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Original Article

# Effectiveness of Combination Intravenous Ibuprofen and Paracetamol on the Quality of Analgesia after a Third Molar Odontectomy – A Comparative Study

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**ABSTRACT**

**Introduction:** Odontectomy is a surgical extraction procedure performed to remove an impacted tooth, which often leads to local inflammation and postoperative complications. Interleukin 6 (IL-6) is closely associated with the pathophysiology of inflammation and pain. Ibuprofen and paracetamol act on different pain stages, strengthening the pain processing barrier. This study aims to assess the effectiveness of a combination of intravenous ibuprofen and paracetamol in comparison to intravenous paracetamol alone on pain intensity and IL-6 levels after a third molar odontectomy.
**Methods:** This comparative clinical study involved 38 patients undergoing odontectomy for third molars, who were divided into two groups of postoperative analgesics. Group A received intravenous ibuprofen (400 mg) and intravenous paracetamol (1,000 mg), while Group B received intravenous paracetamol (1,000 mg). Pain scores were evaluated using Visual Analog Scale (VAS), and IL-6 levels were assessed before the surgery and 24 hours after the procedure.
**Results:** The average pain score was lower in the combination group, even though there was no statistically significant difference in pain levels between the combination group and the paracetamol group ($P > 0.05$). VAS scores increased two hours following surgery (Group A = 22, Group B = 32) before decreasing eight hours later (Group A = 19, Group B = 22). The IL-6 levels significantly differed between the group receiving intravenous ibuprofen and paracetamol and the group receiving intravenous paracetamol alone ($P < 0.05$).
**Conclusion:** For controlling inflammation and pain following a third molar odontectomy, the combination of intravenous ibuprofen and paracetamol demonstrated superior analgesic efficacy compared to intravenous paracetamol alone. It represents the most recent choice for managing postoperative pain and inflammation in the oral and maxillofacial region.

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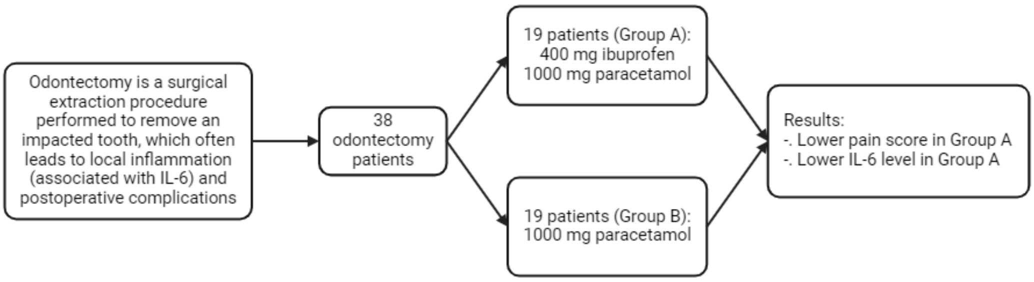
**GRAPHICALABSTRACT**




## Introduction

An impacted tooth refers to a tooth's partial or complete failure to erupt into its normal position. The surgical procedure known as odontectomy is employed to extract impacted teeth. Odontectomy is the most common type of oral and maxillofacial surgery [1-3]. Painful inflammation is experienced by over a third of postoperative patients, and the severity of pain can vary from mild to severe following an odontectomy. The level of pain increases proportionally with the number of teeth removed during the odontectomy procedure, eventually reaching moderate to severe levels. Pain ranges from mild to severe for 40% and 60% of patients [4]. The cyclooxygenase (COX) pathway is activated, which results in a rise in prostaglandin levels at the site of injury, resulting in these clinical signs and symptoms of local inflammation [5-7]. The most common postoperative complications are edema, pain, and trismus [1, 8]. Proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6) are associated with the pathophysiology of pain and inflammation [1]. IL-6 is one of the earliest known cytokines; it controls and stimulates the synthesis of acute-phase proteins by hepatocytes in response to painful stimuli [9, 10]. IL-6 levels typically rise within 1-3 hours following surgical inflammation, peak between 4 and 24 hours later, remain elevated for 48-72 hours, and continue to increase for up to 10 days. It also serves as a marker that best represents the severity of tissue injury. The intensity level of IL-6 rises with surgical trauma [11-13]. Multimodal analgesia is recommended in guidelines for treating acute pain because it can increase analgesia and achieve benefits in low dosage, potentially reducing the side effects risk [3, 9, 14]. Multimodal analgesia uses several pharmacological analgesic drugs that target different receptors along pathways [15-19]. Multimodal analgesia may reduce postoperative pain intensity, decrease hospital stays, and reduce the likelihood of developing persistent postoperative pain [20-22]. The primary effects of paracetamol include the inhibition of prostaglandins and central and peripheral cyclooxygenase enzymes. Ibuprofen primarily affects the transduction stage by inhibiting the production of prostaglandins through cyclooxygenase and other inflammatory mediators. This impact makes pain-processing barriers more potent than they would be after a single use [4]. Research conducted by Atkinson *et al.* in New Zealand, involving 159 patients treated with a combination of paracetamol and ibuprofen at various doses, compared to a placebo, demonstrated that all doses of the analgesic combination had a more potent analgesic effect than a single analgesic [23]. This finding is consistent with Daniels' research, which revealed that the ibuprofen/paracetamol combination produced significantly superior analgesic effects compared to ibuprofen or paracetamol alone in patients experiencing severe postoperative pain following an impacted third molar odontectomy [24].



