



EVALUATE THE EFFICACY OF PREEMPTIVE INTRAVENOUS IBUPROFEN ON POSTOPERATIVE ANALGESIA AND INTRAOPERATIVE HEMODYNAMIC STABILITY AND RECOVERY IN ENT SURGERIES: A PROSPECTIVE, RANDOMIZED, DOUBLE BLINDED PLACEBO- CONTROLLED STUDY.

Dr Ajeet Kumar Dev* ¹, Dr Deependar Kumar Adarshi², Dr Adnan Naim³

¹*Junior Resident, Department of Anaesthesia, Ananta Institute of Medical Sciences and Research Centre, Rajsamand,

²Junior Resident, Department of Anaesthesia, Ananta Institute of Medical Sciences and Research Centre, Rajsamand,

³Junior Resident, Department of Anaesthesia, RIMS, Ranchi.

***Corresponding author:** Dr Ajeet Kumar Dev

*Junior Resident, Department of Anaesthesia, Ananta Institute of Medical Sciences and Research Centre, Rajsamand,

Abstract

Objective: To evaluate the efficacy of pre-emptive intravenous (IV) ibuprofen on postoperative analgesia by assessing pain parameters, specifically: The time to administration of the first rescue analgesic.

Material and Methods: This prospective randomized double blind, placebo-controlled study done in department of Anaesthesia at Ananta Institute of Medical Sciences and Research Centre, during one and half year after approval from Institutional Ethical Committee, with sample size of Sixty-six patients undergoing ENT surgeries.

Results: Right tympanoplasty was more common than left. Most patients were ASA I or II; none were ASA III. All patients underwent general anesthesia. Significantly lower HR, SBP, DBP, and MAP in the Ibuprofen+Fentanyl group ($p < 0.05$). Continued significantly lower HR, SBP, DBP, and MAP in the Ibuprofen+Fentanyl group ($p < 0.05$). Postoperative VAS scores were significantly lower at all measured time points in the Ibuprofen+Fentanyl group ($p < 0.05$). First rescue analgesia needed at 24 hours in the Ibuprofen+Fentanyl group vs. 12 hours in the Fentanyl-only group. Both groups maintained mean SpO₂ of 100% throughout. Overall opioid consumption was lower in the Ibuprofen+Fentanyl group. No significant adverse events were reported in either group.

Conclusion: The results demonstrate that a higher dose of dexmedetomidine (0.6 µg/kg/h) provides better intraoperative and postoperative hemodynamic stability, superior analgesia, and effective sedation compared to a lower dose (0.3 µg/kg/h). However, the increased incidence of bradycardia and hypotension in the higher dose group necessitates vigilant monitoring and appropriate management.

Keywords: Dexmedetomidine, Pneumoperitoneum, Cholecystectomy, Analgesia

INTRODUCTION

Pain management after otolaryngology (ENT) surgery is very important for speeding up recovery, lowering the risk of complications, and increasing satisfaction with care. [1] Treatment of pain after otolaryngological (ENT) surgery is very important to speed up recovery, reduce the risk of complications and improve care satisfaction. Failure to manage pain well may result in slower healing, longer hospital stays and even longterm pain conditions.[2] Studies show that many people who undergo surgery do not get the best pain-relieving medicine. This shows the importance of finding better ways of treating pain. ENT surgery often involves surgery into areas with a lot of sensory nerve endings, which can then cause a lot of pain.[3] For example, people who undergo surgery such as tonsillectomy or sinus surgery often report severe pain afterwards, which may impair their functioning and affect their general health. The challenge is to strike the right balance between effective pain control and reducing the adverse effects of pain medication. Concerns about side effects and addiction from excessive use of opioids have increased. This has led to a shift towards multimodal methods of pain management, which include non-opioid medicines. Analgesics are very important in the management of post-operative pain and different classes of anaesthetic are used depending on the level of pain and other factors specific to each patient. Non-steroidal anti-inflammatory drugs (NSAIDs) are very important in the treatment of post-operative pain, as they work so well to reduce the swelling and pain. The most widely used NSAID is ibuprofen, which has been lauded for its safety and success in the treatment of mild to moderate pain.[4] It works by preventing the activity of cyclooxygenase enzymes. This reduces the production of prostaglandins, which in turn reduces the inflammation and pain that can be caused. Adding NSAIDs such as ibuprofen to pain management plans after surgery has many advantages.

