after major surgeries. It was a prospective, interventional study and was conducted on 71 patients undergoing major different surgical interventions. Almost half (36) patients received ketorolac (15 mg, intramuscularly 6 hourly) and the remaining 35 patients received pethidine (100 mg, intramuscularly 6 hourly) for 48 hours post-operatively. Results were measured after 1, 6, 12, 24, 32, and 48 hours of drug administration. At 12th and 48th hour by VAS and 1st and 48th hour by VRS, both drugs showed similar pain control effects. In later periods of observation, pethidine exhibited much better analgesic effects than ketorolac. Ketorolac showed better tolerance than pethidine and had fewer adverse effects.

Numerous studies have also been performed to observe the effects of IV ibuprofen in post-operative pain management. The work of Matinez et al. was about the effects of IV ibuprofen in post-operative patients in reducing the requirement of morphine as compared to placebo. The study showed a reduction in the morphine requirements within the 24 hours post-surgery, to almost half of the mean compared to a placebo group. Statistically, significant pain control was observed at rest and after mobilization in patients receiving ibuprofen as compared to placebo.[15]

According to the study carried out by Kayhan et al., IV ibuprofen did not significantly reduce opioid consumption compared to IV acetaminophen, however, it reduced the severity of pain in patients undergoing bariatric surgery. The trial suggested that IV ibuprofen may be used as asafe and efficacious alternative to IV acetaminophen as part of multimodal post-operative analgesia in patients undergoing bariatric surgery.[16]

There are some research studies available that compared the post-operative analgesic effect of IV ketorolac with ibuprofen. Uribe et al. have conducted such a study in post-operative knee arthroscopy patients. In their study, there were 20 subjects in the ibuprofen group and 31 subjects in the ketorolac group. The median VAS pain score at rest upon PACU arrival was 33 (12, 52) vs. 9 (2, 25) (p = 0.0064) for the ketorolac and ibuprofen group, respectively. The median visual analog scale (VAS) pain score at movement upon PACU arrival was 38 (20, 61) vs. 15 (6, 31) (p = 0.0018) for the ketorolac and ibuprofen group, respectively. Median VAS pain scores during movement taken at subsequent 30 min intervals in the ibuprofen group were less than half of those reported in the ketorolac group for up to 90 min after arriving in PACU. The difference in the median VAS pain scores at rest and movement in the course of 120 min–24 h after PACU arrival was not statistically significant in both groups. Rescue opioid medication during PACU stay was required in 55.0% (N = 11) and 83.9% (N = 26), with a mean amount of narcotic consumption (oral morphine conversion) of 5.53±5.89 mg vs. 19.92±15.63 mg for the ibuprofen and ketorolac group, respectively (P < 0.001). However, opioid consumption during the first 24 hours after PACU discharge was not statistically significant (p= 0.637). The mean time to first rescue medication was 77.62±33.03 and 55.78 ± 35.37 for the ibuprofen and ketorolac groups, respectively. There were no significant differences in patient satisfaction and documented adverse events during the first 24 hours.[8]

In another randomized controlled trial, D warica et al. recorded the results of comparison of both drugs after different abdominal Uro-gynecological surgeries. A total of 224 patients (112 in each arm) were included. Pain scores (SD) at rest in all patients who received ketorolac versus those who received ibuprofen was 2.30 (2.1) versus 2.68 (2.34) (p=0.20). Pain scores (SD) with ambulation was 3.94 (2.57) versus 4.16 (2.73) (p=0.57) in patients who received ketorolac and ibuprofen, respectively. Patients who received ketorolac rated their satisfaction with their pain regimen similar to those who received ibuprofen (p=0.50). The average amount (SD) of hydromorphone used in the ketorolac and ibuprofen arm was 3.68 (4.58) mg and 4.04 (4.97) mg, respectively (p=0.58).[17] They concluded that there was no significant difference in both

drugs for pain control. In our study, we found the comparable similar results in terms of analgesic effects of both drugs. The visual analogue scale (VAS) calculated at 6, 12, 24 and 48 hours showed p-values of 0.70, 0.46, 0.17 and 0.36 respectively. Hence, it didn't show any significant difference in two groups. However, patients in Ketorolac group were found to be taken more of rescue analgesia than the Ibuprofen group. The difference was statistically significant i.e.17 patients in Ibuprofen group v/s 25 in Ketorolac group (p-value 0.024).