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Recent studies have focused on the use of intravenous ibuprofen to alleviate pain after odontectomy. However, there is no consensus regarding its clinical application [2]. Tablet formulations are less efficient than intravenous ones due to their longer time to reach peak plasma concentrations [3]. According to a comprehensive study, the combination of ibuprofen 400 mg and paracetamol 1,000 mg has a Number Needed to Treat (NNT) of 1.5 to achieve a 50% or greater reduction in postoperative pain intensity [21]. This study aims to compare the reduction in pain intensity and IL-6 levels between multimodal analgesics (intravenous ibuprofen and paracetamol) and a single analgesic (intravenous paracetamol) in post-odontectomy patients.

## Materials and Methods

This study constituted a comparative clinical study. Ethical approval for this study was obtained from the ethical committee health research, Unhas Dental Hospital (Approval No.: 0102/PL.09/KEPK FKG-RSGM UNHAS/2022, dated July 27$^{th}$, 2022). All procedures of this study adhered to the ethical principles outlined in the 2013 revision of the 1964 Declaration of Helsinki.

### *Sample*

A total of thirty-eight patients who sought treatment at the Oral and Maxillofacial Department of Unhas Dental Hospital and Hasanuddin University Hospital from July to October 2022 and exhibited third molar impactions categorized as medium to difficult according to Pederson's classification were included in this study extracted third molar performed by one dentist. Eligible patients were between 18 and 45 years old, possessed class I or II physical conditions as per the American Society of Anesthesiologists (ASA) criteria, and expressed a willingness to participate in the study. Exclusion criteria encompassed individuals who had taken NSAIDs within 24 hours before surgery, had a Body Mass Index (BMI) exceeding 30, reported allergies to the drugs under investigation, had chronic pain conditions, presented with active third molar infections characterized by swelling, trismus, or purulent discharge, or had tumors surrounding the impacted third molars.

Prior to the surgical procedure, the participants were informed about the research methodology, and written informed consent was obtained from each of them. A preoperative blood sample of up to 1 ml was collected to measure IL-6 levels, and pain assessment was carried out using the Visual Analog Scale (VAS) pain scale rulers, ranging from 0 to 100 mm. To quantify IL-6 levels in serum, the Enzyme-Linked Immunosorbent Assay method was employed, utilizing the Quantikine HS Human IL-6 Immunoassay, and readings were taken using the ELISA Reader Organon 680 (Biorad) at a wavelength of 640 or 690 nm.

A one-hour surgical procedure was performed, involving the removal of three to four impacted third molars, under general anesthesia. Two treatment groups were randomly assigned to the study sample: Group A, which received IV ibuprofen 400 mg (Peinlos) in combination with IV paracetamol 1,000 mg (Paracetamol; Quantum Laboratories), and Group B, which received IV paracetamol 1,000 mg (Paracetamol; Quantum Laboratories) immediately after the completion of the operation. VAS scores were reassessed at 2, 8, 16, and 24 hours following the surgery. In addition, IL-6 levels were measured 24 hours post-surgery.

The VAS values were categorized into four groups: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm) [25]. The duration of hospitalization was set at three days. The first day was designated for surgical preparation, the second day for the surgical procedure, and the third day for postoperative care. Afterwards, patients continued as outpatients.

### *Data processing*

Data processing was conducted utilizing SPSS version 27. To assess the normality of the data distribution, the Kolmogorov-Smirnov test was employed. If the data distribution was found to be normal, a parametric Independent Sample T-test was performed. In contrast, if the data



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distribution was non-normal, the Mann-Whitney and Wilcoxon non-parametric tests were employed. Significance was considered at a level of *P < 0.05*. The processed data was presented in the form of tables and diagrams.

## Results and Discussion

The study involved 38 participants, with an average age of 22 years in group A and 25 years in group B. There are 19 male and 19 female participants distributed between 2 groups. The average BMI was 23 in group A and 22 in group B, as presented in Tables 1 and 2. Tables 1 and 2 inidcate no statistically significant differences between groups A and B concerning gender, age, BMI, or the number of teeth removed (*P* > 0.05). In other words, both groups can be considered homogeneous.