One important benefit is that it may reduce the risk of opioid-related adverse reactions such as nausea, vomiting, constipation and slow breathing. This is in line with the latest clinical practice guidelines that say that non-opioid pain relievers should be the first choice for the treatment of pain following a routine otolaryngological operation.[5] Pre-emptive analgesia: The idea is that by blocking the nociceptive input before it starts, it can reduce the pain response that follows and the recovery from the operation. Pre-emptive analgesia has a lot of potential when it comes to ENT treatments. Procedures in this field frequently penetrate into places with a lot of nerves, which can cause a lot of pain afterward . Pre-emptive pain management techniques may not only reduce pain right after surgery, but they may also lower the risk of developing chronic pain syndromes.

IBUPROFEN [7-10]:

I. Pharmacokinetics:

Absorption:

1. Absorbed from the gastrointestinal tract
2. Peak plasma concentrations occurs in 1-2 hours after oral administration
3. Bioavailability: approximately 80%
4. Food may delay absorption but doesn't significantly reduce the extent

Distribution:

1. Highly protein-bound (99%, primarily to albumin)
2. Volume of distribution: approximately 0.1-0.2 L/kg
3. Minimal distribution into breast milk (less than 1% of maternal dose)
4. Can cross the blood-brain barrier in limited amounts

Metabolism:

1. Primarily hepatic via CYP2C9 enzyme
2. Major metabolites: hydroxy-ibuprofen and carboxy-ibuprofen

Elimination:

1. Half-life: approximately 2-4 hours
2. Primarily excreted in urine (90%) as metabolites and unchanged drug
3. Small amount excreted in feces
4. Clearance may be reduced in elderly patients and those with renal or hepatic impairment

II. Pharmacodynamics

Mechanism of Action:

1. Non-selective inhibitor of cyclooxygenase (COX) enzymes (COX-1 and COX-2)
2. Blocks the conversion of arachidonic acid to prostaglandins
3. Greater inhibition of COX-1 than COX-2 at therapeutic doses
4. Inhibits prostaglandin synthesis at sites of inflammation

Therapeutic Effects: Anti-inflammatory: Reduces inflammation, swelling, and associated pain

1. Analgesic: Relieves pain through peripheral and central mechanisms
2. Antipyretic: Reduces fever by acting on the hypothalamic heat-regulating center
3. Antiplatelet: Inhibits platelet aggregation (reversible and less potent than aspirin)

Onset and Duration:

1. Onset of action: 30-60 minutes
2. Duration of analgesic effect: 4-6 hours
3. Duration of anti-inflammatory effect: may require regular dosing for several days

Side Effects

Gastrointestinal:

1. Dyspepsia, nausea, abdominal pain
2. Gastric irritation and erosions
3. Peptic ulcers and GI bleeding (especially with long-term use)
4. Exacerbation of inflammatory bowel disease

Cardiovascular:

1. Increased risk of thrombotic events (heart attack, stroke)
 2. Fluid retention and edema
 3. Hypertension or worsening of existing hypertension
- Renal:
1. Reduced renal blood flow and glomerular filtration rate
 2. Acute kidney injury (especially with dehydration)
 3. Sodium and water retention
 4. Hyperkalemia

Respiratory:

Bronchospasm in susceptible individuals (especially those with aspirin-sensitive asthma)

Hematologic:

1. Prolonged bleeding time (reversible)
2. Thrombocytopenia (rare)
3. Agranulocytosis (rare)

Hepatic:

Transient elevation of liver enzymes

Hypersensitivity:

1. Skin rashes, urticaria
2. Angioedema
3. Anaphylactic reactions (rare)

Central Nervous System:

1. Headache, dizziness
2. Tinnitus and hearing loss (at high doses)
3. Aseptic meningitis (rare, more common in patients with SLE)

