INDONESIAN JOURNAL OF ANESTHESIOLOGY AND REANIMATION
Volume 2 Number 2, July 2020 : 38-46

Original Article

# KETAMINE VERSUS TRAMADOL EFFECTIVENESS AS POSTOPERATIVE ORAL ANALGESICS ON PEDIATRIC PATIENTS AGE 5-10 YEARS IN ELECTIVE SURGERY AT DR. SOETOMO HOSPITAL SURABAYA

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## ABSTRACT

**Introduction:** The use of ketamine and tramadol as postoperative analgesics for pediatric are still relatively rare, especially orally administrated. As an analgesic, ketamine blocks the NMDA receptor, the main excitatory transmitter in CNS; whereas tramadol blocks serotonin and norepinephrine uptake, thus preventing pain transmission on the spinal cord. **Objective:** The aim of this study is to compare the effectiveness of oral ketamine and oral tramadol as analgesics for postoperative acute pain in children. **Method:** A double-blind randomized clinical trial was conducted at Dr. Soetomo Hospital. The hospital ethical committee had approved this study. The subject includes thirty children aged 5-10 years old who fulfilled the inclusion criteria. They were divided into either ketamine groups or the tramadol group, in which each group consisting of fifteen patients. The regimen dosage that been given was 2mg/kg tramadol and ketamine as postoperative oral analgesics in the form of simple syrup. The FLACC table was used to evaluate pain score before and after administration of drugs (30-minutes, 1-hour, 2-hours, 3-hours, 4-hours, and at discharge from the recovery room). **Result and Discussion:** Based on the quantitative parameter of the FLACC (scale 0-10), there was a significant difference ($p<0.05$) between the first-hour postoperative administration and patient discharge from the recovery room. The patient of ketamine group had far lower FLACC value compared to the tramadol group. Rescue analgesics in the form of intravenous fentanyl were given to one patient (6.7%) in the ketamine group and four patients (26.7%) in the tramadol group. **Conclusion:** Ketamine proved to be a better and more effective postoperative oral analgesic compared to tramadol in this study.

**Keywords:** Ketamine; Oral Analgesic; Pediatric; Postoperative Pain; Tramadol

## ABSTRAK

**Pendahuluan:** Penggunaan ketamine dan tramadol sebagai analgesik pasca operasi untuk pediatrik masih relatif jarang, terutama pemberian secara oral. Sebagai analgesik, ketamine bekerja dengan menghambat reseptor NMDA, pemancar rangsang utama dalam SSP; Sedangkan tramadol bekerja dengan menghambat penyerapan serotonin dan norepinefrin, sehingga menghambat nyeri di sumsum tulang belakang. **Tujuan:** Tujuan dari studi ini adalah untuk membandingkan efektivitas oral ketamine dan tramadol sebagai analgesik untuk nyeri akut pasca operasi pada pasien anak. Metode yang digunakan adalah studi *double-blind randomized clinical trial* dilakukan di rumah sakit Dr. Soetomo. Studi ini telah disetujui oleh komite etika rumah sakit. Sampel studi berjumlah tiga puluh anak berusia 5-10 tahun setelah kriteria inklusi. Mereka dibagi menjadi salah satu kelompok ketamin atau kelompok tramadol, yang masing-masing kelompok yang terdiri dari lima belas pasien. Dosis obat yang diberikan adalah 2mg/kg baik tramadol maupun ketamine sebagai analgesik oral pasca operasi dalam bentuk sirup sederhana. Tabel FLACC digunakan untuk mengevaluasi nyeri sebelum dan sesudah pemberian obat (30-menit, 1 jam, 2-jam, 3-jam, 4-jam, dan pada saat keluar dari ruang pemulihan). **Hasil dan Pembahasan:** Berdasarkan parameter kuantitatif dari FLACC (skala 0-10), perbedaan yang signifikan ($p < 0.05$) ditemukan antara jam pertama setelah pemberian obat dan saat pasien dari keluar dari ruang pemulihan. Pasien dalam kelompok ketamin memiliki nilai FLACC jauh lebih rendah dibandingkan dengan kelompok tramadol. Obat analgesik dalam bentuk fentanyl intravena diberikan kepada satu pasien (6,7%) dalam kelompok ketamin dan empat pasien (26,7%)



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dalam kelompok tramadol. **Kesimpulan:** Ketamin terbukti lebih baik dan lebih efektif sebagai analgesik oral pasca operasi dibandingkan dengan tramadol dalam studi ini.

