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by Perpustakaan IIK Bhakti Wiyata

Submission date: 04-Sep-2025 11:26AM (UTC+0700)
Submission ID: 2501118648
File name: K_OF_POSTOPERATIVE_CLOSED_FRACTURE_PA_-_Dyah_Ayu_Kusumaratni.pdf (377.03K)
Word count: 4738
Character count: 25138

MedClip
Journal of Medicine and Clinical Pharmacy

ISSN 2302-4283 (print)
ISSN 2580-9571 (online)
Online di https://jurnal.poltekkes-soepraoen.ac.id
DOI: 10.47794/jkhws

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METAMIZOLE VERSUS KETOROLAK OF POSTOPERATIVE CLOSED FRACTURE PAIN MANAGEMENT AT Dr. ISKAK TULUNGAGUNG HOSPITAL : A COST EFFECTIVENESS ANALYSIS

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ABSTRAK

Pendahuluan : Nyeri yang muncul pada pasien pasca operasi merupakan nyeri akut, namun nyeri yang tidak tertangani dengan baik akan berkembang menjadi nyeri kronik dan berdampak negatif jangka panjang serta berdampak pula pada sisi finansial. Metamizole umum digunakan dalam manajemen nyeri, sedangkan ketorolak saat ini diposisikan sebagai pilihan alternatif. Ketersediaan berbagai pilihan analgetik harus disertai dengan data perbandingan tentang efektivitas dan penilaian biaya. Tujuan dari penelitian ini adalah untuk membandingkan biaya-efektivitas dua terapi untuk nyeri akut sedang dan berat, yaitu Metamizole (3x1g) dan Ketorolak (3x30mg) untuk manajemen nyeri pasca operasi fraktur tertutup. **Metode :** Penelitian ini merupakan penelitian deskriptif komparatif dengan menggunakan rancangan cross sectional dengan pengumpulan data retrospektif. Sampel dalam penelitian ini adalah rekam medis dan catatan keuangan pasien operasi fraktur tertutup BPJS kelas III. Estimasi biaya diukur dari sudut pandang penyedia layanan. Jenis biaya yang dipertimbangkan adalah semua biaya yang terkait langsung dengan pelayanan kesehatan di rumah sakit. Biaya diukur dalam satuan mata uang rupiah (IDR). Penelitian ini merupakan penelitian jangka pendek sehingga peneliti tidak menganalisis tingkat diskonto (0%). **Hasil** penelitian ini menunjukkan bahwa Metamizole merupakan obat dengan efektivitas lebih tinggi (37,93%) dibandingkan ketorolak (35,48%), dengan total biaya medis langsung metamizole sebesar Rp. 21.990.051 dan ketorolak Rp. 23.041.427. Nilai ACER metamizole sebesar Rp. 579.754 dan ketorolak Rp. 649.420. **Kesimpulan :** Berdasarkan perhitungan angka riil tersebut, Metamizole lebih cost-effective dibandingkan ketorolak dalam penatalaksanaan nyeri pascaoperasi fraktur. Namun, secara statistik efektivitas dan biaya kedua terapi tersebut tidak memiliki perbedaan yang signifikan.