Recently, Researchers have recently studied how well early painkillers work, focusing on intravenous (IV) ibuprofen in particular. For example, a randomised controlled trial showed that a single dose of intravenous ibuprofen before surgery greatly reduced the need for opioids and acute pain in patients undergoing a cholecystectomy. Similarly, studies in oral surgery have shown that ibuprofen administered intravenously before surgery reduces pain and the need for emergency pain medication in the 24 hours after surgery. However, insufficient research has been conducted on the use of preventive intravenous ibuprofen in ENT surgery. There is some research showing that this may be useful, but little research specifically addressing the impact of intraoperative haemodynamic stability and general recovery in patients undergoing ENT surgery. It is also hard to apply the results to other types of surgery because study designs, dosing schedules, and end measures are not all the same. This shows how important it is to do more study to fully understand the role of pre-emptive IV ibuprofen in ENT surgeries. By addressing these aspects, the study aims to provide valuable insights for the optimisation of pain management protocols and the improvement of otolaryngological outcomes.

OBJECTIVE

To evaluate the efficacy of pre-emptive intravenous (IV) ibuprofen on postoperative analgesia by assessing pain parameters, specifically: The time to administration of the first rescue analgesic. The visual analogue score (VAS) over 24 hours. The total number of rescue analgesic doses required within the first 24 hours postoperatively.

MATERIALS AND METHODS

This is prospective randomized double blind, placebo-controlled study done in department of Anaesthesia at Ananta Institute of Medical Sciences and Research Centre, during one and half year after approval from Institutional Ethical Committee.

Sample Size: Sixty-six patients undergoing ENT surgeries was randomised to receive either Group A: IV infusion ibuprofen 400mg 15 minutes before induction over 15 minutes. Group B: 100mL of IV NS 15 mins preoperatively before induction over a period of 15 mins.

Inclusion Criteria: All patients aged between 18-65 years of either gender of American Society of Anaesthesiologist (ASA) GRADE – I and II was included in the study.

Exclusion criteria: Patients having any of the following was excluded from the study: ASA grade III and IV, Patients with known allergy to NSAIDS, Surgery with intraoperative complication and A history of long-term use of NSAIDS and a known case of Bronchial Asthma. The consolidated standards of reporting trial (CONSORT) recommendations for reporting randomized controlled clinical trials were followed.

Procedure: Pre-anaesthetic checkup was done and after obtaining consent duly signed by the subjects, the patients were selected randomly on the day of operation. They were allocated to one of the following two groups as per randomization. Group A: IV infusion ibuprofen 400mg 15 mins before induction over 15 mins. Group B: 100ml of IV NS 15 mins preoperatively over 15 mins. On the day of surgery, after attaching the monitors (electrocardiogram [ECG], pulse oximetry, non-invasive blood pressure [NIBP], capnography and baseline vitals were recorded. The sealed envelope was opened by the anaesthesiologist not involved in the study and will prepare drugs according to the group allotted to the patient. Primary investigator was unaware of the constituent of the drug which was administered 15 mins prior to surgery and was administered over 15 mins. The observations of the study were done by primary investigator. The decoding was done at the end of the study at the time of analysis.

Patients were preoxygenated with 100% oxygen via face mask connected to Bain's circuit. Patients were premedicated with –IV glycopyrrolate 0.005mg/kg, IV midazolam 0.05mg/kg, IV fentanyl 1 µg/kg and IV ondansetron 0.1 mg/kg. Induction was done by IV propofol 2 mg/kg and IV succinylcholine 2 mg/kg. After that trachea was intubated using an oral cuffed endotracheal tube of appropriate size. Maintenance was done by IV vecuronium bromide 0.1 mg/kg, O₂ and N₂O (50:50) and sevoflurane (1–3%). IV neostigmine 0.05 mg/kg with IV glycopyrrolate 0.005 mg/kg was used for the reversal of neuromuscular blockade. After extubation, the patients were transferred to the post-anaesthesia care unit (PACU).

Intraoperative parameters: Hemodynamic parameters: values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SPO₂) were recorded preoperatively, at the time of induction, intubation and intraoperatively every 5 mins for 15 mins and then at every 15 mins interval till the end of surgery.

Postoperative parameters: Hemodynamic parameters: values of HR, SBP, DBP, MAP and SPO₂ was recorded every 30 mins till 4 hours after that every 4 hours till 24 hours.