**Kata kunci:** Ketamin; Analgetik Oral; Pediatric; Nyeri Paska Operasi; Tramadol

**Article info:** Received June 9th 2020, Received in revised from June 16th 2020, Accepted July 21st 2020

## INTRODUCTION

Acute pain, in general, is considered as an unpleasant stimulus and experience in children's population as result from postoperative, their illness, wound, or medical procedures that need to be done. Fourty percents of pediatric surgical patients, from a survey from 20 years ago, experienced moderate or severe postoperative pain and 75% of them had insufficient analgesia. (1) Pain in children is usually under treatment because of some reasons: worries the risk of opioid (respiratory depression) and the unproven safety and efficacy of the analgesics. A dogma suggested that the children do not feel pain, it is dangerous giving powerful analgesia in children and it will cause the children on the risk of addiction. (2) In highly developed health care system countries, several studies conducted that even in the first decade of the 21st century, postoperative pain for children was not managed well in most of the patients. For example, an epidemiological study in the Czech Republic (2006), 18.5% of patients complained about pain to be the worst experience in postoperative and 36% of them complained after surgery. In 2014, the study was repeated at the same place (the results in 2006 have not been published yet) and revealed that less than 20% of patients suffered from severe pain, none of them reported excruciating pain and 6 hours after surgery the incidence of severe pain fell below 10% (3). In Indonesia, there is still no specific study about postoperative pain in children.

The selection of analgesics and the role of administration, especially for young children, which give the most beneficial regarding the effectiveness and continuance, are still to be examined further. Therefore, this study is subjected to find the efficacy of the oral drug in treating postoperative pain in children. Ketamine and Tramadol are analgesics that often used for the treatment of postoperative pain in adult patients (4)(5). Usage in children as postoperative oral analgesics, especially on per-oral route is still rare (6).

Ketamine is a chemically stable non-opioid drug with analgesic effect at low doses (7). Ketamine gives analgesia by antagonism of the N-Methyl-D-Aspartate (NMDA) receptor in the Central Nervous System (CNS). Intravenous (IV) ketamine can provide postoperative analgesia in many clinical trials, especially to reduce opioid consumption. However, IV administration has limitations, such as ketamine is considered as an anesthetic drug and should be administered in the monitored location. Therefore, using oral ketamine for the management of acute pain for postoperative surgery or after trauma is highly desirable (7). In research conducted by Saied et. Al showed that oral ketamine at a dose of 1-2 mg kg-1 administrated in 8-hour period, can be effective analgesics not that occurrence of emergence (8)(9).

Tramadol is a medium potency analgesic drug. Tramadol is a unique drug because of its two mechanisms of action. First, its metabolites have a weak affinity for mu-opioid receptors and no affinity for delta or kappa receptors. The second mechanism is the ability to inhibit the reuptake of the norepinephrine and serotonin

neurotransmitters. Tramadol provides less sedation compared to other opioids with minimal effects on respiration, which is an advantage over another opioid and can be used for postoperative pain relief in children. A study for oral tramadol in children showed a dose-ranging effect, with patients receiving 2 mg kg-1 dose, requiring 42% less rescue analgesia than patients who received 1 mg kg-1 dose (10). Tramadol also has a different advantage because of its lack of inhibition on prostaglandin synthesis over NSAIDs. Oral tramadol has the same analgesic efficacy as oral sodium diclofenac for 11 years and older patients post-tonsillectomy pain, without the side effects of NSAIDs (10). It is best used as an analgesic supplement to treat mild to moderate pain because of its opioid-sparing effect and low incidence of side effects.

The author has conducted preliminary research on the use of both drugs intravenously. The research is in collaboration with Kanudjoso Djatiwibowo Hospital in Balikpapan and Interplast Australia-New Zealand. It was held in May 2012, from 84 patients with congenital lip cleft abnormalities (> 6 months) undergoing surgery and administered ketamine and tramadol intravenously 10 minutes before surgery was completed, only 3.57% (3 people) were guided (emergence) after the operation in the recovery room and 2.38% (2 people) who experienced vomiting after surgery so that requires additional therapy in the ward.

