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MANAGEMENT OF PERIOPERATIVE PAIN IN ANTERIOR CRUCIATE LIGAMENT SURGERY PATIENTS RECEIVING OXYCODONE, GABAPENTIN, NSAID AND PLACEBO: CLINICAL TRIAL STUDY

Ramin Abrishami[1], Seyed Hadi Aghili[1], Cyrus Afshar[1], Mehri Farhang Ranjbar[2], Ibrahim Mohammadzadeh[3], Farzin Dehghani Mahmoodabadi[4*]

[1]Research Center for Trauma in Police Operations, Directorate of Health, Rescue & Treatment, Police Headquarter, Tehran, Iran.
[2]Department of Medical Surgical Nursing, School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran
[3]Neuroscience Lab, Anatomy and Cell Biology Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4*]Shahid Beheshti University of Medical Science, Tehran, Iran.

***Authors Contributed Equally (Dual first authorship):**
Ramin Abrishami & Seyed Hadi Aghili

***Corresponding Author**: Farzin Dehghani Mahmoodabadi,
Email: farzindr1996@gmail.com

Abstract
Anterior cruciate ligament reconstructions (ACLR) are a common orthopedic sports medicine procedure, with around 130,000 arthroscopic cases annually, mostly performed on an outpatient basis. While ACLR boasts success rates of up to 95%, postoperative pain remains a significant obstacle to timely patient discharge, leading to prolonged care and increased costs. Despite its prevalence and high success rates, there is a lack of consensus and clear protocols regarding the most effective perioperative pain management strategies. This parallel clinical trial involved 200 participants undergoing ACL surgery, randomly assigned to receive placebo, oxycodone, gabapentin, or NSAIDs one hour prior to surgery. Pain levels were assessed using the Visual Analog Scale (VAS) at various post-operative time intervals, and pethidine usage was recorded. Findings indicated gender-based discrepancies in post-operative pain, with females experiencing higher intensity, particularly at three and 6hours post-surgery. Oxycodone demonstrated superior immediate relief, while placebo recipients were more likely to seek additional pain relief, indicating perceived ineffectiveness. The study emphasizes the evolving nature of post-operative pain and underscores the necessity for effective long-term pain management strategies, offering significant insights for optimizing pain relief approaches in ACL surgery patients.

Keywords: Perioperative pain, Anterior Cruciate Ligament Surgery, oxycodone, Gabapentin. NSAIDs, Placebo, Postoperative pain.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), commonly known as NSAIDs, represent one of the most commonly used drug categories worldwide [1] . This class of drugs has analgesic, anti-inflammatory, and antipyretic properties and also has the ability to inhibit platelet aggregation [2-4]. This classification includes various medications such as aspirin, ibuprofen and naproxen, which are widely used not only in Iran but also in many other countries to relieve conditions such as joint pain [5-7]. However, it is noteworthy that excessive consumption of NSAIDs can lead to a number of complications, including neurological, renal, hematological and gastrointestinal problems, with the latter presenting particularly notable side effects [8-12]. Research studies have shown that patients undergoing NSAID treatment are three to four times more susceptible to gastrointestinal bleeding or perforation compared to the general population [13, 14].

Opioid medications, on the other hand, show widespread distribution throughout the body's tissues. They develop their analgesic effect by inhibiting synaptic activity. This mechanism is carried out in part through the direct stimulation of opioid receptors as well as the release of endogenous opioid peptides, which also have an inhibitory effect on neurons [15, 16]. All three main types of opioid receptors are connected to their effectors via G proteins and trigger activation of phospholipase C or inhibition of the enzyme adenylyl cyclase. This activity at the postsynaptic level leads to the opening of potassium channels, which subsequently induce hyperpolarization of the cell membrane, thus generating a postsynaptic inhibitory potential. In addition, the activity of the opioid receptor at the postsynaptic level leads to the closure of ion channels depending on calcium voltage, thereby preventing the discharge of neurotransmitters. In addition, presynaptic effects impede the release of a variety of neurotransmitters, including acetylcholine, norepinephrine, serotonin, glutamate, and substance P [17, 18].

