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Studying the Effect of Intravenous Injections of Ketorolac (IVIK) on Analgesia Control before and after using Tourniquet in Orthopedic Surgery of Femur and Tibia by General Anesthesia

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ABSTRACT

Postoperative pain is an unpleasant experience created due to different stimuli to which human reacts. This process leads to physiological disorders in all body systems. The purpose of this study was, thus, to evaluate the effect of IVIK on analgesia control before and after using tourniquet in orthopedic surgery of femur and tibia by general anesthesia. One hundred patients, candidate for femur and tibia surgeries aged 15-75, entered this double-blind clinical trial. Each patient was randomly assigned to one of the two groups of Ketorolac before and after tying the tourniquet. The visual criteria for pain during recovery were measured and completed at 6 and 12 hours after operation. Data were analyzed using descriptive (mean and percent) and inferential statistics (Man-Whitney). Mann-Whitney test showed no significant differences in pain scores in the two groups, before and after using tourniquet, in femur and tibia orthopedic surgery with general anesthesia (p-value>0.05). T-test showed a significant difference in heart rate between the two groups before and after tying the tourniquet at 30 minutes (p<0.05). No significant difference was found during the surgery between the two groups before and after tying the tourniquet regarding other vital signs (p> 0.05). The results showed no significant differences in the pain score in the groups before and after the use of tourniquet. Thus, as this used 30-mg of ketorolac was performed, it could not evaluate higher doses to reduce the need for analgesic in the two groups.

Keywords: Ketorolac, Analgesia, Tourniquet, Orthopedic

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INTRODUCTION

Pain is a physiological response showing the presence of an injury or a disease. Pain increases the sympathetic response of the body, followed by increased heart rate, cardiac workload, and oxygen consumption [1]. Postoperative pain is one of the most common complications after each surgery, whose degree and control method depend on the organ involved in the surgery. Controlling acute postoperative pain is done in different ways, including oral, intravenous, muscular, cutaneous, peripheral nerve, regional administration (epidural and intrathecal) [2] of analgesic, and electrical stimulation of the nerve through cutaneous. The mechanisms of creating postoperative pain are inflammation in damaged tissues, direct damage to the nerves, or vague pain caused by the tissues adjacent to cutaneous incision [3]. Ketorolac, generically called ketorolac trometamol, is a non-steroidal anti-inflammatory drug that reduces pain and inflammation by inhibiting the activity of cyclooxygenase and synthesis of prostaglandin. Currently, ketorolac syringe is widely used in the United States and Europe as an injectable analgesic. Not having respiratory depression, lack of physical dependence and prolonged analgesic effect are of the most important advantages of ketorolac syringe compared to injectable opioids. In

addition, ketorolac coupled with intravenous opioids have a synergistic effect and can reduce the dose of opioids by simultaneous administration of injectable ketorolac and opioids [4-6]. The administration of narcotics during the operation causes the patient's body to get addicted; it can also cause nausea, vomiting, constipation, drowsiness, and at higher doses respiratory depression and hypotension, all of which have made the doctors seek alternative drugs for it [7]. Thus, it is necessary to measure the effect of other analgesic drugs and, if possible, use them to reduce the side effects of the narcotic effects. Pain is the most common symptom that forces a person to use urgent medical help, a fact that does not depend on age, gender and culture. Pain is an unpleasant sensation and experience associated with actual or potential tissue damage and is a common phenomenon in surgical procedures that can have adverse effects on the hemodynamic status of the patient [2]. Recently, great attention has been paid to the importance of postoperative analgesia. Two types of drugs have the highest analgesic effect and are the most commonly used ones: narcotic and non-steroids anti-inflammatory drugs. Narcotic drugs, such as morphine, have extensively been used in hospitals given their high potential in sedation and analgesic effects, but it is seen that the drug has many side effects, such as dependence in the patient and at higher doses respiratory depression and other complications and deaths in patients [2]. Thus, doctors look for drugs that besides the high analgesic effect have less clinical complications. Accordingly, non-steroidal anti-inflammatory drugs, such as ketorolac, can replace narcotics due to their effects, and minimize clinical complications in patients. Therefore, it is necessary to evaluate the effects of this class of drugs alongside their clinical complications and compare them with narcotic drugs to minimize the administration of narcotics.