Therefore, this study is subjected to compare the effectiveness of oral ketamine and oral tramadol as analgesics for acute postoperative pain in children. The subject in this study were children aged 5-10 years old who underwent surgery with moderate to severe pain levels. Children age 5-10 years old can express pain response more accurately, and also can memorize well, so if postoperative pain is not be handled well, it will impact their psychological development. Drugs choice for this study are chosen because ketamine and tramadol have a good analgesic effect, easy to get and cheap; also given orally to reduce the children's fear of injection.

## MATERIAL AND METHOD

This double-blinded clinical trial was conducted in 2014 on 30 children aged 5-10 years old who were referred to Dr. Soetomo Hospital in Surabaya. Inclusion criteria were: being aged 5-10 years old, meeting ASA I or II criteria and candidate for elective surgery with general anesthesia. Exclusion criteria were: children who had organ failure, septic, increased intracranial pressure (ICP), history of using MAO inhibitor drugs, neuroleptics or other sedative, seizures, and they who need fasting after surgery. The ethics committee of the Dr. Soetomo Hospital approved this study. After informed consent was obtained from the parents, patients who met inclusion criteria were divided randomly into two groups: group A (ketamine 2 mg kg-1 orally) and group B (tramadol 2 mg kg-1 orally). Hospital pharmacist, who was not involved in patient management, made both study drugs into simple syrup coded bottle A and B with the same dosage 10 mg ml-1 and given to the patients by responsible anesthetists who were blinded study group allocations. Before premedication was given, the pain scale was recorded with FLACC (Table 1) and WBFS (Figure 1). Midazolam 0.05-0.1 mg kg-1 and Atropine Sulphate 0.01 mg kg-1 intravenous were used as premedication. General anesthesia was induced with fentanyl 2 µg kg-1 followed by propofol 2 mg kg-1 and atracurium 0.5 mg kg-1. Morphine 0.05-0.1 mg kg-1 intravenous was given as analgesia during surgery, maintenance with Isoflurane, and O2. If the surgery was more than 3 hours, additional fentanyl 0.5 - 1µg kg-1 can be



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administered when necessary. Standard monitoring was used throughout anesthesia. 30 minutes before surgery was ended, NSAID 10 mg kg-1 intravenous was given.

In recovery room patients were given drug A or B according to randomization. After that, FLACC and WBFS were used to score the pain intensity in 30-minutes, 1-hour, 2-hours, 3-hours, 4-hours, and when the patients were discharged from the recovery room. If the patients experienced severe pain, they were given the following analgesics according to the pain measurement: NSAID 15 mg kg-1 iv for FLACC 4-6 or WBFS 2-3; and fentanyl 0.1 µg kg-1 iv for FLACC 7-10 or WBFS 4-5.

Side effects such as emergence, nausea, and vomiting were recorded after the intervention. If the patients were emergence, midazolam 0.1 mg kg-1 was given. If nausea and vomiting occurred, metoclopramide 0.1 mg kg-1 iv and dexamethasone 0.1 mg kg-1 iv were given.

Power calculation had indicated that 15 children would be required per group to detect a difference of FLACC and WBFS with a power of 84% and $\alpha = 0.05$. SPSS 12 software was used for data analysis. To compare two groups, a T-two free sample test was used. A P-value less than 0.05 was considered as a significant level.

**Table 1.** FLACC (Face, Legs, Activity, Consolability) Scale

| Category | Scoring | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| ***Face*** | *No particular expression or smile* | *Occasional grimace or frown, withdrawn disinterested* | *Frequent to constant quivering chin, clenched jaw* |
| ***Legs activity*** | *Normal position or relaxed* | *Uneasy, restless, tense* | *Kicking or legs were drawn up* |
| ***Cry*** | *No cry (awake or asleep)* | *Moans or whimpers; occasional complaint* | *Crying steadily, screams or sobs, frequent* |
| ***Consolability*** | *Content, relaxed* | *Reassured by occasional touching, hugging or being talked to distractible* | *Difficult to console or comfort* |