Gabapentin, which is structurally similar to gamma-aminobutyric acid (GABA), was first introduced in 1994 as an antiepileptic drug specifically tailored to certain types of partial epilepsy[19]. Currently, gabapentin has application in the relief of pain associated with a variety of conditions such as chronic pain syndromes, postherpetic neuralgia, diabetic neuropathy, and reflex sympathetic dystrophy[20, 21]

2. Material and Method

This study will be conducted in the form of a parallel clinical trial. After obtaining the necessary approvals from the ethics committee, this study will be started in the orthopedic department of Vali Asr Naja Hospital. Registration in the national IRCT system also provides the license to conduct this clinical trial with the registration number of: IRCT202307160588004N1. The study adhered to the ethical guidelines outlined in the Declaration of Helsinki, including obtaining written consent from all human research participants.

The target group is patients undergoing anterior cruciate ligament surgery. The studied population is patients undergoing anterior cruciate ligament surgery at Vali Asr Naja Hospital. Study samples take part in the study with written consent and are informed about the study conditions. Inclusion criteria include candidacy for ACL surgery, no history of peptic ulcer, renal and hematologic diseases, no opioid dependence, and no use of anticonvulsants. Patients may withdraw from the study at any point during the study. Further exclusion criteria include gastrointestinal bleeding, drop in platelet count, and renal and cardiac dysfunction during the study. The number of samples in each group is 50 and a total of 200 people will participate in this study. The number of samples was determined according to the simple logistic regression formula and according to a similar study by Imani et al. calculated. (30). To balance the number of samples in each group, the block method (with unequal size of four) is used for random allocation. This study is designed and conducted blindly, so patients do not know which group they belong to, and each patient is assigned a unique code by the computer, based on which the final conclusion is made. will be in addition, the patients are randomly distributed into four groups (placebo, oxycodone and gabapentin and NSAID) and the randomization is carried out by computer. Each group will receive the medication for their group

one hour before surgery. Gabapentin is prescribed as a single dose of 600 mg before surgery. Oxycodone is prescribed as a single 10 mg dose before surgery. The NSAID medication used is injectable ketorolac in the amount of 30 mg, which is prescribed to the respective patients one hour before the operation. An oral placebo will also be prescribed one hour before surgery. After surgery, patients in each group will be treated with injectable pethidine (rescue medication) in case preventive treatment fails and greater relief is required and preoperative medicine is insufficient. Additionally, the cumulative amount of pethidine used in each patient will be recorded. Patients will be evaluated at 1,3 and 6 hour intervals after regaining consciousness. According to the VAS measurement criterion, the patient is asked at any time to indicate the intensity of his pain on a scale of 1 to 10 points. Each patient's pain intensity will be recorded at the specified intervals. In addition, the patient's pain intensity is measured with the same scale before the operation. In addition, for each patient, the cumulative amount of pethidine injected in the first 6 hours after regaining consciousness will be calculated and recorded. The examined result in the patients will finally be compared the intensity of pain after regaining consciousness according to the VAS scale and the amount of pethidine injected to relieve pain. Finally, information about each patient is entered into the questionnaire. The information will then be transferred to Excel and finally analyzed in SPSS software and the effect of the type of preoperative pain medication on pain relief in the first hours after surgery and the reduction of injectable pethidine intake is determined

2.1. Preoperative medicine:

Based on the data presented in Table 1, it is evident that individuals were administered medication in uniform cohorts of 50 prior to the surgical procedure. The allocation of individuals for pre-operative medication was consistent. The pharmaceuticals administered encompassed gabapentin (25%), oxycodone (25%), ketorolac (25%), and a placebo (25%), with 50 patients assigned to each specific drug.

Table 1: The frequency of research participants based on the type of medication used before surgery

Frequency	Abundance	Preoperative medicine
25	**50**	**Gabapentin**
25	**50**	**Ketorolac**
25	**50**	**Oxycodone**
25	**50**	**Placebo**
100	**200**	**Total**

2.2. To compare the difference in patients' pain levels over time from 1 to 6 hours after surgery:

Null hypothesis: There is no significant difference between the pain level of research patients 1 hour, 3 hours and 6 hours after surgery. (H0: $P>0.05$) To test this hypothesis, Friedman's ranking test is used, the results of which are as follows: The results of Friedman's analysis proved that pain intensity increases with time. Therefore, the null hypothesis was rejected and a very significant difference was observed between pain intensity at different hours after surgery ($p<0.001$). The average pain score ranged from 1 at one hour after surgery to 5 at six hours after surgery. See Table 2 for more information