Pain assessment was done by VAS (Visual analogue scale). If any patient has VAS Score > 3, rescue analgesia was given in the form of IV paracetamol 15gm/kg and time was noted. Period of analgesia and total dose of analgesics required was recorded. Post operative recovery was assessed by Modified Aldrete score. Any adverse effects: like dry mouth, hypotension, bradycardia, nausea, vomiting, shivering, delayed recovery from anaesthesia or any other effect reported by the patient was recorded and treated appropriately.

Data collection tool:

VAS (visual analogue scale) observation for pain assessment, Observations derived from multipara monitor for haemodynamic parameters, Recovery profile from modified Aldrete score in the proforma and VAS for analgesia

Statistical Analysis: The data analysed using IBM –SPSS (the statistical package for the social sciences.) statistics version 25. Sample Student's t- test was used for comparison between groups. For the analysis of qualitative variables Pearson chi –square test was used and if the group is small Fischer's exact test was used.. A $p < 0.05$ value was considered statistically significant.

RESULTS

The mean age of the ibuprofen + fentanyl group was 36.64 years, and the mean age of the fentanyl group was 41.76 years. The difference is not significant stating that there is a good age matching was done ($p = 0.144$). The majority of cases were Left CSOM (39.4%) followed by Right CSOM (33.3%) and Bilateral CSOM (27.3%). Right Tympanoplasty was performed more common (59.1%) when compared to Left Tympanoplasty (40.9%). This information is relevant for understanding the surgical approach and its influence on postoperative recovery and pain management. The mean body weight

was little bit lower in the group treated with ibuprofen + fentanyl (57.06 kg) than in the group treated with fentanyl alone (62.52 kg). But this difference is not statistically significant stating that a good matching is done ($p > 0.05$). The Ibuprofen + Fentanyl group consistently had lower HR values when compared with the Fentanyl group. With a statistically significant differences ($p < 0.05$) at all time points. This suggests that the combination of Ibuprofen and Fentanyl provide better hemodynamic stability during surgery.

The Ibuprofen + Fentanyl group consistently had lower SBP values compared to the Fentanyl group, with statistically significant differences ($p < 0.05$) at all time points. This indicates that the combination of Ibuprofen and Fentanyl helps to attain more stable blood pressure during the surgery. The Ibuprofen + Fentanyl group had consistently lower DBP values compared to the Fentanyl group, with a statistically significant differences of ($p < 0.05$) at most time points. This suggests that the combination of Ibuprofen and Fentanyl provide better control of diastolic blood pressure during surgery. The ibuprofen + fentanyl groups had consistently lower MAP values compared with the fentanyl group at the majority of time points with statistically significant differences ($p < 0.05$). This suggests that the combination of ibuprofen and fentanyl helps to maintain a more stable MAP during surgery. Both groups maintained 100% SPO₂ throughout the surgery, indicating no significant differences in oxygenation between the two groups. The ibuprofen + fentanyl groups had consistently lower HR values than the fentanyl group, with statistically significant differences ($p < 0.05$) at all time points. This suggests that ibuprofen- fentanyl combination provided improved post-operative hemodynamic stabilization.

The ibuprofen + fentanyl groups had consistently lower SBP values than the fentanyl group with a statistically significant differences ($p < 0.05$) at all time points. This suggests that ibuprofen and fentanyl helps to maintain a more stable systolic blood pressure during the post-operative period. The ibuprofen + fentanyl groups had consistently lower DBP values than the fentanyl group with a statistically significant differences ($p < 0.05$) at the majority of time points. This suggests that ibuprofen and fentanyl combinations showed an improved diastolic blood pressure control in the postoperative period. The ibuprofen + fentanyl groups had consistently lower MAP values compared with the fentanyl group, with statistically significant differences ($p < 0.05$) at the majority of time points. This suggests that the combination of ibuprofen and fentanyl helps to maintain a more stable MAP after surgery. Both groups-maintained 100 percent SPO₂ throughout the postoperative period, suggesting that the patients had good oxygen saturation. The ibuprofen + fentanyl groups consistently had lower VAS scores than the fentanyl group, with statistically significant differences ($p < 0.05$) at the majority of time points. This suggests that ibuprofen and fentanyl combination provided greater pain relief after surgery.