Kata kunci: Analgesik , Postoperative , Fraktur , Nyeri , Farmakoekonomi

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DOI: 10.47794/jkhws

ABSTRACT

Introduction: *The pain that appears in postoperative patients is acute pain, but pain that is not properly managed will develop into chronic pain and have long-term negative effects and also have financial impacts. Metamizole is commonly used in pain management, while ketorolac is currently positioned as an alternative option. The availability of various analgesic options must be accompanied by comparative data on effectiveness and cost assessment.This aim to compare the cost–effectiveness of two therapies for moderate and severe acute pain, Metamizole (3x1g) and Ketorolac (3x30mg) for closed fracture postoperative pain management.* ***Methods:*** *This study is descriptive comparative research using a cross sectional design with retrospective data collection. The sample in this study was the medical records and financial records of BPJS class III closed fracture surgery patients. Cost estimation measured from the provider's perspective. The types of costs considered are all costs directly related to health care at the hospital. Costs are measured in Indonesian rupiah (IDR) currency units. This research is short-term research so the researcher did not analyze the discount rate(0%).* ***Results:*** *The findings of this study showed that Metamizole is a drug with higher effectiveness (37.93%) than ketorolac (35.48%), with a total direct medical cost of metamizole of IDR. 21,990,051 and ketorolac IDR. 23,041,427. ACER value of metamizole IDR. 579,754 and ketorolac IDR. 649,420.* ***Conclusion:*** *Based on the calculation of these real numbers, Metamizole is more cost effective than ketorolac in postoperative fracture pain management. However, statistically the effectiveness and cost of the two therapies did not have a significant difference.*

Keywords: *Analgesic ; Postoperative ; Fracture ; Pain ; Cost Effectiveness Analysis*

INFO ARTIKEL

Riwayat Artikel:
Diterima: 3 Juni 2025
Disetujui: 10 Juli 2025
Tersedia secara online 20 Juli 2025

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INTRODUCTION

A fracture is a condition where there is a break or fracture in the bone. Fractures can occur due to strong physical trauma, such as accidents, falls, sports injuries, or due to medical conditions that reduce bone strength, such as osteoporosis or bone tumours. Based on Riset Kesehatan Dasar data in 2018, fracture-related cases in Indonesia were 5.5% of 92,976 injury cases in Indonesia. The prevalence of fracture patients is 6% of all fracture cases in Indonesia in East Java Province (Kemenkes RI, 2019).

Fractures can be classified in various forms, including open fractures (when the bone breaks through the skin) and closed fractures (when the bone breaks but does not break through the skin) (Noorisa et al., 2017). Fracture management can be done conservatively or operatively (surgery). The installation of casts and traction is a

conservation process while surgery on fractures by means of Open Reduction and Internal Fixation (ORIF), external fixation and bone graft is an operative process (Solomon et al., 2017). The main goal of fracture surgery is to reposition and stabilise the broken bone so that it can recover properly.

Surgery on fracture patients is carried out by making additional wounds, causing the intensity of the pain felt to be higher. The pain that appears in postoperative patients is acute pain, but pain that is not properly managed will develop into chronic pain and have long-term negative effects on pain sensitivity, immune function, neurophysiology, attitudes, and health care behaviour (Nasriati et al., 2016). In addition, from a financial perspective, untreated postoperative pain will increase the cost of patient care.

The use of analgesic drugs is one way to reduce pain in postoperative bone surgery patients and increase patient comfort. Several types of analgesics are commonly used in fracture surgery patients, including: Opioid analgesics (morphine, tramadol, oxycodone, and codeine), Non-opioid analgesics (paracetamol, ibuprofen, naproxen, metamizole and diclofenac), Local anaesthesia (injected around the area to be operated on), and nerve block (injection of anaesthetic or analgesic around the nerve) (Goel et al., 2023).

Opioid analgesics are the foundation of treatment for moderate-to-severe postsurgical pain and are among the most effective agents for the management of pain in many settings (Schumacher et al., 2015). However, opioids are associated with the potential risks of opioid-related adverse drug events (ORADEs), (such as respiratory and gastrointestinal related events) and abuse or dependence, which can significantly increase the cost of medical care (McAdam-Marx et al., 2010). Based on these considerations, non-opioid analgesic therapy is recommended. One of the most commonly used in Indonesia is metamizole (MTZ).

MTZ is a frequently used drug that has been introduced to the market for a long time. It is widely available in the market under various brands. It has analgesic, antipyretic, and spasmolytic effects. MTZ is a non-steroidal anti-inflammatory drug (NSAID) that has good gastrointestinal tolerability, so it is widely used worldwide. Ketorolac (KTL) is one of the NSAID class of drugs used as an alternative drug of choice in the management of pain and inflammation. KTL works by inhibiting the peripheral synthesis of prostaglandins through inhibition of COX-1 and COX-2, and is considered to have analgesic effects more

than anti-inflammatory effects (Andrade et al., 2016).