The mean VAS scores for group A increased after 2 hours post-surgery and decreased at 8, 16, and 24 hours post-surgery. Statistically significant differences (*P* < 0.05) were observed in pain scores (VAS) at the preoperative assessment and at 2, 8, 16, and 24 hours after surgery.

Group B exhibited similar trends (Table 3). However, there were no significant differences in pain scores (VAS) between the two groups at 2, 8, 16, and 24 hours after surgery (*P > 0.05*) (Table 4, 5, and Figure 1).

**Table 1:** Sex distribution in the two groups

| Sex | Group A | | Group B | | Total | | *P*-value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | 0.194 |
| Male | 12 | 63.2 % | 7 | 36.8 % | 19 | 50.0 % | |
| Female | 7 | 36.8 % | 12 | 63.2 % | 19 | 50.0 % | |
| Total | 19 | 19 | 19 | 100 % | 38 | 100 % | |

*Note: The chi-square test was employed for analysis, and statistical significance was considered at P< 0.05*

**Table 2:** Distribution in the two groups

| Characteristic | Mean ± SD | | *P*-value |
|---|---|---|---|
| | Group A (n = 19) | Group B (n = 19) | |
| Age | 22.16 ± 3.64 | 25.21 ± 6.19 | 0.113** |
| BMI | 23.32 ± 3.37 | 22.98 ± 3.03 | 0.752* |
| Number of teeth | 3.68 ± 0.48 | 3.79 ± 0.42 | 0.467** |

*Note: * The Independent T-test and ** the Mann-Whitney test was used for analysis, and statistical significance was considered at P< 0.05. SD: standard deviation*

**Table 3:** Number of extracted teeth for each group

| No. of Extracted Teeth | Group A | | Group B | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Three | 5 | 13,2 % | 5 | 13,2 % | 10 | 36,4 % |
| Four | 14 | 36.8 % | 14 | 36.8 % | 28 | 73.6 % |
| Total | 19 | 100 % | 19 | 100 % | 38 | 100 % |

*Pain scores*

**Table 4:** Comparison of pain scores (VAS) for each time measurement in each group

| Group | Pain Scores (Mean ± SD) | | | | | *P*-value |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T3 | T4 | |
| A | 0.00 ± 0.00 | 22.16 ± 24.15 | 19.63 ± 22.59 | 16.95 ± 20.96 | 11.26 ± 13.94 | 0.001 |
| B | 0.00 ± 0.00 | 32.21 ± 28.31 | 22.79 ± 22.12 | 17.11 ± 20.67 | 15.00 ± 21.31 | 0.001 |

*Note: The Friedman test was utilized for analysis, with statistical significance set at P< 0.05. SD: Standard Deviation, T: Time*



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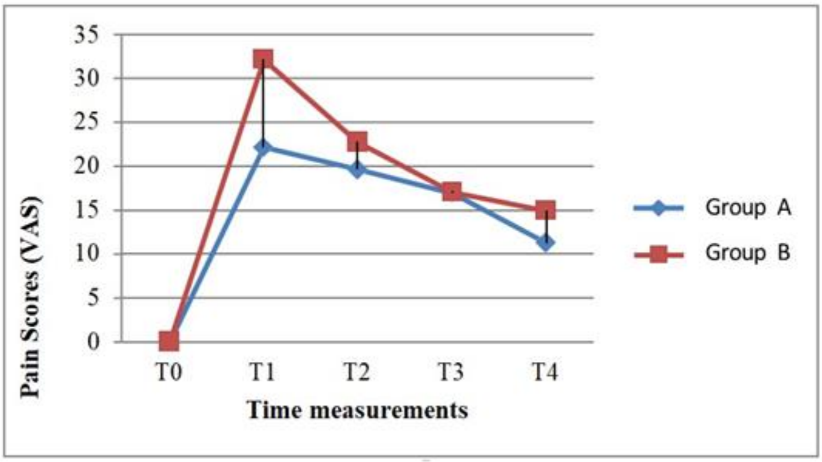


**Figure 1:** Comparison of pain scores (VAS) for each time measurement in each group

**Table 5:** Comparison of pain scores (VAS) between groups at preoperative examination, 2 hours, 8 hours, and 24 hours after surgery

| Pain scores | Mean ± SD | | *P*-value |
|---|---|---|---|
| | Group A | Group B | |
| T0 (preop.) | 0.00 ± 0.00 | 0.00 ± 0.00 | - |
| T1 (2 hours) | 22.16 ± 24.15 | 32.21 ± 28.31 | 0.239 |
| T2 (8 hours) | 19.63 ± 22.59 | 22.79 ± 22.12 | 0.418 |
| T3 (16 hours) | 16.95 ± 20.96 | 17.11 ± 20.67 | 0.627 |
| T4 (24 hours) | 11.26 ± 13.94 | 15.00 ± 21.31 | 0.626 |