MATERIALS AND METHODS

This is an experimental, clinical trial study. Sampling method was convenient done on patients undergoing orthopedic fracture surgery of the lower limbs (femur and tibia) under general anesthesia at Peimanieh Hospital in Jahrom. The method of calculating the sample size was through the assumptions of target difference = 0.4 and SD = 0.5 and standard difference = 0.8, taking into account 95% confidence interval and power = 80%, assuming equal number of samples in both groups using the Normogram Altman sample size per group of 50 people (100 people in total). The inclusion criteria were patients undergoing orthopedic fracture surgery of the lower limbs (femur and tibia) under general anesthesia at Peimanieh Hospital in Jahrom, weighing more than 100 kg, age over 75 years or less than 15 years. Moreover, these criteria were history of drug addiction, hypertension, gastrointestinal and migraine discomfort, inability to establish proper patient communication for evaluation of postoperative pain, need for hospitalization in ICU after operation. Grade 3 and grade 4 patients, ASA class 3 and grade 4, bradycardia and tachycardia, and patients whose continued presence in the study caused a potential death risk were excluded. Written consent was received from all people and the Ethics Committee approved this study. The sampling was convenient and the patients were randomly divided into two groups of 50. The first group was the patients receiving 30 mg of ketorolac (IV injection) before tying the tourniquet (10 minutes before tying the tourniquet); the second group received 30 mg of ketorolac (IV injection) after tying the tourniquet (immediately after tying the tourniquet). After going to the operating room and the provision of initial preparations, all patients underwent a similar procedure under general anesthesia. Anesthetic induction was done using the following drugs: Thiopental (morphine 4 mg/kg, 0.15 mg/kg, fentanyl 2 mg/kg (2 μg/kg), xylocaine 1 mg / kg, midazolam 0.03 mg/kg, Atracurium 0.5 mg / kg). Blood pressure, pulse and respiration were measured immediately after injection and then at 5, 10, 20, 60, 90 and 120 minutes later. The pain was immediately checked after the operation, and 6 hours and 12 hours after the operation. The use of opiates was checked for first and second 6 hours after surgery. The severity of pain was measured by VAS (VISUAL ANALOG SCALE) scale and divided into four groups: painless, mild, moderate and severe pain. People with no pain were in the painless group, those with a pain score of 1-3 in mild, 3-7 in moderate, and more than 7 were in severe pain group.

It should be noted that ketorolac was given before and after tying the tourniquet. Data analysis was performed in spss21 and descriptive statistics such as mean and percentages, and inferential statistical tests (Anova and repeated measurement and Chi-square test).

RESULTS

The mean age of the patients participating in the group before tying the tourniquet was 40.21 ± 19.13 and in the group after tying the tourniquet was 42.59 ± 25.59 years. The two groups, before and after tying the tourniquet, were similar in terms of age and gender (Table 1).

Table 1: Comparison of two groups in terms of demographic factors

Factor		Group: Before tying the tourniquet	Group: After tying the tourniquet	p-value
Age[1]		40.21 ± 19.13	42.59 ± 25.59	0.888
Gender	Male	35(71.4)	29(63)	0.384
	Female	14(28.6)	17(37)	

[1]Mean ± standard deviation, [2]Frequency (percent)

In recovery, in the group before tying the tourniquet, 2.1% of the patients had severe pain, whereas in the group after tying the tourniquet, 2.2% of the patients had severe pain. In the first 6 hours, 8.3% of the patients had severe pain in the group before tying the tourniquet, while in the group after tying the tourniquet, 13.3% of the patients had severe pain. At second 6 hours, in the group before tying the tourniquet, 8.3% of the patients had severe pain, whereas in the group after tying the tourniquet, 4.4% of the patients had severe pain (Table 2).

Table 2: Frequency of pain degrees in groups before and after using tourniquet

Scale of pain		Group: Before tying the tourniquet	Group: After tying the tourniquet
VAS.R	Painless	29(60.4%)	21(45.7%)
	Mild pain	14(29.2%)	20(43.5%)
	Moderate pain	4 (8.3%)	4(8.7%)
	Severe pain	1(2.1%)	1(2.2%)
VAS.6hour Post op	Painless	11(22.9%)	8(17.8%)
	Mild pain	20(41.7%)	20(44.4%)
	Moderate pain	13(27.1%)	11(24.4%)
	Severe pain	4(8.3%)	6(13.3%)
VAS.12 hour Post op	Painless	13(27.1%)	14(31.1%)
	Mild pain	21(43.8%)	17(37.8%)
	Moderate pain	10(20.8%)	12(26.7%)
	Severe pain	4(8.3%)	2(4.4%)