The number of alternatives and the selection of various drugs both in terms of brands and types of drugs cause pharmacology to be accompanied by economic aspects that play a role in the selection of drug use, namely by reviewing its cost. The number of analgesic drugs needed, it is better to review the drug costs of patients who use analgesic therapy and at Dr. Iskak Tulungagung Hospital, which is a hospital used as a referral hospital in East Java Province with the most fracture surgery cases that use analgesic drugs as pain therapy. Based on the background that has been described, it is necessary to conduct research on cost effectiveness analysis of the use of analgesic drug therapy in patients after closed fracture surgery at Dr. Iskak Hospital in 2023.

METHODE

This study is descriptive comparative research using a cross sectional design with retrospective data collection. The sample in this study was the medical records and financial records of BPJS class III closed fracture surgery patients who received MTZ or KTL as an analgesic postoperative pain management therapy at Dr. Iskak Hospital, for the period 2023 (January-December). Data were collected after authorization by the Medical Ethics Committee of the Hospital.

The inclusion criteria set were Medical Records and financing records of BPJS Class III patients undergoing closed fracture surgery who received post-operative analgesics of MTZ therapy (3x1 g) or KTL (3x30 mg) alone during the first 24 hours of inpatient care in Dr. Iskak Hospital, Tulungagung Regency. Exclusion criteria were medical records and financial records of patients who received therapy with analgesic replacement before 24 hours, patients who were forced to go home and died, incomplete data, missing data, or data that can't be read clearly.

The outcome of analgesic effectiveness was measure based on criteria for decreasing 2 of the Wong Baker Face Scale/WBFS (0-10 scale) after 24 hours of postoperative analgesic administration or decrease pain intensity to mild pain (1-3 scale). The pain intensity was recorded with WBFS before theraphy was given and at three times (6,12 and 24 hours) after the first administration of postoperative analgesics.

Cost estimation measured from the provider's perspective, in this case is the Dr.Iskak hospital. The types of costs considered are all costs directly related to health care at the hospital which include radiology examination costs, doctor visits,

procedure costs, analgesic costs, other drug costs, medical equipment costs, consumable medical materials, and treatment costs. Costs are measured in Indonesian rupiah (IDR) currency units. This research is short-term research so the researcher did not analyze the discount rate (0%).

RESULTS

This study examines the cost-effectiveness analysis of analgesic given to patients after closed fracture surgery in the inpatient installation at RSUD Dr. Iskak Tulungagung Regency in 2023. The population of medical records of patients after closed fracture surgery was 404 patients, while based on the inclusion criteria, a sample of 60 patients was observed, consisting of 29 patients who used MTZ and 31 patients who used KTL.

Table 1. Type of patient surgical procedure

No	Operation Type	n(%)
1.	ORIF	45 (75,00)
2.	ORIF + Skinflap	1 (1,67)
3.	ORIF + Bone graft	3 (5,00)
4.	Hemiarthroplasty	8 (13,32)
5.	Interlocking Nail	1 (1,67)
6.	Interlocking Nail + Bone graft	1 (1,67)
7.	Rescontruction	1 (1,67)

There are several types of pain scale effectiveness measurements in postoperative patients, including being declared effective if the pain scale decreases by 50% from baseline within 4-6 hours after drug administration (Cristancho et al., 2015), a decrease in the pain scale from severe-moderate and moderate-mild, (Hanley et al., 2006) and a decrease in the pain scale ≥2 on the NRS 0-10 so that the treatment effect is considered clinically important (Smith et al., 2020). In this study, the reference used for therapy was declared effective if there was a decrease in the pain scale ≥2 from baseline to 24 hours after administration of MTZ or KTL analgesic therapy.