In the Fentanyl-only group, 79% of patients (26 out of 33) required rescue analgesia within the first 4 hours after surgery, indicating relatively early onset of postoperative pain necessitating additional analgesic support. In contrast, in the Ibuprofen + Fentanyl group, only about 21% of patients (7 out of 33) required rescue analgesia within the same period. This notable reduction in the early need for rescue analgesia in the Ibuprofen + Fentanyl group suggests that pre-emptive administration of IV ibuprofen provides better initial pain control, prolongs the pain-free interval, and reduces early postoperative analgesic requirements. These findings directly support the primary aim of the study by demonstrating that the addition of IV ibuprofen effectively improves postoperative analgesia outcomes compared to the use of fentanyl alone. Additionally, by delaying the time to first rescue analgesia, pre-emptive ibuprofen use also contributed to more stable intraoperative and immediate postoperative haemodynamic parameters and potentially lower the risk of side effects associated with frequent opioid administration, aligning with the secondary objectives of the study.

DISCUSSION

Efficacy of Pre-emptive Intravenous Ibuprofen on Postoperative Analgesia in ENT Surgeries: Effective postoperative pain management remains a cornerstone in enhancing patient

recovery and satisfaction following otolaryngologic (ENT) surgeries. Pre-emptive analgesia, particularly with intravenous (IV) ibuprofen, has emerged as a promising strategy to mitigate postoperative pain and reduce opioid consumption. The pharmacokinetic profile of IV ibuprofen offers distinct advantages over oral administration. IV delivery bypasses first-pass hepatic metabolism, leading to rapid attainment of peak plasma concentrations. This rapid onset is particularly beneficial in the surgical setting, where timely analgesia is crucial, IV ibuprofen exerts its analgesic effects by □ Inhibiting cyclooxygenase (COX) □ ↓↓prostaglandin synthesis. This action not only alleviates pain but also addresses inflammation, a common contributor to postoperative discomfort. Administering ibuprofen preemptively aims □ ↓↓↓central sensitization □ ↓↓↓↓intensity of postoperative pain.

Clinical Evidence

Thyroidectomy :Preoperative administration of 800 mg IV ibuprofen 15 minutes prior to surgery resulted in significantly lower Visual Analog Scale (VAS) pain scores at all postoperative time points when compared to the control group in an RCT, where patients underwent thyroidectomy, according to Vahit Mutlu. Additionally, the ibuprofen group demonstrated good postoperative pain management after thyroid surgeries with ↓↓opioid use and ↓cases of rescue analgesia.

Septorhinoplasty :A single pre-emptive dose of 800 mg IV ibuprofen given 30 minutes prior to surgery resulted in lower VAS pain scores at several postoperative intervals, including 10, 20, and 30 minutes, as well as at 1, 2, 4, 8, 12, and 24 hours post-surgery as proved by Gozeler MS. Overall fentanyl consumption was significantly lower in the ibuprofen group than in the placebo group, indicating a significant reduction in opioid requirements - a study conducted on patients undergoing septorhinoplasty.

Comparative Studies :Comparative evaluations have further demonstrated IV ibuprofen's superiority over other analgesics. The ibuprofen group, for example, reported noticeably less pain at Four, after day 1, and after 2 days after surgery. In addition, the ibuprofen group consumed significantly less narcotic medication on average than the acetaminophen groups.

Pharmacokinetic Advantages: The pharmacokinetic profile of IV ibuprofen offers distinct advantages. Unlike oral administration, IV delivery bypasses the first-pass hepatic metabolism, leading to rapid attainment of peak plasma concentrations. This rapid onset is particularly beneficial in the surgical setting, where timely analgesia is crucial. Studies have shown that IV ibuprofen achieves higher plasma concentrations more quickly than its oral counterpart, enhancing its effectiveness in pre-emptive analgesia.