*Note: The Mann-Whitney test was employed for analysis, and statistical significance was set at P< 0.05. SD: Standard Deviation; T: Time.*

*IL-6 levels*

In group A, a significant difference in IL-6 levels was observed between the pre-surgery and 24 hours post-surgery ($P$ = 0.009), indicating a notable decrease in IL-6 levels following the administration of the drug combination. However, in group B, no significant difference was noted in IL-6 levels between the pre-surgery and 24 hours post-surgery ($P$ = 0.07), indicating that paracetamol alone did not lead to a significant decrease in IL-6 levels (Table 6). Moreover, significant differences in IL-6 levels were observed both preoperatively ($P$ = 0.001) and 24 hours postoperatively ($P$ = 0.003) between groups A and B (Table 7 and Figure 2).

This study observed an increase in VAS scores two hours following surgery (Group A = 22, Group B = 32) before a subsequent decrease at the eight-hour mark (Group A = 19, Group B = 22). We did not find a significant difference in pain scores (VAS) between the two groups at 2, 8, 16, and 24 hours after surgery. However, it is worth noting that the average VAS score was consistently lower in the combination group compared to the single paracetamol group at all time points. This suggests that the combination group, utilizing multimodal analgesia, continued to provide better pain relief after the third molar odontectomy, even though statistical significance was not achieved ($P$ > 0.05). The lack of significance in the pain parameter (VAS Score) may be due to individual variations in pain perception and several contributing factors.

This finding aligns with a study conducted by Erdi *et al.*, which demonstrated no statistically significant difference between acetaminophen and ibuprofen in terms of reducing abdominal pain, shoulder pain, nausea, vomiting, and the need for fentanyl in patients undergoing elective laparoscopic cholecystectomy surgery. However, a significant difference in pain was observed compared to the control group (normal saline). The timing bias of medication administration and pain score measurement may account for these results [21].



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**Table 6:** Comparison of preoperative and postoperative IL-6 values in each group

| Group | IL-6 level (pg/ml) | | | | *P*-value |
|---|---|---|---|---|---|
| | T0 | | T4 | | |
| | Mean ± SD | Median | Mean ± SD | Median | |
| A | 40.71 ± 8.45 | 39.05 | 38.11 ± 5.41 | 37.42 | 0.009 |
| B | 63.91 ± 43.04 | 49.38 | 59.01 ± 37.58 | 49.14 | 0.077 |

*Note: The Mann-Whitney test was utilized for analysis, and statistical significance was set at P< 0.05. SD: Standard Deviation, T: Time.*

**Table 7:** Comparison of IL-6 values in each group

| Time measurement (Hour) | IL-6 level (pg/ml) | | | | *P*-value |
|---|---|---|---|---|---|
| | A | | B | | |
| | Mean ± SD | Median | Mean ± SD | Median | |
| T0 | 40.71 ± 8.45 | 39.05 | 63.91 ± 43.04 | 49.38 | 0.001 |
| T4 | 38.11 ± 5.41 | 37.42 | 59.01 ± 37.58 | 49.14 | 0.003 |

*Note: The Mann-Whitney test was utilized for analysis, and statistical significance was set at P< 0.05. SD: Standard Deviation, T: Time*