Conclusion:
Our study concluded that there is no difference in post-operative analgesia provided by intravenous Ketorolac and Ibuprofen medications. Ketorolac is proven by data to be an extensively safe drug and a substantially lower (generic) cost compared to parenteral ibuprofen.[18] On the other hand, Ibuprofen showed decrease requirement of rescue analgesia as compared to Ketorolac. In our opinion, both drugs can be used with confidence for cure of post-operative pain in patients undergone Para-umbilical hernioplaty.

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Role and contribution of authors:
Rabbia Zubair, collected the data, references and wrote the initial writeup

Masoom Raza Mirza, critically review the article and advised useful changes

Muhammad Ali Channa, critically review the article and did the final changes

Dr Uzair Yaqoob, collected the data and helped in introduction and discussion writing.

References:

1. Luo J, Min S. Postoperative pain management in the post-anesthesia care unit: an update. Journal of pain research. 2017;10:2687.
2. Kulik A, Bykov K, Choudhry NK, Bateman BT. Non-steroidal anti-inflammatory drug administration after coronary artery bypass surgery: utilization persists despite the boxed warning. pharmacoepidemiology and drug safety. 2015 Jun;24(6):647-53.
3. Fischer HB, Simanski CJ, Sharp C, Bonnet F, Camu F, Neugebauer EA, Rawal N, Joshi GP, Schug SA, Kehlet H. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. Anaesthesia. 2008 Oct;63(10):1105-23.
4. Chang RW, Tompkins DM, Cohn SM. Are NSAIDs Safe? Assessing the Risk-Benefit Profile of Nonsteroidal Anti-inflammatory Drug Use in Postoperative Pain Management. The American Surgeon. 2020 Nov 25:0003134820952834.
5. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. The Journal of clinical investigation. 2006 Jan 4;116(1):4-15.
6. Kroll PB. Intravenous ibuprofen for postoperative pain. Pain management. 2012 Jan;2(1):47-54.
7. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. Journal of clinical pharmacy and therapeutics. 2001 Aug 20;26(4):257-64.
8. Uribe AA, Arbona FL, Flanigan DC, Kaeding CC, Palettas M, Bergese SD. Comparing the efficacy of IV ibuprofen and ketorolac in the management of postoperative pain following arthroscopic knee surgery. A randomized double-blind active comparator pilot study. Frontiers in surgery. 2018 Oct 3;5:59.
9. Kohring JM, Orgain NG. Multimodal analgesia in foot and ankle surgery. Orthopedic Clinics. 2017 Oct 1;48(4):495-505.
10. Kokki H. Nonsteroidal anti-inflammatory drugs for postoperative pain. Pediatric Drugs. 2003 Feb;5(2):103-23.
11. Brocks DR, Jamali F. Clinical pharmacokinetics of ketorolac tromethamine. Clinical pharmacokinetics. 1992 Dec;23(6):415-27.
12. Cohen MJ, Schecter WP. Perioperative pain control: a strategy for management. Surgical Clinics. 2005 Dec 1;85(6):1243-57.
13. Eftekharian HR, Ilkhani Pak H. Effect of Intravenous Ketorolac on Postoperative Pain in Mandibular Fracture Surgery; A Randomized, Double-Blind, Placebo-Controlled Trial. Bull Emerg Trauma. 2017;5(1):13-17.
14. Uddin MB, Hossain AM, Alam MM, Hossain AS. Ketorolac and pethidine in post-operative pain relief. ||| Bangladesh Journal of Pharmacology|||. 2007;2(1):35-42.
15. GagoMartínez A, Escontrela Rodriguez B, Planas Roca A, Martínez Ruiz A. Intravenous ibuprofen for treatment of post-operative pain: a multicenter, double blind, placebo-controlled, randomized clinical trial. PloS one. 2016 May 6;11(5):e0154004.
16. Kayhan GE, Sanli M, Ozgul U, Kirteke R, Yologlu S. Comparison of intravenous ibuprofen and acetaminophen for postoperative multimodal pain management in bariatric surgery: A randomized controlled trial. Journal of clinical anesthesia. 2018 Nov 1;50:5-11.
17. Dwarica DS, Pickett SD, Zhao YD, Nihira MA, Quiroz LH. COMPARING KETOROLAC TO IBUPROFEN FOR POSTOPERATIVE PAIN: A RANDOMIZED CLINICAL TRIAL. Female pelvic medicine & reconstructive surgery. 2020 Apr;26(4):233.
18. Lowder JL, Shackelford DP, Holbert D, Beste TM. A randomized, controlled trial to compare ketorolac tromethamine versus placebo after cesarean section to reduce pain and narcotic usage. American journal of obstetrics and gynecology. 2003 Dec 1;189(6):1559-62.