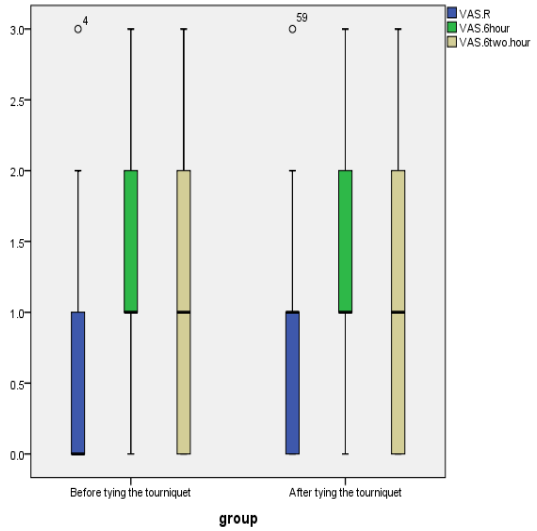

Figure 1: Frequency of pain degrees in the groups before and after using the tourniquet

The result of the Mann-Whitney test in Table 3 showed no significant differences in pain scores before and after using tourniquet in lower extremity orthopedic surgery of femur and tibia with general anesthetic technique (p-value>0.05). In the recovery, the degrees of pain in the group before tying the tourniquet (m = 0) were higher than the group after tying the tourniquet (m = 1), but it was not statistically significant. In the first 6 hours, 50% of the subjects in both groups had mild or no pain. At the second 6 hours, the degrees of pain in the group before tying the tourniquet (m = 1) were equal to the group after tying tourniquet (m = 1) (Table 3). The pain process in the group before and after tying the tourniquet increased from the time of recovery until the first and second six hours. However, the pain in the group remained constant after tying the tourniquet from the recovery to the first and second six hours (Table 3).

Table 3: Comparison of pain score in the groups before and after using the tourniquet

Factor	Group: Before tying the tourniquet	Group: After tying the tourniquet	p-value
Pain score of recovery 1	0(0-1)	1(0-1)	0.211
Pain score of the first 6 hours	1(1-2)	1(1-2)	0.555
Pain score of the second 6 hours	1(0-2)	1(0-2)	0.810
Trend p-value	0.001	0.018	

The results of t-test in Table 4 showed a significant difference between the two groups before and after tourniquet in the heart rate at times 30 during the operation (p<0.05). The heart rate at times 30 during the surgery was lower in the group after tying the tourniquet compared to before tying the tourniquet. No significant difference was seen during the operation between the two groups before and after tying the tourniquet (p> 0.05).

Table 4: Comparison of vital signs at different times during the surgery in the groups before and after tying the tourniquet

	Group				p-value
	Before tying the tourniquet		After tying the tourniquet		
	Mean	SD	Mean	SD	
BP sistol. during. Surgery	124.29	20.10	131.11	22.60	0.201
BP sistol. 30minutes	122.12	24.65	133.02	21.40	0.044
BP sistol. 60 minutes	128.76	19.51	133.19	21.37	0.278
BP Distol. 15 minutes	75.88	13.35	77.80	14.16	0.548
BP Distol. 30 minutes	78.12	12.84	78.96	12.78	0.737
BP Distol. 60 min	81.22	13.23	80.77	12.56	0.902
HR.15.during. surgery	81.16	16.17	78.46	16.96	0.427
HR.30.during. surgery	80.59	16.73	77.33	16.77	0.387
HR.60.during. surgery	82.20	16.12	78.07	17.10	0.380
Breathing.15. during.surgery	16.90	4.75	17.22	4.62	0.618
Breathing.30. during.surgery	17.20	4.73	17.02	5.06	0.793
Breathing.60. during.surgery	17.41	4.51	17.05	4.83	0.577
O2.15.during. surgery	97.59	1.89	97.96	1.40	0.603
O2.30.during. surgery	97.12	1.91	97.59	1.87	0.149
O2.60.during. surgery	97.17	1.77	97.30	1.85	0.644

The results of t-test in Table 5 showed a significant difference between the two groups before and after tying the tourniquet in terms of diastolic blood pressure in recovery (p<0.05). However, in recovery between the two groups before and after tying the tourniquet, there was no significant difference in terms of vital signs at different times (p>0.05).