**Figure 1.** Wong-Baker Faces Pain Scale



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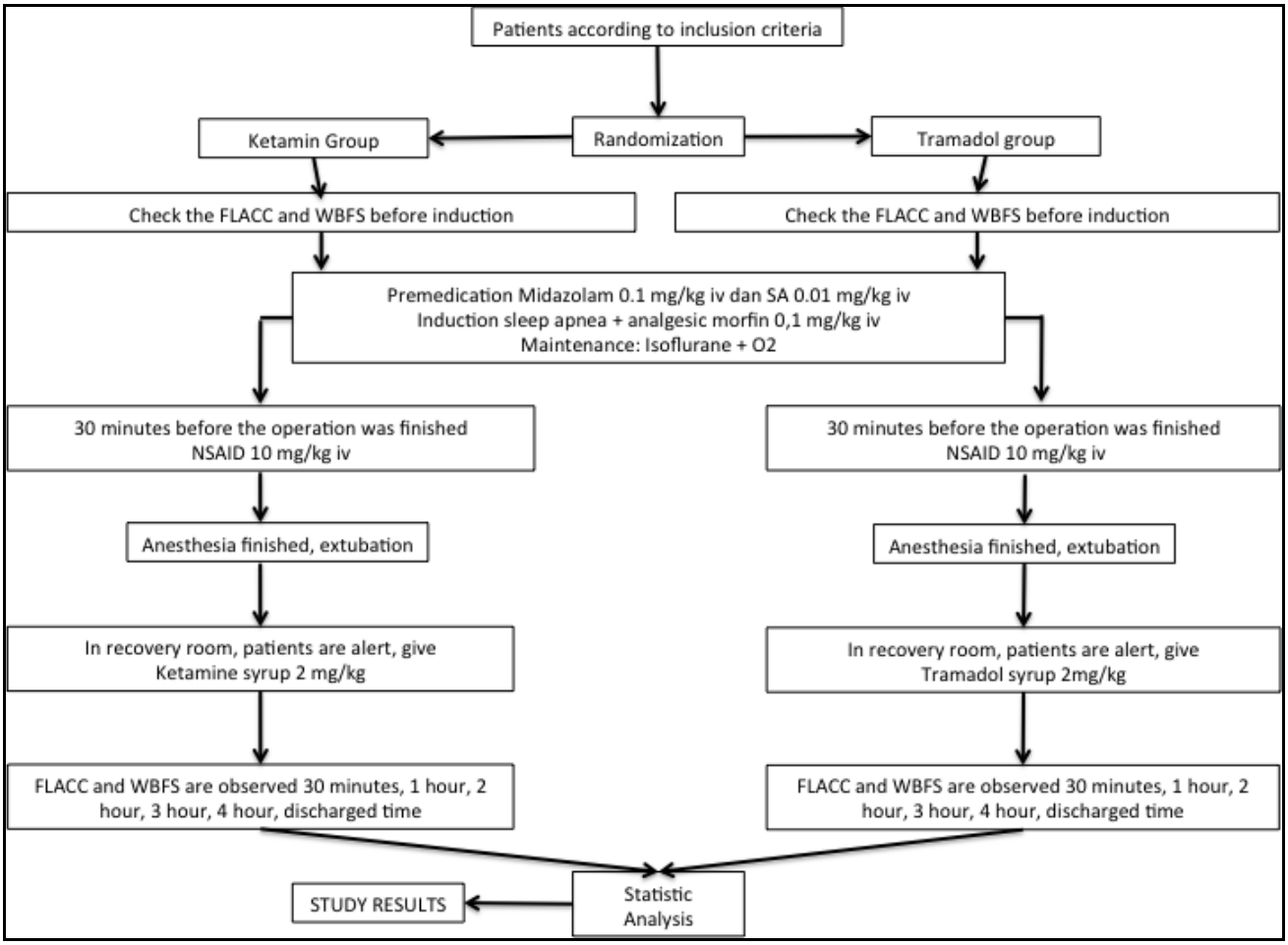


**Figure 2.** Method scheme

## RESULT AND DISCUSSION

There were no significant differences among the groups for sex distribution, age, body weight, height, ASA status, and duration of surgery (Table 2).

A Significant difference was found starting from 1-hour post-intervention until the patients discharged from the recovery room. FLACC score in the ketamine group was significantly lower than the tramadol group (p = 0.04) (Figure 3), while there was no significant difference in WBFS score (Figures 4 and 5). In pain assessment with the WBFS parameter at 2-hour post-intervention cannot be analyzed statistically due to homogeneous samples (all samples included in no-pain scale).