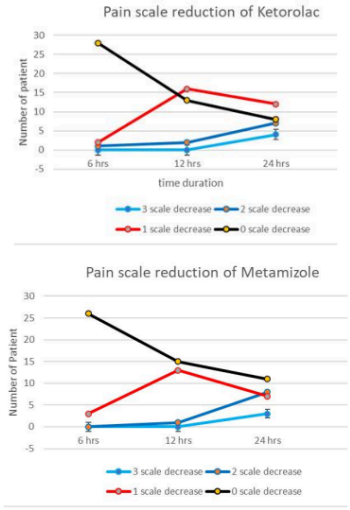

Figure 1. distribution of pain scale reduction based on time duration

The decrease in Wong-Baker Faces Pain Rating Scale (WBFS) scores was seen at three times, 6 hours, 12 hours, and 24 hours after analgesic therapy. The results of the observation of pain levels showed that MTZ and KTL therapy provided a lot of reduction in 24 hours after drug administration. Patients with

MTZ therapy showed effectiveness (≥2 scale reduction) of 37.93% (11 patients), while 7 patients showed a decrease of 1 scale and 11 patients did not even improve the pain scale (decrease of 0 scale). KTL therapy showed effectiveness (decrease in scale ≥2) by 35.48% (11 patients), while 12 patients showed a decrease of 1 scale and 8 patients did not even experience improvement in pain scale (decrease of 0 scale).

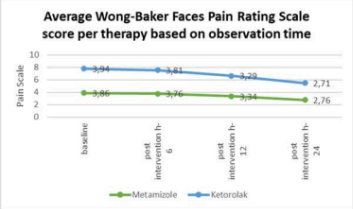

Figure 2. Distribution of Decreased Pain Intensity Based on Observation Time

The average total cost (C) of analgesic therapy in patients with closed fracture post-operative hospitalization at the dr. Iskak Hospital, Tulungagung Regency who used MTZ analgesics were 29 patients at IDR. 21,990,051 / patient. While patients who used KTL analgesics were 31 patients at IDR. 23,041,427 / patient. The total direct medical costs for both analgesic therapies obtained a p-value of 0.217 so that there was no difference between the two analgesic therapies, MTZ and KTL, but there was 1 component that was significantly different, namely the cost of analgesic drugs with a p-value of 0.000.

Table 2. Direct Medical Cost MTZ vs KTL

Direct Medical Cost	MTZ	KTL	*p-value*
Radiology Examination	511.106	546.129	0,180
Doctor visite cost	160.000	155.000	0,917
Procedure cost	6.872.375	6.950.163	0,763
Analgesic cost	18.360	7.525	0,000
Other drug cost	722.888	626.113	0,539
Medical devices and consumables materials	12.912.046	14.146.336	0,105
Treatment cost	793.276	610.161	0,387
Total	**21.990.051**	**23.041.427**	**0,217**

However, if referring to the unit price of analgesic therapy, each vial has a different price. The unit price of MTZ is IDR 4,930/vial while KTL is IDR 1,728/vial with a p-value of 0.317 (>0.05), then there is no significant difference in price between the two analgesic therapies when viewed from the statistical test. Regarding the cost of the services evaluated, in any type of economic evaluation the cost cannot be generalized for all hospitals, this is because the cost may vary from hospital to hospital. However, the cost that we recorded at Dr. Iskak Hospital Tulungagung can be compared with similar hospitals or at least hospitals in the same area (East Java Province).

The effectiveness of MTZ and KTL analgesic therapy can be seen in table

4 with the results of patients using MTZ who reached the theraphy target (decrease in WBFS ≥ 2 point) amounted to 11 out of 29 patients (37.93%) while in KTL analgesics that reached the theraphy target amounted to 11 patients out of 31 patients (35.48%). From the results obtained, a statistical test was carried out to determine whether the data obtained was normally distributed or not, using Shapiro-Wilk (sample < 50) with the results that the data was not normally distributed, namely the value of Sig. 0.000 (α <0.05), so a non-parametric test was performed using the Mann-Whitney Difference Test with the results of the Asymp. Sig. (2-tailed) was 0.845 (α> 0.05) so there was no significant difference between MTZ and KTL therapy.