Table 5: Comparison of vital signs at different times in recovery in the groups before and after tying the tourniquet

Recovery	Group				p-value
	Before tying the tourniquet		After tying the tourniquet		
	Mean	SD	Mean	SD	
BP.S	130.22	15.68	127.98	15.67	0.558
BP.S.5	131.32	17.71	133.03	14.28	0.520
BP.S15	127.54	21.12	131.21	15.53	0.385
BP.S30	121.33	12.82	123.00	26.87	0.739
BP.D.	81.64	10.75	75.86	11.42	0.008
BP.D.5	79.82	11.77	80.35	10.56	0.986
BP.D15	82.38	12.33	81.33	11.34	0.587
BP.D30	79.17	6.65	82.00	2.83	0.615
HR.R.	79.30	12.09	77.07	19.31	0.868
HR.5	78.05	13.12	71.79	14.90	0.263
HR15	77.38	12.82	75.21	19.08	0.823
HR30	81.33	5.05	92.50	7.78	0.096
B.R.	19.16	12.74	17.66	5.26	0.979
B5	17.79	12.49	16.09	4.13	0.851
B15	16.86	4.13	17.18	5.13	0.843
B30	30.00	26.48	23.00	.	0.823
O2.R	97.00	1.77	97.57	1.19	0.237
O2.5MIN	96.78	2.12	97.24	1.39	0.479
O2.15M	96.81	1.82	97.03	1.53	0.815
O2.30M	97.33	1.37	95.00	.	0.199

DISCUSSION

Despite modern techniques and new, innovative analgesic therapies, pain is still one of the controversial issues. Orthopedic surgeries are associated with much post-operative pain due to surgical procedures on the bone and joints [8]. One of the drugs used is ketorolac. Ketorolac, generically called ketorolac trometamol, is a non-steroidal anti-inflammatory drug that reduces pain and inflammation by inhibiting the activity of cyclooxygenase and synthesis of prostaglandin. This study was conducted to evaluate the effect of IVIK before and after tying the tourniquet on the opioid used after surgery. There were no significant differences between the two groups in terms of gender and age. Therefore, these factors did not have a confounding effect on the study. According to the results, the changes in the pain scores in the groups using ketorolac before and after tying the tourniquet in orthopedic surgery of femur and tibia had no significant differences. Accordingly, the need for postoperative analgesic and the medication needed to control pain in both groups of ketorolac injections before and after tying the tourniquet became similar. In a randomized controlled trial, where 32 patients were undergoing ankle fracture surgery, higher pain score was obtained in 24 hours and 48 hours after surgery in the tourniquet group [10],

suggesting that the tourniquet itself can be effective in increasing postoperative pain. In the study by Cassin Elli, when a comparison was made between intravenous injection of ketorolac with placebo group in lower back surgery and laminectomy, it was seen that after operation in ketorolac using group, there was need for lower morphine and better pain score were seen [11]. This is similar to this study where postoperative pain score has reduced in both groups. In a study, Shankariah *et al.,* compared the effects of intramuscular injection of ketorolac and tramadol, and concluded that although both of these drugs reduce pain intensity from 2 to 24 hours postoperatively, tramadol was always more effective in controlling pain than ketorolac [12]. This shows the need for comparing analgesics for better control of pain. A study by Kao *et al.,* in Thailand aimed at investigating the effect of morphine with and without ketorolac on postoperative analgesia in live liver donors showed that administration of ketorolac with morphine has no significant effect on pain relief after operation compared to the group receiving morphine [13], which contradicted the results of this study. The other results of the study showed a significant difference between the two groups before and after tying the tourniquet in terms of heart rate at times 30 during the surgery ($p<0.05$). The heart rate at the time 30% during the operation and in the group after tying tourniquet was lower than that of the group after tying the tourniquet. Although the precise mechanism of this increase in heart rate is not known, the likelihood of factors like the release of stimulants released from muscular and nervous ischemia is not known. Moreover, the pain from tourniquet and sympathetic nervous system stimulation can be mentioned [14]. In their study, Zaidi *et al.,* concluded that the increase in blood pressure induced by tourniquet significantly increased in using ketorolac (30 mg) compared to low ketamine dose (25 mg) in knee surgery under general anesthesia [15], which was consistent with the results of this study.

CONCLUSION

Given the results of the study, it was found that the use of drugs like ketorolac before the operation reduces the need for postoperative opioids, but it seems that it is better to use these drugs in orthopedic surgery before tying the tourniquet. Moreover, attention should be paid to this more blood pressure and heart rate increase while prescribing ketorolac.

Suggestions

Since the number of people surveyed was 100, it seems that more samples are needed to reduce bias, and to attain more comprehensive information. Moreover, as 30-mg dose of ketorolac was used in the study, it could not evaluate higher doses to reduce the need for analgesic in the two groups.

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