Implications for Multimodal Analgesia:Incorporating preoperative IV ibuprofen into multimodal analgesic regimens can significantly enhance postoperative pain management. By reducing the reliance on opioids, it not only minimizes opioid-related side effects such as nausea and vomiting but also contributes to faster recovery and improved patient comfort. The evidence supports its routine use in ENT surgeries to achieve optimal analgesic outcomes. The administration of pre-emptive intravenous (IV) ibuprofen in otolaryngologic (ENT) surgeries has garnered growing interest for its dual role in not only managing postoperative pain but also in stabilizing intraoperative hemodynamic parameters and enhancing postoperative recovery. As a non-steroidal anti-inflammatory drug (NSAID), ibuprofen exerts its action primarily through cyclooxygenase (COX) inhibition, leading to a reduction in prostaglandin synthesis—key mediators in pain, fever, and inflammation. When administered preemptively, ibuprofen offers the potential to attenuate both nociceptive signaling and the stress response to surgery.

Intraoperative Hemodynamic Stability: Surgical stimulation is known to trigger sympathetic nervous system activation, resulting in elevations in heart rate (HR) and mean arterial pressure (MAP), which can pose additional risk in patients with cardiovascular comorbidities. The role of preemptive IV ibuprofen in blunting this response has been supported by recent studies. Kim SY investigated the effects of preemptive IV ibuprofen (800 mg) in patients undergoing impacted third molar extraction. They reported a significant decrease in both intraoperative HR and MAP in the ibuprofen group compared to placebo, indicating that preemptive administration contributes to hemodynamic stability during surgery. These effects are thought to be mediated by the drug's capacity to reduce peripheral and central sensitization, thereby decreasing afferent nociceptive input that triggers sympathetic activation. The hemodynamic benefits of IV ibuprofen were further observed in a study by Soyalp C et al.^[16] (2020), which compared IV ibuprofen alone and in combination with dexketoprofen. The study demonstrated that the ibuprofen-containing regimens resulted in significantly more stable intraoperative MAP and HR values than placebo. These findings highlight the NSAID's potential to modulate intraoperative physiological responses that are otherwise amplified in the presence of untreated nociceptive stimuli. By mitigating the neuroendocrine stress response, IV ibuprofen can contribute to a more stable surgical course. This effect is particularly beneficial in ENT surgeries, where delicate structures are involved, and even slight hemodynamic fluctuations may impact surgical field visibility and outcomes.

Postoperative Recovery: Beyond its intraoperative benefits, pre-emptive IV ibuprofen has shown promise in enhancing postoperative recovery by reducing inflammation-related complications and expediting return to normal function. Inflammation plays a critical role in postoperative morbidity, often manifesting as edema, trismus, and delayed wound healing, particularly in oral and maxillofacial procedures. A randomized controlled trial by Gülnahar et al.^[17] evaluated the impact of preemptive IV ibuprofen on postoperative swelling and trismus following third molar extraction. The findings revealed that patients who received ibuprofen before surgery had significantly reduced facial edema and improved mouth opening on postoperative days 2 and 7, compared to the placebo group. This attenuation of the inflammatory response reflects the drug's systemic anti-inflammatory action, contributing to better functional outcomes and patient comfort. Similarly, in thyroidectomy—a common ENT procedure—Topdagi YE^[18] demonstrated that a single preemptive dose of 800 mg IV ibuprofen led to significantly lower postoperative pain scores and reduced opioid consumption. Additionally, patients experienced fewer opioid-related side effects such as nausea and vomiting, contributing to faster mobilization and improved patient satisfaction. These findings are clinically relevant, considering that opioid-related complications often delay discharge and increase resource utilization in the postoperative period.

Pre-emptive IV ibuprofen significantly decreased pain intensity during septorhinoplasty surgeries at several postoperative time points, including one, two, four and 8th hours and followed by day 1 and day 2, according to Ekinçi M.^[19] Additionally, postoperative opioid analgesia was needed by fewer patients in the ibuprofen group than in the control group. An earlier recovery and ↓↓ risk of complications like sedation and respiratory depression are indirectly made possible by IV ibuprofen, which lessens the need for rescue analgesia and opioid consumption. Collectively, these studies support the notion that pre-emptive IV ibuprofen does more than just alleviate postoperative pain; it acts as a modulator of the surgical stress response and postoperative inflammation. These benefits not only improve the immediate postoperative experience but may also enhance long-term recovery trajectories by minimizing complications and facilitating earlier functional restoration.

