

(Research/Review) Article

# Comparison of Visual Analog Score in Fentanyl Drip Administration with Ketorolac Injection as Post-Operative Analgesic Therapy in Post-ORIF Patients with Closed Clavicle Fracture: A Case Report

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**Abstract:** Introduction: Adequate post-operative pain controls a concern for patients after undergoing operative procedures, especially after undergoing orthopedic surgical procedures which are often associated with severe post-operative pain. Multimodal analgesia therapy is a superior therapeutic option in post-operative pain management. Clinical Report: In the first patient who received fentanyl drip and paracetamol, the VAS values obtained at 6 h, 12 h, 24 h, 48 h, and 72 h postoperatively were as follows: 3, 4, 4, 2, and 2. In the second patient who received ketorolac and paracetamol injection, the VAS values were obtained at evaluation 6 h, 12 h, 24 h, 48 h, and 72 h postoperatively as follows: 5, 4, 3, 3, and 2. Discussion: There were differences in the results of VAS measurements in the two patients. The difference in VAS measurement results between the two patients may be due to the administration of different postoperative analgesic agents. Conclusions: In the first patient who received fentanyl drip and paracetamol, it was found that the VAS value at the 6 hours evaluation was lower than the evaluation at 12 h and 24 h. Meanwhile, in the second patient who received ketorolac and paracetamol injections, the VAS value at the 6 h and 12 h evaluation were higher than at the 24 h postoperative evaluation. At the 48 h and 72 h evaluation, the VAS value was lower in the second patient.

**Keywords:** Fentanyl; Ketorolac; Multimodal Analgesic; Postoperative Analgesic; VAS

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## 1. Introduction

The clavicle is highly susceptible to fracture due to impact to the shoulder joint. The superficial location of the clavicle and the thin anatomical shape of the clavicle shaft make it highly susceptible to injury when force is transmitted from impact to the shoulder joint. The incidence of clavicle fractures accounts for 44% of all shoulder injuries and accounts for 2.6-10% of all fractures. A multicenter study reported that operative intervention provides better functional outcomes with a higher union rate compared to conservative methods. The standard operative procedure for complex midshaft clavicle fractures is Open Reduction and Internal Fixation (ORIF) using plates or intramedullary fixation.

Surgical procedures, particularly orthopedic surgery, are among the most painful surgical procedures reported by patients and carry a high risk of inadequate postoperative pain control. A study of 78 patients undergoing ORIF surgery for shoulder injuries found that 28% of patients complained of severe post-procedure pain. Postoperative pain is often associated with prolonged hospital stays, high readmission rates, and even morbidity, which are related to the pain and discomfort experienced by patients. Therefore, adequate post-operative pain management is crucial for patients after surgery.

Opioid analgesics, such as fentanyl, have good analgesic and sedative effects. However, intravenous administration of fentanyl is associated with nausea and vomiting, pruritus, urinary retention, decreased bowel movements, respiratory depression, and dependence, which limits its dosage.

Non-steroidal anti-inflammatory drugs (NSAIDs) have a lower analgesic effect than opioids, but they can be used to safely control post-operative pain without causing dependence, withdrawal symptoms, or nausea and vomiting. One NSAID with a fairly strong analgesic effect is ketorolac tromethamine.

Multimodal analgesia therapy has become a superior treatment option in postoperative pain management in recent years. Multimodal analgesia therapy utilizes multiple analgesic medications, such as opioid and non-opioid analgesics, physical modalities, and even cognitive approaches to influence the peripheral and central nervous system in pain management. This allows patients to benefit from several different medications working synergistically, minimizes the side effects of certain drug classes, and reduces the incidence of morbidity associated with opioid monotherapy.

In this case study, a Visual Analog Score (VAS) assessment was performed on a male patient following ORIF for a clavicle fracture who received a combination of different postoperative analgesic agents, namely a fentanyl drip and ketorolac injection.