**Table 2.** Comparison of demographic characteristic between groups

| | Group A Ketamine | Group B Tramadol |
|---|---|---|
| **Age** | 7.73±1.86 | 7.26±1.79 |
| **Sex (Female / Male)** | 9 / 6 | 6 / 9 |
| **Weight (kg)** | 26.73±11.34 | 25.93±10.29 |
| **Height (cm)** | 118.80±18.46 | 113.8±13.18 |
| **ASA status (I / II)** | 7 / 8 | 9 / 6 |
| **Duration of surgery (h)** | 2.36±1.61 | 2.63±1.49 |

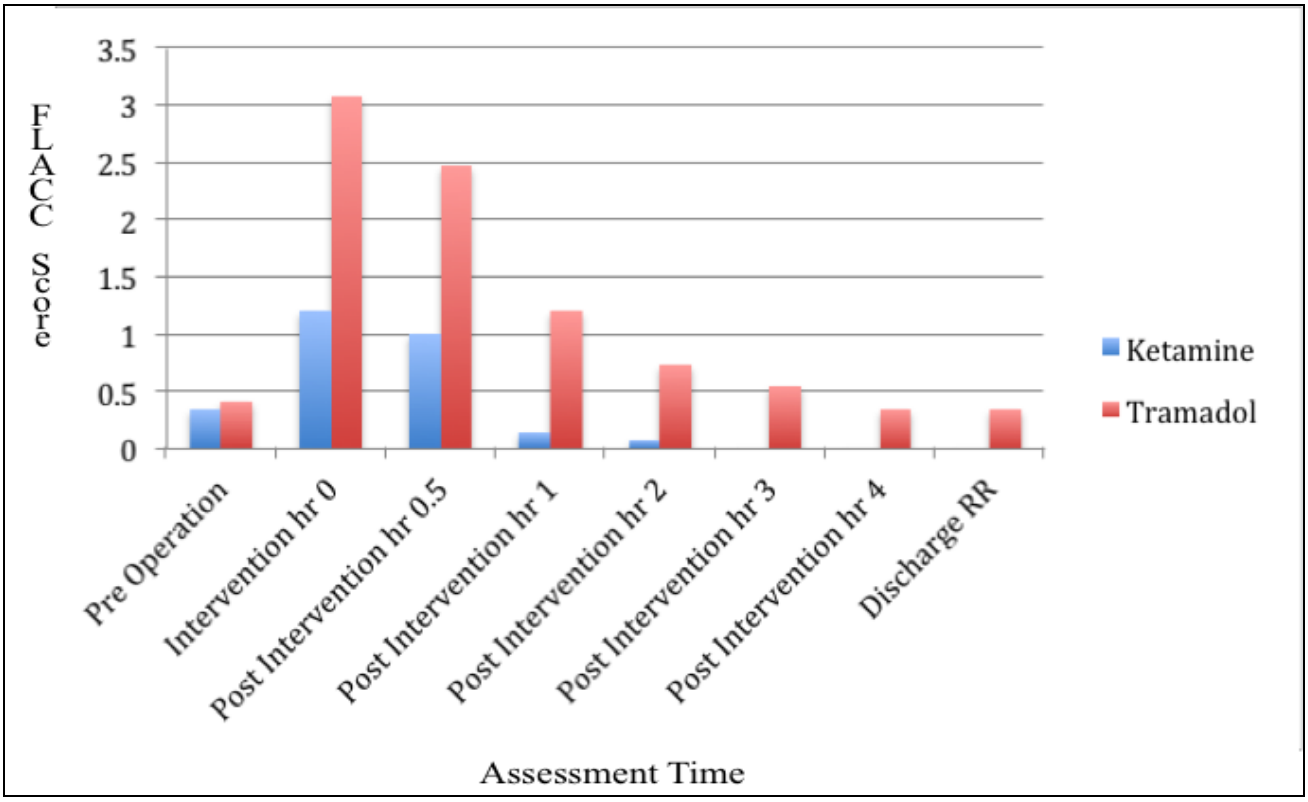


**Figure 3.** FLACC Score During The Intervention of Both Groups

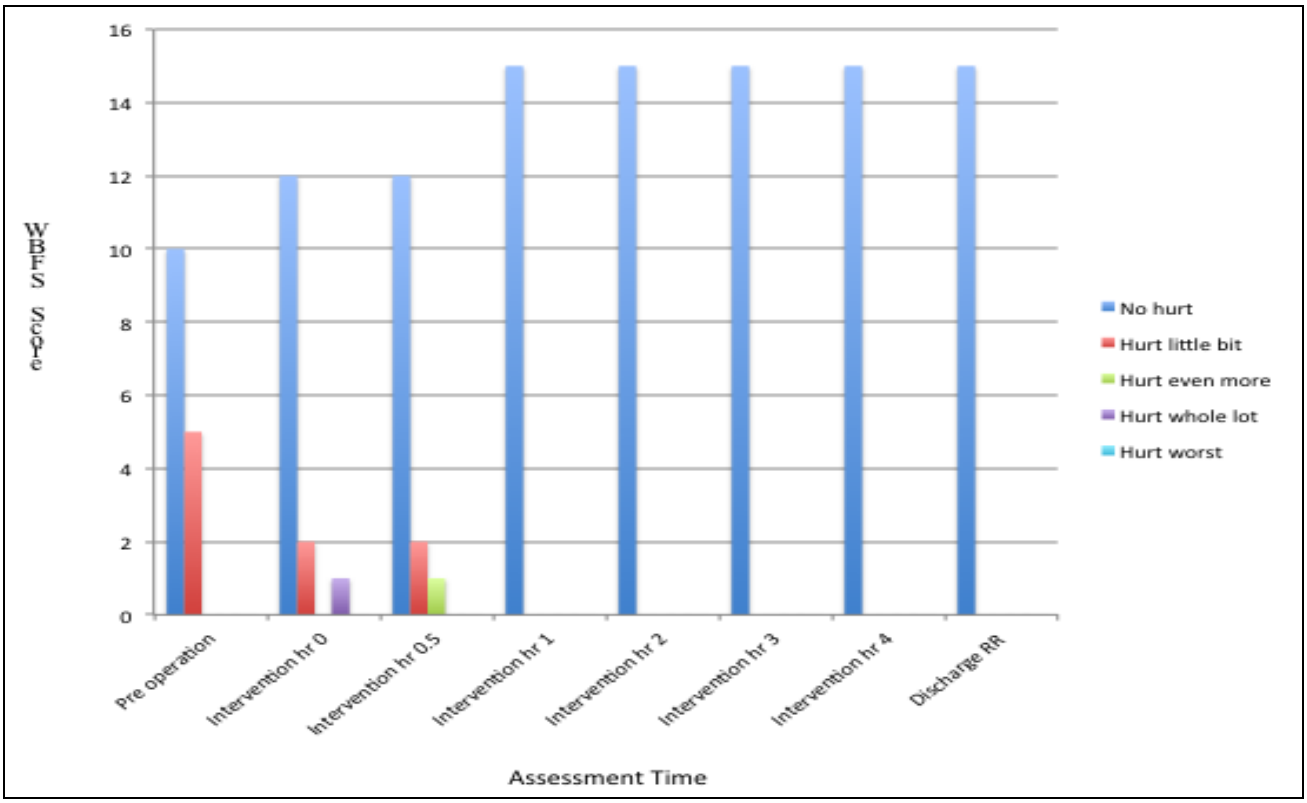


**Figure 4.** WBFS Score During The Intervention in the Ketamine Group

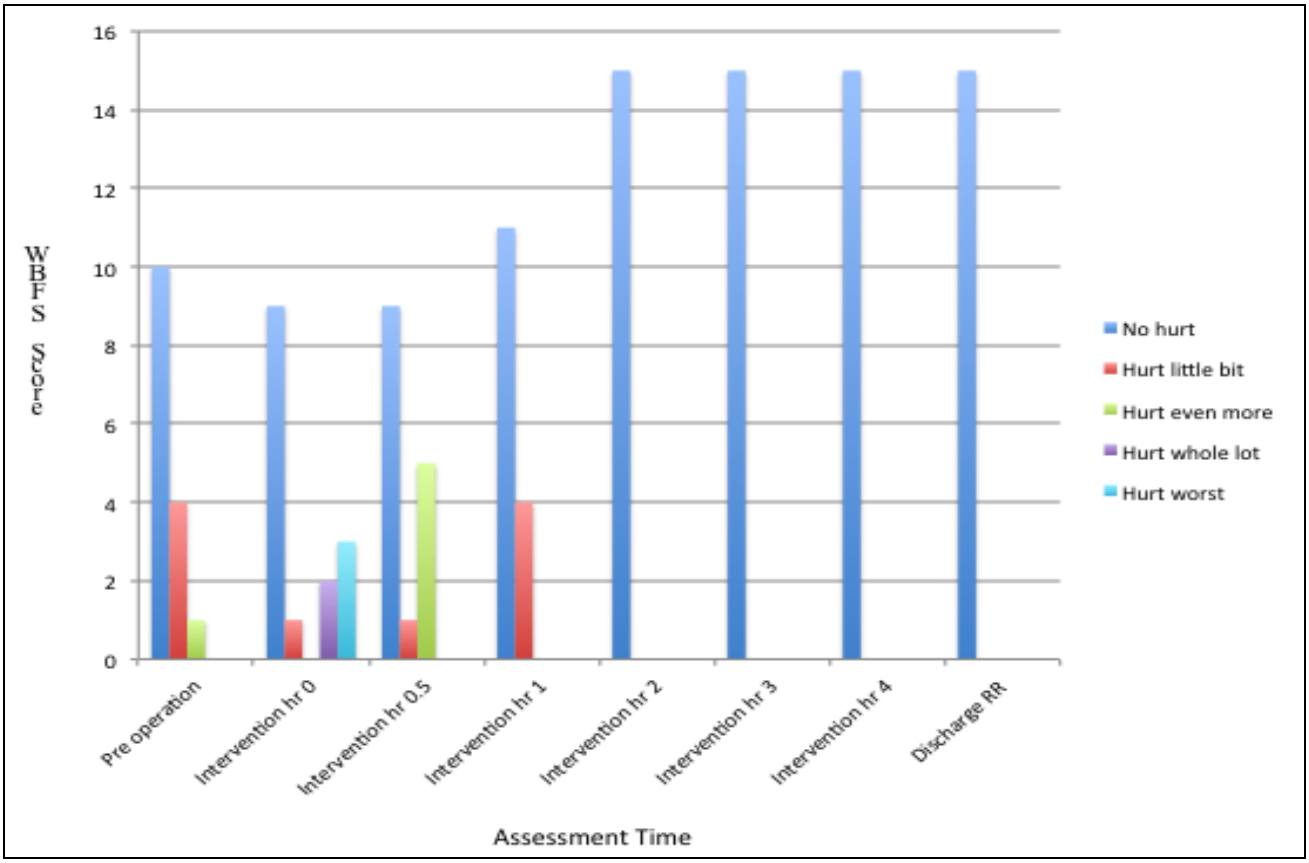


**Figure 5**. WBFS Score During The Intervention in Tramadol Group

Rescue analgesics in form intravenous fentanyl were given to one patient (6.7%) in the ketamine group and 4 patients (26.7%) in the tramadol group with $p > 0.05$. One patient (6.7%) in the ketamine group experienced vomiting as a drug side effect, whereas 2 patients (13.3%) in the tramadol group experienced nausea and 3 patients (20%) had vomiting with no significant differences.

Generally, oral analgesia was well accepted and comfortable for both parents and children. The measuring instruments used are WBFS Scale and FLACC Scale, as they are simple, have been widely recognized and used. Pain in children of kindergarten age (pre-schoolers) and school-age is most precisely rated with behavioral observation (11). The use of FLACC is felt to be the most appropriate method of pain assessment for children aged 5-10 years, while the use of WBFS depends on the subjectivity of the child, where the surrounding environment is very influential. Therefore, in this study the results of a pain assessment with WBFS were more homogeneous and cannot be assessed statistically or that there was no meaningful difference between the two groups.