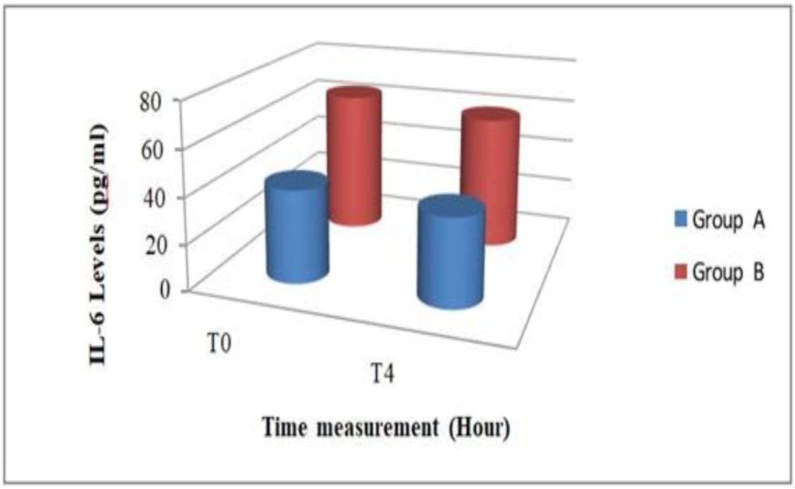


**Figure 2:** Comparison of preoperative and postoperative IL-6 levels in each group

Postoperative pain is a subjective experience influenced by a multitude of variables, including age, gender, the type of surgery performed, concurrent medical conditions, as well as psychological factors such as fear, anxiety, and depression. The degree of tissue damage also plays a role in the intensity and duration of postoperative pain [4]. Variations in the extent of tissue damage and the intensity of postoperative pain can be attributed to the duration of the surgical procedure. Another research showed that the benefits obtained are proper pain control, being able to maintain the patient's hemodynamic indicators well and not causing bad effects after surgery. These are the advantages of using intravenous acetaminophen injection in controlling pain after caesarean section with a PCA pump (Bahman et al., 2023). Some researchers showed that the use of Diosmin 500 mg oral tablets can cause a decrease in pain intensity after hemorrhoidectomy (Mansour et al., 2023). In a different case, Kasper *et al.* reported that among postoperative patients who underwent total hip arthroplasty surgery, the combination of paracetamol 1,000 mg and ibuprofen 400 mg resulted in the lowest morphine consumption and resting pain scores, as well as a reduced risk of nausea at 24 hours following surgery, compared to other combination groups [26]. This finding aligns with Daniel *et al.*, who observed that intravenous ibuprofen 300 mg and acetaminophen 1,000 mg produced a more effective analgesic effect than either drug alone following bunionectomy



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surgery. The combination group exhibited a quicker onset of analgesia and a longer duration to reach peak pain relief [27]. Akbas *et al.* found a similar outcome in postoperative lumbar disc patients, where IV ibuprofen significantly reduced VAS scores and cumulative opioid use compared to paracetamol [28]. In a study conducted by Andribert *et al.* among post-total knee arthroplasty patients, a significant difference in the Numeric Rating Scale (NRS) value for motion was observed when administering the combination of paracetamol and ibuprofen compared to single use [29].

Briggs and Closs emphasize that pain can be influenced by several intrinsic and extrinsic factors and different aspects of pain are assessed in various ways. Pain intensity is subject to the individual's perception, influenced by each person's pain threshold, and can serve as a reference for comparing pain intensities despite the unique nature of pain perception among individuals [30]. The choice of assessing IL-6 levels 24 hours after surgery was based on the observation that IL-6 levels typically peak 24 hours after an operation. Our analysis indicated that the combination group was more effective than the paracetamol-only group in reducing IL-6 levels. This is consistent with findings from Andrew et al., who reported that patients with persistent spinal injuries in the ibuprofen group exhibited IL-6 levels of 3.2 pg/ml compared to 4.0 pg/ml in the control group. James C. *et al.*'s research, involving high-dose ibuprofen (20-30 mg/kg intravenously, maximum 3200 mg) over 28 days in cystic fibrosis patients, revealed a decrease in IL-6 levels in sputum samples with a mean reduction of 0.13 pg/mL ($P = 0.04$) [31, 32].

One of the early cytokines, IL-6, regulates and stimulates the production of acute-phase proteins by hepatocytes in response to painful stimuli such as trauma. IL-6 serves as a robust indicator of tissue damage, with the duration of IL-6 presence in the plasma correlating with the severity of postoperative morbidity. A correlation exists between IL-6 levels and the extent of tissue injury and inflammation. For instance, abdominal hysterectomies typically exhibit higher IL-6 levels compared to laparoscopic hysterectomies. Kraychete *et al.* reported higher IL-6 levels in patients with chronic back pain related to herniated nucleus pulposus [9, 33, 34]. Various inflammatory mediators, such as IL-1b, tumor necrosis factor-alpha (TNF-α), and PGE2, have been demonstrated to stimulate the release of IL-6 in in vitro investigations. IL-6 subsequently triggers the secretion of chemokines such as IL-8 and CCL2. In the context of inflammatory pain, IL-6 can induce short-term prostaglandin (PG)-dependent hyperalgesia while also contributing to local analgesia through the secretion of opioids. The expression of cytokines and chemokines in response to inflammation and tissue injury is a dynamic and multifaceted process. The established mechanism of inflammatory hyperalgesia involves the induction of central sensitization by peripheral inflammation. Recent research suggests that IL-6 serves as a carrier of inflammatory information from the peripheral nervous system to the brain [13, 35].

Cyclooxygenase inhibitors play a role in reducing the production of prostacyclin and prostaglandin, which are associated with edema and hyperalgesia during surgery. By pharmacologically diminishing inflammation, postoperative consequences such as pain, edema, and trismus can be mitigated and rendered less severe [36]. Paracetamol primarily operates at the perceptual stage by inhibiting prostaglandins and central and peripheral cyclooxygenase enzymes. On the other hand, ibuprofen primarily acts at the transduction stage by inhibiting the synthesis of prostaglandins by cyclooxygenase and other inflammatory mediators [4]. In a study by Afif *et al.*, postoperative patients who received a combination of IV Ibuprofen and Paracetamol following sectio secaria observed a decrease in IL-6 levels during the $6^{th}$ and $12^{th}$-hour assessments. However, this decrease in IL-6 levels was not consistently followed by a reduction in pain as measured on the NRS scale. This observation can be explained by the subjective nature of pain perception, which is significantly influenced by numerous factors. Consequently, each individual interprets and perceives the NRS value uniquely [9].