## 2. Preliminaries or Related Work or Literature Review

### Multimodal Analgesia

Multimodal analgesia is defined as the simultaneous use of more than one pain management modality to achieve effective analgesia. Multimodal analgesia reduces opioid consumption and can mitigate opioid-related side effects. Multimodal analgesia therapy utilizes multiple analgesic medications, including opioid and non-opioid analgesics, physical modalities, and even cognitive approaches to influence peripheral and central nervous systems in pain management. <sup>9</sup> A single-center study of 357 patients undergoing head and neck surgery found that a combination of postoperative analgesics was effective in reducing opioid consumption in the post-anesthesia care unit. Several multimodal analgesic therapy regimens recommend a combination of an NSAID and/or a COX inhibitor, along with paracetamol. Some protocols also include gabapentin to further enhance the analgesic effect. Opioids are then used for uncontrolled pain and are only considered if a multimodal analgesic approach is inadequate to manage the patient's post-operative pain. Many surgical specialties have implemented multimodal analgesic protocols in an effort to reduce the proportion of opioids used in the postoperative period and further reduce the negative side effects associated with opioid use. The Calgary Protocol uses a combination of ibuprofen, acetaminophen, and gabapentin and is administered to all patients without contraindications to these medications. In addition to these medications, N-methyl-D-aspartate (NMDA) receptor antagonists, anticonvulsants (gamma-aminobutyric acid (GABA) analogs), beta-blockers, alpha-2 agonists, transient receptor potential vanilloid receptor agonists (capsaicin), glucocorticoids, and magnesium can also be used. Fentanyl is used as a postoperative analgesic agent at a dose of 1-2 mcg/kgBW with a duration of analgesia of 30 minutes to one hour. Fentanyl is superior in that it is 100 times more potent than morphine and can be used in patients with renal impairment, unstable hemodynamics, or bronchospasm. Ketorolac, an NSAID, is administered at a dose of 15-30 mg per dose, which can be repeated every four to six hours. The maximum daily dose of ketorolac is 120 mg. Concurrent use of ketorolac with opioid agents can reduce the opioid dose required by 25-45%. It is important to note that ketorolac should be avoided in patients with a history of coronary artery bypass graft (CABG) surgery.

### Fentanyl as a Postoperative Analgesic Agent

#### a. Pharmacokinetics

Fentanyl is a lipophilic molecule, allowing it to be absorbed across membranes. Fentanyl has good penetration into the nervous system and reduces pain. Furthermore, fentanyl is widely distributed in muscle, bone, and fat. The onset of action of fentanyl is rapid, generally within 30-60 minutes after intravenous administration. Fentanyl is metabolized in the liver and eliminated through urine and feces.

#### b. Pharmacodynamics

Fentanyl is a synthetic form of phenylpiperidine derivative with anesthetic and analgesic effects. Structurally, fentanyl is similar to morphine, but has a potency 50-100 times higher. The estimated analgesic effect of 100 mcg of fentanyl is equivalent to 10 mg of morphine.

Fentanyl's interaction with  $\mu$ , delta, and kappa opioid receptors in the brain, spinal cord, and other tissues causes clinical effects in patients.

The analgesic effect of fentanyl is due to activation of various opioid receptors, particularly the  $\mu$ -opioid receptor. Activation of opioid receptors leads to the exchange of GTP and GDP across G proteins, which in turn downregulates adenylate cyclase and cAMP concentrations. Decreased cAMP leads to cell hyperpolarization and decreased neuronal activity. However, with long-term use, tolerance to opioids can develop.

#### **c. Mechanism of Action**

Fentanyl targets a subclass of opioid receptors in the body, located in the cerebrum within a specific neuroanatomical structure, specifically those involved in the control of emotions, pain, and speech, leading to its well-known addictive properties, namely "reward." Biochemically, it is a  $\mu$ -selective opioid agonist. However, it has the ability to activate other opioid receptors, such as delta and possibly kappa receptors. Consequently, activation of these receptors, particularly  $\mu$  receptors, produces analgesia. Furthermore, the neurotransmitter dopamine (Da) increases in the "reward" area of the cerebrum, leading to stereotypical euphoria and relaxation, and is commonly associated with drug addiction. Fentanyl is metabolized in the liver via the CYP450 enzyme system, specifically CYP3A4. The drug has a half-life of 3 to 7 hours. It is excreted 75% in the urine and 9% in the feces.

#### **d. Dosage as a postoperative analgesic**

As a postoperative pain control agent, fentanyl can be administered intravenously or intramuscularly at a dose of 50-100 mcg every 1-2 hours as needed; or, if administered continuously via an infusion pump, at a dose of 0.5-1.5 mcg/kg/hour. When used as a patient-controlled analgesia (PCA) modality, 10-20 mcg can be administered intravenously every 6 to 20 minutes as needed, starting with the lowest effective dose for the shortest effective duration.