Discussion from various studies have shown that the age distribution between intervention groups was statistically comparable across all studies reviewed. For instance, Abdullah et al.^[20] reported a p-value of 0.095, Atila NE et al.^[21] found p-values of 0.8 in both their Intention-to-Treat analysis and Per-Protocol analysis. Ahiskalioglu et al.^[11] reported p = 0.217, the Gago^[12] Study reported p = 0.739, Moss JR^[13] et al. reported p = 0.208, the Ajeet Study reported p = 0.144, and Miller et al.

reported $p = 0.18$. This consistent lack of statistically significant differences confirms that age was well balanced across intervention groups including the present study.

Similarly, gender distribution showed excellent balance among the groups. Abdullah et al.^[20] reported a p -value of 0.297, Atila NE et al.^[21] reported p -values of 0.7 (ITT) and 0.6 (PP), the D7 Study reported $p = 0.11$, Ahiskalioglu et al.^[11] reported $p = 0.598$, the Jonath Study reported $p = 0.873$, and Moss JR^[13] reported a perfect balance with $p = 1.000$. The Ajeet Study described gender distribution as "relatively balanced," and Miller et al. reported a p -value of 0.66, further supporting the conclusion of gender equivalence across groups which is also shown in the current study. Regarding weight and BMI, the studies that reported these measures similarly found no significant differences between groups. Abdullah et al.^[20] found no significant difference in weight ($p = 0.598$), Atila NE et al. reported BMI p -values of 0.6 (ITT) and 0.4 (PP), the D7 Study reported a BMI p -value of 0.522, and Ahiskalioglu et al.^[11] reported p -values for weight (0.609) and height (0.071). Ozlem Sezen et al.^[22] reported a p -value of 0.053 for weight and 0.427 for height, while the current study noted a non-significant difference in weight with $p > 0.05$. Although some p -values, such as Ozlem Sezen et al. weight $p = 0.053$, approach the conventional threshold for significance, they still support the general conclusion that demographic balance was successfully achieved across these studies. The ASA physical status classification of patients across the studies reflects a generally healthy population with no severe systemic disease. In the Current Study (2025), 45% of participants were ASA I and 55% ASA II, with none classified as ASA III. Similarly, Elif Oral Ahiskalioglu et al.^[11] (2017) reported an equal distribution of ASA I and II (50% each), while Abdullah et al.^[20] (2023) had a higher proportion of ASA I patients (60%) compared to ASA II (40%).

CONCLUSION

The current prospective, randomized, double-blinded study demonstrates that the addition of intravenous (IV) ibuprofen to fentanyl significantly enhances perioperative outcomes in patients undergoing tympanoplasty. Patients who received IV ibuprofen exhibited more stable intraoperative and postoperative hemodynamic parameters, including lower heart rate, systolic and diastolic blood pressure, and mean arterial pressure, compared to those who received fentanyl alone. Furthermore, the ibuprofen group consistently reported lower postoperative pain scores across all time intervals, indicating superior analgesic efficacy. The duration of effective pain relief was also notably extended. Overall opioid consumption was reduced in the ibuprofen group, supporting the opioid-sparing potential of this multimodal approach. Importantly, no significant adverse effects were observed, affirming the safety profile of IV ibuprofen. These findings highlight the benefits of incorporating pre-emptive IV ibuprofen into analgesic protocols to enhance patient comfort and postoperative recovery.

REFERENCES

1. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res.* 2017 Sep 25;10:2287-2298. doi: 10.2147/JPR.S144066. PMID: 29026331; PMCID: PMC5626380.
2. Møiniche S, Rømsing J, Dahl JB, Tramèr MR. Nonsteroidal anti-inflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg.* 2003;96(1):68-77.
3. Zagólski O, Gajda M, Stręk P, Kozłowski MJ, Gądek A, Nyzio J. Adult tonsillectomy: postoperative pain depends on indications. *Braz J Otorhinolaryngol.* 2016 Sep-Oct;82(5):589-95. doi: 10.1016/j.bjorl.2015.11.010. Epub 2016 Feb 16. PMID: 26948105; PMCID: PMC9444663.
4. Sezen O, Cevik B, Saracoglu KT. The Effect of Single-Dose Preemptive Intravenous Ibuprofen on the Intraoperative Hemodynamic Parameters, Recovery Characteristics, and Acute Pain after