Therefore, in this study, we suggest that IL-6 assessment may be a more appropriate method



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for evaluating the effectiveness of drugs in reducing pain following odontectomy surgery. Several findings support the notion that IL-6 has a modulating effect on nociception and pain in humans. IL-6 enters the systemic circulation, and its concentration is correlated with the surgical severity. The limitation of this study was the variation in the extent of postoperative trauma among samples due to differences in the total number of impacted teeth. In addition, IL-6 levels were not assessed at 1 hour postoperatively, making it difficult to determine the baseline levels of increased IL-6. Therefore, future studies should replicate the same sample and assess IL-6 levels at various time points postoperatively to further elucidate the relationship between IL-6 and postoperative pain. Besides, we did not make comparison among combination IV paracetamol + IV Ibuprofen and single IV Ibuprofen because need more sample and will need more funding and time for the research.

## Conclusion

The combination of intravenous Ibuprofen and Paracetamol has demonstrated its effectiveness in reducing the proinflammatory factor IL-6 in patients undergoing third molar odontectomy, which is likely to translate into lower pain scores. We recommend considering Paracetamol and Ibuprofen as viable analgesic options for third molar odontectomy surgery. Future research should further assess the efficacy of Paracetamol and Ibuprofen when administered through various routes and in the context of different surgical procedures.

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## References

[1]. Albuquerque A.F.M., Fonteles C.S.R., Do Val D., Chaves H.V., Bezerra M.M., Pereira K.M.A., de Barros Silva P., De Lima B., Soares E.C.S., Ribeiro T.R., Effect of pre-emptive analgesia on clinical parameters and tissue levels of TNF-α and IL-1β in third molar surgery: a triple-blind, randomized, placebo-controlled study, *International journal of oral and maxillofacial surgery*, 2017, **46**:1615 [Crossref], [Google Scholar], [Publisher]

[2]. Yilmaz S., Adisen M.Z., Misirlioglu M., Yorubulut S., Assessment of third molar impaction pattern and associated clinical symptoms in a central anatolian turkish population, *Medical Principles and Practice*, 2016, **25**:169 [Crossref], [Google Scholar], [Publisher]

[3]. Degirmenci A., Yalcin E., The effect of pregabalin and ibuprofen combination for pain after third molar surgery, *Nigerian journal of clinical practice*, 2019, **22**:503 [Google Scholar], [Publisher]

[4]. Manuapo H., Tavianto D., Sudjud R.W., Perbandingan preemptive analgesia kombinasi ibuprofen 75 miligram dan parasetamol 250 miligram per oral dengan parasetamol 1 gram per oral terhadap lama analgesik pascabedah odontektomi, *Jurnal Anestesi Perioperatif*, 2019, **7**:181 [Crossref], [Google Scholar], [Publisher]

[5]. Kusmardi K., Adare P.D., Kodariah R., The Effect of Omega-3-enriched Fish oil on the Inflammation of Mice Colon Induced by AOM and DSS: Study on COX-2, *Research Journal of Pharmacy and Technology*, 2019, **12**:5265 [Crossref], [Google Scholar], [Publisher]

[6]. Sudha R., Devi P.B., Nithya G., In-Silico Analysis of various Benzilate Derivatives towards Cyclooxygenase 2 Enzyme, *Research Journal of*



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*Pharmacy and Technology*, 2019, **12**:347 [Crossref], [Google Scholar], [Publisher]

[7]. Salim H.M., Awwalia E.S., Alam I.P., Anti-inflammatory effects and potential mechanisms of Mitragyna speciosa methanol extract on λ-karagenan-induced inflammation model, *Bali Medical Journal*, 2022, **11**:1172 [Google Scholar], [Publisher]

[8]. Demirbas A.E., Karakaya M., Bilge S., Canpolat D.G., Kütük N., Alkan A., Does single-dose preemptive intravenous ibuprofen reduce postoperative pain after third molar surgery? A prospective, randomized, double-blind clinical study, *Journal of Oral and Maxillofacial Surgery*, 2019, **77**:1990 [Crossref], [Google Scholar], [Publisher]

[9]. Afif Y., Gaus S., Ambo, A., Comparison of Multimodel Analgesia for Pain Control and Measuring Inflammation Levels Using Paracetamol with Various Dosage of Ibuprophene in Caesarian Surgical Patients, *Jurnal Kesehatan*, 2022, **15**:71 [Google Scholar]