### **3. Ketorolac as a Postoperative Analgesic Agent**

#### **a. Pharmacokinetics**

Ketorolac can be administered intramuscularly, intranasally, and orally, with varying bioavailability. Ketorolac is metabolized in the liver and cannot cross the blood-brain barrier. However, it can cross the placenta and is excreted in breast milk and urine.

#### **b. Pharmacodynamics**

The pharmacodynamics of ketorolac are related to its ability to inhibit the activity of cyclooxygenase 1 and 2 (COX-1 and COX-2) enzymes, which metabolize arachidonic acid into prostaglandins and thromboxane-2. Ketorolac is a non-selective inhibitor of both COX-1 and COX-2 enzymes. COX-1 enzymes are found in platelets, gastric mucosa, and blood vessel endothelium. Meanwhile, COX-2 enzymes stimulate and mediate inflammation, pain, and fever. Ketorolac's inhibitory effect on the COX-1 enzyme can increase the incidence of gastrointestinal bleeding and the risk of gastric ulcers. Inhibition of the COX-2 enzyme provides ketorolac's desired therapeutic effects, namely anti-inflammatory and analgesic properties.

#### **c. Mechanism of Action**

Ketorolac, like other NSAIDs, blocks cyclooxygenases (COX), enzymes that convert arachidonic acid into prostaglandins, prostacyclin, and thromboxane. Inhibition of these enzymes reduces pain, fever, and inflammation. Ketorolac blocks both COX-1 and COX-2 enzymes. This drug exhibits higher potency than most other NSAIDs.

#### **d. Dosage as a Post-operative Analgesic**

The recommended dose for adult ketorolac is 30 mg per dose, which can be repeated every four to six hours. The maximum daily dose of ketorolac is 120 mg. It can be administered intravenously, intramuscularly, or orally. The recommended oral dose in adults is a single 20 mg dose after IV or IM therapy, then 10 mg every 4 to 6 hours, not to exceed 40 mg in 24 hours. The half-life is 5.6 hours for a single 30 mg dose given IM or a single 10 mg oral dose.

#### **e. VAS**

The Visual Analog Score, commonly abbreviated as VAS, is a pain assessment scale first used in 1921 by Hayes and Patterson.<sup>22</sup> This scale is frequently used in epidemiological and clinical research to measure the intensity or frequency of various symptoms. The simplest VAS is a straight horizontal line of fixed length, usually 100 mm. Its ends are defined as the extreme limits of the parameter being measured (symptom, pain, or health). In some studies, the horizontal scale is oriented from right to left, and many researchers use a vertical VAS.<sup>23</sup> No difference between the horizontal and vertical VAS was demonstrated in a survey involving 100 subjects, but other authors argue that the two orientations differ due to possible differences in viewing angle. In VAS assessments, patients mark a point on the provided line according to their condition. The VAS score is determined by measuring in millimeters from the left end of the line to the point marked by the patient using a ruler. Higher scores indicate greater pain intensity. The following is a recommended interpretation of the VAS: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm). Normative values are not available. The scale must be demonstrated to the patient; otherwise, it is an auditory scale, not a visual scale.

### **3. Materials and Method**

The research method used in writing this report is a case study, namely a descriptive approach that aims to describe in depth the conditions, management, and results of care for one research subject.

### **4. Results and Discussion**

Both patients underwent ORIF procedures for clavicle fractures under general anesthesia. General anesthesia is preferred for ORIF placement in clavicle fractures because it requires deep and efficient anesthesia to completely anesthetize the clavicle and surrounding structures. General anesthesia in this case is known to provide a shorter total operative duration compared to regional anesthesia. Postoperatively, the patients received analgesics in the form of paracetamol 1000 mg intravenously every eight hours and fentanyl dissolved in 0.9% NaCl infusion fluid at a dose of 30 mcg/hour using an infusion pump. Continuous intravenous fentanyl administration has been reported to provide better postoperative pain control compared to intramuscular administration. A study conducted on patients undergoing surgical procedures in a single day care setting found that administering multimodal analgesics to postoperative patients resulted in an average reduction in pain scores (as measured using the Verbal Pain Intensity Scale/VPIS) of  $1.90 \pm 0.46$ , compared to administering a single analgesic, which decreased pain scores by  $1.0 \pm 0.44$ . In the second patient, the procedure was also performed under general anesthesia. The postoperative analgesics received by the patient were intravenous paracetamol at a dose of 1000 mg every eight hours and three injections of ketorolac 30 mg. Opioids are known to be effective and synergistic when used in conjunction with NSAIDs, compared to using opioids as monotherapy. The synergy between NSAIDs, which work primarily through modulation of the arachidonic acid cascade in peripheral locations, and opioids, which work primarily centrally at specific receptors, is effective in various types of surgery. The use of a combination of NSAIDs with opioid analgesics is also known to reduce the opioid requirements that patients will need, as well as reduce the side effects caused by opioid consumption.