The findings of this study showed that oral ketamine was better and more effective for postoperative pain in children compared to tramadol. Based on the FLACC parameter numerically (0-10 scale), there was no difference in FLACC pre-operation scale before surgery, 0-hour treatment, and 30 minutes after treatment. But there was a significant difference after 1 hour of intervention until the patient discharged from the recovery room ($p=0.04$). On 1 hour after intervention in the ketamine group had a lower FLACC scale compared to the tramadol group. As for the parameters of WBFS was not obtained meaningful differences between the two groups because the scale on WBFS was ordinal, so in this study which hadonly a small



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number of samples, the p-value was not significant. In addition to the pain assessment with the parameters of WBFS in 2 hours after intervention until the patient discharged from the recovery room could not be statistically analyzed because of a homogeneous sample (all research samples included in the scale were no pain).

In this study, the number of subjects that need rescue analgesics in the ketamine group was less than in the tramadol group. This can be caused by the difference in the pain level of the patient during surgery. Pain is complex, it depends on the family factors; how mothers educate the children in dealing with pain, culture absorbed in the child, newly known environment, and previous pain experience (3).

Based on this study, 1 patient in the ketamine group experienced a side effect of vomiting, while in the tramadol group obtained 2 patients who had nausea, and 3 patients experienced vomiting (Table 3). It is said in literature that both ketamine and tramadol can cause nausea and vomiting, as both drugs also work on opioid receptors (6). For ketamine, there are rare side effects of nausea and vomiting, since the primary target of the ketamine molecule is NMDA receptors. Ketamine inhibits these receptors thus lowering neuronal activity and can lead to anesthetic conditions (4). Also, the dose used for the analysis is not the amount of dose used for sedation and anesthesia, so the side effect is expected to be minimal. Oral tramadol can be absorbable quickly and has considerable bioavailability after the initial dose. Because after administration both intravenously and orally will achieve the highest concentration in a very fast time, so this causes nausea and vomiting to occur (6).

**Table 3.** Comparison of Side Effect Between Groups

| Side Effects | Group A Ketamine n = 15 (100%) | Group B Tramadol n = 15 (100%) |
|---|---|---|
| **No Side Effect** | 14 (93.3%) | 10 (66.7%) |
| **Nausea** | 0 (0%) | 2 (13.3%) |
| **Vomiting** | 1 (6.7%) | 3 (20%) |

## CONCLUSION

Oral ketamine provided more effective for postoperative pain in children with minimum side effects compared to oral tramadol. The majority of patients in this group had less pain scores in the postoperative period in the recovery room. Further studies in bigger numbers may be needed to conclude whether oral analgesics are better to avoid trauma from injection in children.

### Conflict of Interest

There is no conflict of interest in this study.

## REFERENCES

1. Lönnqvist PA, Morton NS. Postoperative analgesia in infants and children. *Br J Anaesth*. 2005;95(1):59–68.
2. Anaesth IJ, Gehdoo RP. Post-operative pain management in paediatric patients. *Indian J Anaesth*. 2004;48(5):406.
3. Meserve JR, Sager SL. Management of postoperative pain in children. *Essent Clin Anesth Rev Keywords, Quest Answers Boards*. 2015;417–9.
4. Bell RF, Kalso EA. Ketamine for pain management. *Schmerz*. 2019;3:1–8.
5. Fortenberry M, Crowder J, So TY. The use of codeine and tramadol in the pediatric population-what is the verdict now? *J Pediatr Health Care* [Internet]. 2019;33(1):117–23. Available from: https://doi.org/10.1016/j.pedhc.2018.04.016

6. Schnabel A, Reichl SU, Meyer-Frießem C, Zahn PK, Pogatzki-Zahn E. Tramadol for postoperative pain treatment in children. *Cochrane Database Syst Rev*. 2015;2015(3).
7. Buvanendran A, Kroin JS, Rajagopal A, Robison SJ, Moric M, Tuman KJ. Oral ketamine for acute pain management after amputation surgery. *Pain Med* (United States). 2018;19(6):1265–70.
8. Blonk MI, Koder BG, Bemt PMLA va. den, Huygen FJPM. Use of oral ketamine in chronic pain management: A review. *Eur J Pain*. 2010;14(5):466–72.
9. Norouzi A, Jafari A. Peritonsillar infiltration of ketamine in pain reduction after tonsillectomy : a Randomized Clinical Trial. 2015;23(Md).
10. Greco CD. Acute pain management in children. *Ital J Pediatr*. 2002;28(2):105–11.
11. Beltramini A, Milojevic K, Pateron D. Pain assessment in newborns, infants, and children. *Pediatr Ann*. 2017;46(10):e387–95.