[10]. Shinde M.G., Sayyad K.D., Swami G.V., Savant P.B., Yalmar P.R., Mane S.T., A Review on Inflammation and its Pharmacotherapy, *Asian Journal of Pharmacy and Technology*, 2023, **13**:201 [Crossref], [Google Scholar], [Publisher]

[11]. Luggya T.S., Roche T., Ssemogerere L., Kintu A., Kasumba J.M., Kwizera A., Tindimwebwa J.V., Effect of low-dose ketamine on post-operative serum IL-6 production among elective surgical patients: a randomized clinical trial, *African Health Sciences*, 2017, **17**:500 [Crossref], [Google Scholar], [Publisher]

[12]. Roofthooft E., Joshi G., Rawal N., Van de Velde M., Anaesthesia P.W.G.o.t.E.S.o.R., Therapy P., Association s.b.t.O.A., Joshi G., Pogatzki-Zahn E., Van de Velde M., Schug S., Kehlet H., PROSPECT guideline for elective caesarean section: updated systematic review and procedure-specific postoperative pain management recommendations, *Anaesthesia*, 2021, **76**:665 [Crossref], [Google Scholar], [Publisher]

[13]. Reikeras O., Borgen P., Reseland J.E., Lyngstadaas S.P., Changes in serum cytokines in response to musculoskeletal surgical trauma, *BMC research notes*, 2014, **7**:1 [Crossref], [Google Scholar], [Publisher]

[14]. Gascon N., Almansa C., Merlos M., Miguel Vela J., Encina G., Morte A., Smith K., Plata-Salamán C., Co-crystal of tramadol-celecoxib: preclinical and clinical evaluation of a novel analgesic, *Expert opinion on investigational drugs*, 2019, **28**:399 [Crossref], [Google Scholar], [Publisher]

[15]. Schwenk E.S., Mariano E.R., Designing the ideal perioperative pain management plan starts with multimodal analgesia, *Korean Journal of Anesthesiology*, 2018, **71**:345 [Crossref], [Google Scholar], [Publisher]

[16]. Koh W., Nguyen K.P., Jahr J.S., Intravenous non-opioid analgesia for peri-and postoperative pain management: a scientific review of intravenous acetaminophen and ibuprofen, *Korean Journal of Anesthesiology*, 2015, **68**:3 [Crossref], [Google Scholar], [Publisher]

[17]. Wick E.C., Grant M.C., Wu C.L., Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review, *JAMA surgery*, 2017, **152**:691 [Crossref], [Google Scholar], [Publisher]

[18]. Rokade S.A., Jadhav R.V., Review on Analgesic Activity using Tail Immersion Method, 2022, **15** [Crossref], [Google Scholar], [Publisher]

[19]. Panchale W.A., Suroshe R., Rathod M.S., Pandhare Y.L., Chromatographic analysis of famotidine, paracetamol and ibuprofen from tablet formulation, *Research Journal of Pharmacy and Technology*, 2019, **12**:231 [Crossref], [Google Scholar], [Publisher]

[20]. Evans S., McCahon R., Management of postoperative pain in maxillofacial surgery, *British Journal of Oral and Maxillofacial Surgery*, 2019, **57**:4 [Crossref], [Google Scholar], [Publisher]

[21]. Erdi A.M., Arabzadeh A., Isazadehfar K., Masoumzadeh M., Bahadoram M., Comparing the Efficacy and Side Effects of Intravenous Ibuprofen and Acetaminophen in Pain Control Following Laparoscopic Cholecystectomy, *World Journal of Plastic Surgery*, 2022, **11**:117 [Crossref], [Google Scholar], [Publisher]

[22]. Nayak A., Das P., Das A.K., Synthesis and evaluation of amide codrug of ibuprofen and amlodipine for dual inhibition of inflammation and hypertension, *Research Journal of Pharmacy*



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*and Technology*, 2023, **16**:3957 [Crossref], [Google Scholar], [Publisher]

[23]. Atkinson H.C., Stanescu I., Frampton C., Salem I.I., Beasley C.P., Robson R., Pharmacokinetics and bioavailability of a fixed-dose combination of ibuprofen and paracetamol after intravenous and oral administration, *Clinical drug investigation*, 2015, **35**:625 [Crossref], [Google Scholar], [Publisher]

[24]. Mehlisch D.R., Aspley S., Daniels S.E., Southerden K.A., Christensen K.S., A single-tablet fixed-dose combination of racemic ibuprofen/paracetamol in the management of moderate to severe postoperative dental pain in adult and adolescent patients: a multicenter, two-stage, randomized, double-blind, parallel-group, placebo-controlled, factorial study, *Clinical therapeutics*, 2010, **32**:1033 [Crossref], [Google Scholar], [Publisher]