Differences in VAS values were found in patients receiving fentanyl and ketorolac as postoperative analgesic agents. In the first patient who received fentanyl, postoperative pain evaluation in the first six hours after the procedure obtained a VAS value of 3. In the 12-hour and 24-hour post-procedure evaluations, a VAS value of 4 was obtained. Evaluations 48 and 72 hours after the procedure showed a VAS value of 3. In the second patient who received ketorolac, when postoperative pain evaluation was carried out, in the first six hours after the procedure, a VAS value of 5 was obtained. In the 12-hour and 24-hour post-procedure evaluations, VAS values were obtained of 4 and 3, respectively. When VAS values were evaluated at 48 hours and 72 hours later, a VAS value of 2 was obtained. In line with studies conducted on patients undergoing enucleation ophthalmological surgery procedures, a higher VAS score was obtained when measured immediately after surgery in the group receiving ketorolac ( $5.65 \pm 3.21$ ) compared to the group receiving fentanyl ( $2.47 \pm 1.32$ ) as a postoperative therapeutic agent. On the first postoperative day (24 hours postoperatively), results showed that ketorolac also showed good analgesic effects similar to fentanyl. This shows that the onset of analgesia with fentanyl is immediate and very effective in patients with acute and severe pain. In 69 patients undergoing surgery, who were randomized into two groups, between the group receiving 30 mg of ketorolac intravenously and the group receiving 50 mcg of fentanyl intravenously, when pain assessment using VAS at six hours postoperatively, a significant reduction in pain was found in the group receiving ketorolac compared to the group receiving fentanyl. Although fentanyl is still the drug of choice in the early postoperative period, the use of intravenous ketorolac is more effective during the postoperative period in order to provide a longer analgesic effect. Sixty patients were classified into three groups to receive different postoperative analgesic agents: the fentanyl group (fentanyl at a dose of 2 mcg/kgBW), the mixed group (fentanyl 1 mcg/kgBW and ketorolac 0.5 mg/kgBW), and the ketorolac group (ketorolac 1 mg/kgBW). Pain assessments performed at 0, 10, and 20 minutes postoperatively revealed significantly lower postoperative pain scores in the fentanyl and mixed groups compared to the ketorolac group ( $P < 0.05$ ).

In the first patient, the VAS score at 48 and 72 hours postoperatively was 3. In the second patient, the VAS score at 48 and 72 hours later was 2. Tissue damage caused by surgical procedures can lead to the release of complement, oligomorphonuclear leukocytes, and macrophages. These components can increase the production of reactive oxygen species (ROS) and reduce the effectiveness of antioxidants. This condition causes patients to experience oxidative stress. Oxidative stress can affect nociception, which can lead to hyperalgesia due to local oxidative mechanisms. Administration of ketorolac, in addition to its analgesic effect, also has the effect of reducing the level of stress experienced by patients after undergoing surgical procedures. This may also affect the results of VAS measurements in patients, where lower VAS values were found at 48 hours and 72 hours in patients receiving ketorolac as postoperative analgesic management.

## 5. Conclusion

There were differences in the VAS measurement results between the two patients. In the first patient who received fentanyl drip and paracetamol, the VAS value at the 6-hour evaluation was lower than the 12-hour and 24-hour evaluations. Meanwhile, in the second patient who received ketorolac injection and paracetamol, the VAS values at the 6-hour and 12-hour evaluations were higher than the 24-hour postoperative evaluation. At the 48-hour and 72-hour evaluations, the VAS value was lower in the second patient. The differences in results between the two patients are likely related to the different choices of postoperative analgesic agents in each patient. Future research could examine the combination of multimodal analgesics in postoperative patients, combining them with physical modalities and cognitive approaches. The effect of multimodal analgesic use after surgery on other side effects, such as nausea, vomiting, and bleeding, could also be evaluated.

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