Table 2: Comparing the mean patient pain ratings over the period of 1,3 and 6 hours

Statistical indicators				Average rank	Middle (interquartile range)	Time	Variable
Significance level	grade of unattached	kai-do	Number				
0.000	2	335.49	200	1.11	1 (2,0)	1hour after the operation	The amount of pain
				2.07	3(4,2)	3 hours after the operation	
				2.82	5(6,4)	6 hours after the operation	

2.3. Post-operative medicine based on the pethidine dose received:

Among the cohort of 200 patients, 60 individuals, constituting 30%, did not achieve pain relief post-surgery despite medication. In response, 9 patients, or 4.5%, were prescribed a pethidine dose of 20, while 28 patients (14%) received a dose of 25. Additionally, 20 patients (10%) were administered a pethidine dose of 30, and 3 patients (1.5%) were given a dose of 50. For more comprehensive information, please consult Table 3.

Table 3: Frequency of postoperative drug distribution based on pethidine dose received on research patients

Frequency	Abundance	Post-operative medicine
70	140	Failure to receive pethidine
4.5	9	Pethidine dose 20
14	28	Pethidine dose 25
10	20	Pethidine dose 30
1.5	3	Pethidine dose 50
100	200	Total

3. Result

The study found no significant gender-based difference in post-operative pain levels one hour after surgery ($p=0.213$), indicating independence from gender influence. However, 3hours post-operation, females reported higher pain levels ($p=0.004$). Similarly, at the six-hour mark, women experienced elevated pain levels ($p=0.001$).

Pre-operative medication type significantly impacted pain levels one hour after surgery ($p=0.003$). Oxycodone led to the lowest mean rating, while gabapentin resulted in the highest. 3hours post-operation, significant differences persisted ($p<0.001$), with oxycodone demonstrating the lowest mean rating and placebo the highest.

Pre-operatively, patients receiving a placebo were more likely to request pethidine (70% vs. 30%). Among those not needing it, oxycodone patients reported the lowest pain (3 out of 50), while placebo patients reported the highest (36 out of 50). Gender-wise, women received more parenteral pethidine (36 out of 88) compared to men (24 out of 112). The escalation of pain over time was

confirmed by Friedman's analysis, revealing a significant difference ($p<0.001$) from an average pain score of 1hour post-operation to 5 six hours after surgery.

3.1. Comparison of the pain level of patients in 2 groups of men and women in 1 hour after the operation

As indicated in Table 4, there was no statistically significant difference, at the 0.05 significance level, between the gender of the patients and their reported pain levels one hour after the operation. Consequently, the null hypothesis (H0) was upheld, with a p-value of 0.213. This suggests that the level of pain experienced by patients within the first hour following the operation is not influenced by their gender.

3.2. Comparison of the pain level of patients in 2 groups, male and female, 3 hours after the operation:

As evident from Table 5, there exists a statistically significant difference, at the 0.05 significance level, between the gender of the patients and their reported pain levels 3hours post-operation. Consequently, the null hypothesis (H0) was dismissed, with a p-value of 0.004. This signifies that, in reality, women experienced a higher level of pain three hours after the surgical procedure.

3.3. Comparison of the pain level of patients in 2 groups, male and female, 6 hours after the operation:

As depicted in Table 6, there is a notable and statistically significant distinction, at the 0.05 significance level, between the gender of the patients and their reported pain levels 6hours post-operation. As a result, the null hypothesis (H0) was rejected, with a p-value of 0.001. This indicates that, in practice, women experienced a higher level of pain six hours after the surgical procedure.

4. Discussion

Injuries to the anterior cruciate ligament (ACL) are common in sports fans in the United States[22]. To address this risk, healthcare providers frequently opt for cruciate ligament repair (ACLR). An estimated 130,000 such surgical operations are conducted each year, with the majority of patients treated as outpatients [23, 24]. While the ACLR treatment has a 95% success rate, one significant challenge is the optimum management of pain after surgery. In some cases, severe discomfort may necessitate lengthier hospital stays, resulting in increased medical expenses[23, 25, 26].

Our research focuses on perioperative pain treatment in ACL surgery patients, studying the effects of Oxycodone, Gabapentin, NSAID, and Placebo. It identifies important parameters that influence post-operative pain levels and drug preferences.