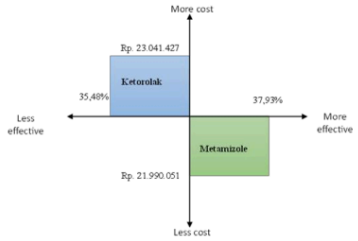

Figure 3. Cost Effectiveness Plane of Metamizole vs Ketorolac

Cost sensitivity analysis was only performed on the dominant therapy. In this study, the dominant therapy was MTZ. We tried to perform a one-way sensitivity analysis, done by changing the value of a variable within a possible range while keeping the value of the other variables constant. The variation of cost changes used was ±5%, the 5% variation was determined based on consideration of the average inflation rate in Indonesia in the current research year.

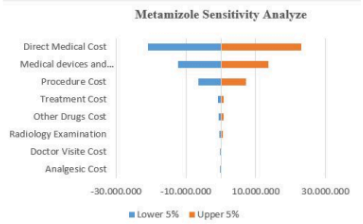

Figure 4. Tornado's diagram sensitivity analysis of Metamizole

DISCUSSION

The Open Reduction Internal Fixation (ORIF) was the most commonly applied type of surgery, recorded in 45 patients (75.00%). ORIF is a surgical procedure commonly used to treat closed fractures, where the skin is not torn and there is no open wound above the fracture site. ORIF is applied by reassembling the broken bone fragments and stabilising them to prevent unwanted movement, but ORIF surgery is not always the best option for all patients but also needs to consider the patient's condition (Grawe et al., 2012).

The degree of postoperative pain is influenced by the type of surgery performed as well as the severity of the fracture. Open surgeries such as ORIF and bone replacement surgery or surgical procedures that involve larger incisions

will lead to higher pain levels. However, the same surgical procedure does not guarantee that the patient will experience the same degree of pain.

MTZ is given at a dose of 3 x 1 gram. The usual dose of MTZ for adult patients is 500 mg - 1000 mg with a maximum dose in a day of 4000 mg. Side effects of MTZ are skin redness, itching, fever, increased blood pressure, dizziness, nausea, vomiting, digestive problems, sore throat, shortness of breath, rash and acute renal failure (Jasiecka et al., 2014).

KTL is given at a dose of 3 x 30 mg, the usual dose of KTL is 10-30 mg every 4-6 hours if necessary with a maximum daily dose of 90 mg. Side effects of KTL include allergic reactions, fever, chest pain spreading to the jaw or shoulder, shortness of breath, swollen legs, sudden numbness on one side of the body, high blood pressure, kidney problems, anaemia (low red blood cells), nausea, vomiting, diarrhoea, constipation, throat irritation, and rash (Mahmoodi et al., 2024).

In this study, there was no observation of the severity of post-surgical patients, on the one hand, the patient's pain threshold factor could be different. This is one of the characteristics of uncertainty, uncertainty will always exist in every pharmacoeconomic study, uncertainty is caused by, among others, the availability of inadequate clinical data, the long-term effects of a therapy to effects that may vary from individual to individual (Prasetyo, 2024).

The average pain scale observed at baseline in patients receiving MTZ was 3.86 (moderate pain), and the decrease in the pain scale after 24 hours was 2.76 (low pain) with a difference in decreasing 1.1 point. Observations in patients receiving KTL from a scale of 3.94 (moderate) to 2.71 (low) with a difference in decreasing 1.23 point. Contrary to (Manurung et al., 2023) finding, which showed the dominance of MTZ as a single analgesic with an average decrease in WBFS pain score of 2 points. KTL is in second place with an average decrease in WBFS pain score of 1.62 points.