[25]. Jensen M.P., Chen C., Brugger A.M., Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain, *The Journal of pain*, 2003, **4**:407 [Crossref], [Google Scholar], [Publisher]

[26]. Thybo K.H., Hägi-Pedersen D., Dahl J.B., Wetterslev J., Nersesjan M., Jakobsen J.C., Pedersen N.A., Overgaard S., Schrøder H.M., Schmidt H., Effect of combination of paracetamol (acetaminophen) and ibuprofen vs either alone on patient-controlled morphine consumption in the first 24 hours after total hip arthroplasty: the PANSAID randomized clinical trial, *Jama*, 2019, **321**:562 [Crossref], [Google Scholar], [Publisher]

[27]. Daniels S.E., Playne R., Stanescu I., Zhang J., Gottlieb I.J., Atkinson H.C., Efficacy and safety of an intravenous acetaminophen/ibuprofen fixed-dose combination after bunionectomy: a randomized, double-blind, factorial, placebo-controlled trial, *Clinical therapeutics*, 2019, **41**:1982 [Crossref], [Google Scholar], [Publisher]

[28]. Akbas S., Ozkan A.S., Durak M.A., Yologlu S., Efficacy of intravenous paracetamol and ibuprofen on postoperative pain and morphine consumption in lumbar disc surgery: Prospective, randomized, double-blind, placebo-controlled clinical trial, *Neurochirurgie*, 2021, **67**:533 [Crossref], [Google Scholar], [Publisher]

[29]. Lubis A.M., Maruanaya S., Tantri A.R., Pontoh L.A.P., Ifran N.N.P.P.S., The use of combination paracetamol and ibuprofen in postoperative pain after total knee arthroplasty, a randomized controlled trial, *Pain physician*, 2021, **24**:E1199 [Google Scholar], [Publisher]

[30]. Sirintawat N., Sawang K., Chaiyasamut T., Wongsirichat N., Pain measurement in oral and maxillofacial surgery, *Journal of dental anesthesia and pain medicine*, 2017, **17**:253 [Crossref], [Google Scholar], [Publisher]

[31]. Park A., Anderson D., Battaglino R.A., Nguyen N., Morse L.R., Ibuprofen use is associated with reduced C-reactive protein and interleukin-6 levels in chronic spinal cord injury, *The Journal of Spinal Cord Medicine*, 2022, **45**:117 [Crossref], [Google Scholar], [Publisher]

[32]. Chmiel J.F., Konstan M.W., Accurso F.J., Lymp J., Mayer-Hamblett N., VanDevanter D.R., Rose L.M., Ramsey B.W., Use of ibuprofen to assess inflammatory biomarkers in induced sputum: implications for clinical trials in cystic fibrosis, *Journal of Cystic Fibrosis*, 2015, **14**:720 [Crossref], [Google Scholar], [Publisher]

[33]. Khan A.N., Jacobsen H.E., Khan J., Filippi C.G., Levine M., Lehman Jr R.A., Riew K.D., Lenke L.G., Chahine N.O., Inflammatory biomarkers of low back pain and disc degeneration: a review, *Annals of the new York Academy of Sciences*, 2017, **1410**:68 [Crossref], [Google Scholar], [Publisher]

[34]. Supomo S., Correlation of Interleukin-6 serum level and surgical site infection in post major surgery patient, *Bali Medical Journal*, 2019, **8**:[Crossref], [Google Scholar], [Publisher]

[35]. Wang X.M., Hamza M., Wu T.X., Dionne R.A., Upregulation of IL-6, IL-8 and CCL2 gene expression after acute inflammation: correlation to clinical pain, *Pain®*, 2009, **142**:275 [Crossref], [Google Scholar], [Publisher]

[36]. Lisboa F.A., Bradley M.J., Hueman M.T., Schobel S.A., Gaucher B.J., Styrmisdottir E.L., Potter B.K., Forsberg J.A., Elster E.A., Nonsteroidal anti-inflammatory drugs may affect cytokine response and benefit healing of combat-related extremity wounds, *Surgery*, 2017, **161**:1164 [Crossref], [Google Scholar], [Publisher]

[37]. Naghipour B., Rahmani V., Efficacy of Intravenous Acetaminophen during the First 24 Hours after Caesarean Section: a Systematic Review, *International Journal of Advanced*



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*Biological and Biomedical Research*, 2023, **11**:104 [Crossref], [Publisher]

[38]. Rezaei M., Azhough R., Efficacy of Diosmin on Post-Hemorrhoidectomy Pain: A Systematic Review of Clinical Trials, *Eurasian Journal of science and Technology*, 2023, **3**:137 [Crossref], [Publisher]

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