Gender disparities in postoperative pain were evident, with females reporting higher pain levels for six hours after surgery. Pre-operative drug choice had a significant impact on immediate post-operative pain, with Oxycodone being the most effective and gabapentin receiving the highest average rating. Placebo recipients were more likely to request pethidine, highlighting the influence of perceived drug effectiveness on additional pain relief decisions. Those using Oxycodone without needing pethidine reported the lowest pain levels. The study also noted gender differences in pethidine usage, indicating potential variations in pain perception and management. Friedman's study emphasized the evolving nature of post-operative pain and the importance of effective, long-term pain management strategies.

Numerous prior investigations exhibit similarities with the present study, while others present inconsistencies. For instance, Beck et al. (2020) demonstrated in their research that variables such as age, weight, gender, and the type of surgical procedure exhibited no discernible impact on pain levels among individuals administered hydrocodone/acetaminophen combination tablets post-operation. Subsequent to a four-week interval, patients were administered a regimen comprising 40 hydrocodone/acetaminophen combination tablets and were subsequently subjected to a pain assessment questionnaire. The outcomes of this investigation revealed a uniform reduction in pain facilitated by this combined pharmaceutical formulation across all patients, with no discernible

disparity in outcomes among those who utilized these tablets[27]. The study by Hah et al. examined the effects of administering gabapentin before surgery on pain management and opioid usage in a group of 1805 individuals aged 18 to 75 undergoing various surgical procedures. These procedures included thoracotomy, mastectomy, hand surgery, carpal tunnel intervention, knee, and shoulder arthroscopy. The results indicated that gabapentin did not have a noticeable impact on the duration of pain relief. However, patients who received gabapentin experienced a noteworthy 24% decrease in opioid consumption. This suggests that while gabapentin did not prolong the relief of pain, it effectively led to a significant reduction in the use of opioids[28].

In the investigation conducted by Bang SR, Yu SK, and their associates, it was discovered that within the cohort administered with gabapentin, there was a notable decrease in pain intensity recorded at 2, 6, and 12hours post-administration. Nevertheless, there was no substantial discernible contrast between the two cohorts concerning the requirement for fentanyl post-operatively. Furthermore, the occurrence of adverse effects, such as nausea and dizziness, exhibited a comparable prevalence in both study Groups[29].

Li Y, Dou Z et al. conducted a study to compare the analgesic effects of oxycodone, pethidine, and fentanyl in 695 patients who were candidates for laparoscopy. The results showed that oxycodone had a greater analgesic effect on the first day following surgery compared to pethidine and fentanyl. However, there was no significant difference in the levels of sedation between the two groups. The study also found that the oxycodone receptor group experienced a higher rate of drowsiness and dizziness compared to other Opioids [30].

5. Conclusion

This research delved into the strategies employed for managing pain during the recovery phase following cruciate ligament surgery. The outcomes revealed several significant findings. Initially, there were discernible disparities in the levels of pain experienced by males and Females post-operation, with females reporting heightened discomfort, particularly at the three and six-hour marks after surgery. Additionally, the type of medication administered before surgery had a discernible impact on postoperative pain levels. Oxycodone was identified as providing immediate relief, while individuals who received a placebo were more inclined to seek additional pain relief, indicating its perceived ineffectiveness.

Furthermore, the study emphasizes the dynamic nature of post-surgery pain, underscoring the necessity for long-term pain management strategies. This investigation offers valuable insights for refining approaches to pain relief for patients undergoing ACL surgery. It sheds light on the potential benefits of medications like oxycodone, gabapentin, and NSAIDs, and underscores the importance of tailoring pain management strategies according to gender. Overall, these findings deepen our comprehensive understanding of perioperative pain management in ACL surgery, potentially leading to improved patient outcomes and reduced healthcare costs.

6. Author Contributions

RA and CA conceived the study and constructed the study design; CA and FDM data collection; MF and IM data analysis and data interpretation; FDM and IM wrote the original manuscript, CA and FDM review & editing final draft; RA, CA and HA supplied the clinical sample & data, made substantial contributions to the coordination of the this study. All authors read and approved the final manuscript.

7. Funding

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8. Competing interests

The author(s) declare that they have no competing interests.

9. Ethics approval

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran with the registration number of:IR.SBMU.TEB.POLICE.REC.1402.011.

10. Informed consent

Informed Consent Written consent was obtained from all patients who were informed that the data would be used for research. Also the use of human specimens is also based on Declaration of Helsinki.

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