In the results of the difference in decreasing the pain scale, KTL has a better difference than MTZ. However, the reduction in pain scale of these two therapies did not differ significantly. Our conclusion Similar to the findings (Oliveira et al., 2012) which showed no statistically significant difference in analgesia produced by KTL and MTZ.

We collected records of other drugs given to patients. There are records of the use of analgesics other than MTZ and KTL. Some analgesics such as Mefenamic acid, paracetamol, diclofenac sodium are given as discharge medication, while strong analgesics such as Morphine,

Dexketoprofen and Tramadol are given while patients are undergoing treatment in the hospital. These strong analgesics are given as replacement therapy when MTZ or KTL alone do not provide significant results after 24 hours. This also indicates the failure of MTZ or KTL in reducing postoperative pain in patients. In addition to having an impact on the outcome of therapy, the addition of other analgesics will certainly affect the cost of treatment.

The selection of the right analgesic is the main foundation in the management of postoperative pain therapy to improve the quality of life of patients. The American Society of Anesthesiologists recommends therapy to overcome postoperative pain such as NSAIDs, COXIBs, and/or acetaminophen for mild to moderate postoperative pain, and KTL for moderate to severe pain. For moderate to severe postoperative pain, it should be preceded by opioid analgesic therapy with or without NSAIDs (American Society of Anesthesiologists, 2012). NSAIDs are widely used for perioperative pain control but have little effect on surgical stress responses and organ dysfunction (Kehlet, 1999). On the other hand, it is well established that NSAIDs provide moderate postoperative analgesia and thereby an opioid-sparing effect of 20±30% (Power & Barratt, 1999). This may be of clinical importance as NSAIDs may reduce the incidence of opioid-related side-effects (respiratory depression, sedation, nausea and vomiting, ileus, urinary bladder dysfunction and possibly sleep disturbances).

Based on the results obtained in this study, MTZ therapy is called "dominant" and "cost-effective" compared to KTL due to its high effectiveness at a lower cost. With the ACER calculation results, it can be said that every 1% success of MTZ in reducing the pain scale of postoperative patients is equivalent to IDR. 579,754 and so is the ACER value of KTL.

Based on the tornado diagram, it is known that the cost component of medical devices & consumables materials is the cost component that is most sensitive to changes in the ACER value, followed by the cost component of the procedure, treatment costs, other drug costs, radiology costs, doctor's visit costs and analgesic costs.

This study has contain a number of limitations, among them we only observed the efficacy of MTZ and KTL, but did not observe how their safety and side effects. The data used in this study is retrospective data that is very likely to have incomplete data recording including confounding factors that affect the real-time condition of the patient. Another limitation is the non-specification of the type of fracture surgery procedure, allowing for varying

levels of pain felt depending on the individual's pain threshold. Another limitation is the lack of diversity in the types of fracture surgical procedures, allowing the level of pain experienced to vary depending on the individual's pain threshold.

CONSCLUSION

The findings of this study showed that MTZ is a drug with higher effectiveness (37.93%) than KTL (35.48%), with a total direct medical cost of MTZ of IDR. 21,990,051 and KTL IDR. 23,041,427. ACER value of MTZ IDR. 579,754 and KTL IDR. 649,420. Based on the calculation of these real numbers, MTZ is more cost effective than KTL in postoperative fracture pain management. However, statistically the effectiveness and cost of the two therapies did not have a significant difference.

Future research is expected to consider the side effects of drugs that occur as well as the long-term impact. Considering the low effectiveness value of both therapies, it is necessary to explore a more potent combination of therapies in postoperative pain management.

ACKNOWLEDGMENT

Thanks are given to the education and training department of Dr Iskak Hospital, and Faculty of Pharmachy, Institut Ilmu Kesehatan Bhakti Wiyata as funders for the implementation of this research.

CONFLICT OF INTEREST

B.Muzayanah work as pharmachist in Dr.Iskak Hospital. All author declared that there was no conflict of interest.

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