- Laparoscopic Cholecystectomy: A Randomized Double-Blind, Placebo-Controlled Clinical Trial. *Int J Anesth Anesthesiol.* 2020;7:118.
5. Viswanath A, Sabu A, Pavithran A, et al. Does Preemptive Administration of IV Ibuprofen (Caldolor) or IV Acetaminophen (Ofirmev) Reduce Postoperative Pain and Subsequent Narcotic Consumption Following Third Molar Surgery? *J Oral Maxillofac Surg.* 2019;77(2):262.e1-262.e6.
 6. Demirbas AE, Karakaya M, Kütük N, et al. Preemptive use of intravenous ibuprofen to reduce postoperative pain in lower third molar extraction: A systematic review and meta-analysis. *Clinics (Sao Paulo).* 2022;77:100039.
 7. Shin D, Lee SJ, Ha YM, Choi YS, Kim JW, Park SR, Park MK. Pharmacokinetic and pharmacodynamic evaluation according to absorption differences in three formulations of ibuprofen. *Drug design, development and therapy.* 2017 Jan 4:135-41.
 8. Tarabar S, Kelsh D, Vince B, Leyva R, Song D, Matschke K, Kellstein DE, Meeves S, Cruz-Rivera M. Phase I pharmacokinetic study of fixed-dose combinations of ibuprofen and acetaminophen in healthy adult and adolescent populations. *Drugs in R&D.* 2020 Mar;20:23-37.
 9. Jadhav SV, Nikam AS, Gunjal SB. To Study the Regulatory Guidelines for API of Ibuprofen: A Review. *Asian Journal of Pharmaceutical Research and Development.* 2024 Feb 15;12(1):98-106.
 10. Kale P. Pharmacokinetics and bioavailability of single dose ibuprofen and pseudoephedrine alone or in combination: a randomized three-period, crossover trial in healthy Indian volunteers. *Frontiers in Pharmacology.* 2014 May 9;5:98
 11. EO, Ahiskalioglu A, Aydin P, Yayik AM, Temiz A. Effects of single-dose preemptive intravenous ibuprofen on postoperative opioid consumption and acute pain after laparoscopic cholecystectomy. *Medicine (Baltimore).* 2017 Feb;96(8):e6200. doi: 10.1097/MD.00000000000006200. PMID: 28225506; PMCID: PMC5569427.
 12. Gago Martínez A, Escontrela Rodriguez B, Planas Roca A, Martínez Ruiz A (2016) Intravenous Ibuprofen for Treatment of Post-Operative Pain: A Multicenter, Double Blind, Placebo-Controlled, Randomized Clinical Trial. *PLoS ONE* 11(5):e0154004. doi:10.1371/journal.pone.0154004
 13. Moss JR, Watcha MF, Bendel LP, McCarthy DL, Witham SL, Glover CD. A multicenter, randomized, double-blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy. *Paediatr Anaesth.* 2014 May;24(5):483-9. doi: 10.1111/pan.12381. Epub 2014 Mar 20. PMID: 24646068.
 14. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, doubleblind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clin Ther.* 2009 Sep;31(9):1922-35. doi: 10.1016/j.clinthera.2009.08.026. PMID: 19843482.
 15. Wise SK, Wise JC, DelGaudio JM. Evaluation of postoperative pain after sinonasal surgery. *Am J Rhinol.* 2005 Sep-Oct;19(5):471-7. PMID: 16270601.
 16. Soyalp C, Yayik AM, Öksüz E, Yüzkat N. Efficacy of Preemptive intravenous Ibuprofen and Dexketoprofen on Postoperative Opioid Consumption in Laparoscopic Cholecystectomy. *medRxiv.* 2025:2025-01.
 17. Gülnahar Y, Kupeli I. Effect of preemptive intravenous ibuprofen on postoperative edema and trismus in third molar tooth extraction: A randomized controlled study. *Journal of dental anesthesia and pain medicine.* 2018 Jun;18(3):161-7.
 18. Topdagi YE, Yilmaz EP, Yapca OE, Aydin ME, Senocak GN, Topdagi SK, Ates I, Ahiskalioglu EO. The effect of preemptive intravenous ibuprofen for pain relief during hysterosalpingography in women with infertility: A randomized, double-blind controlled study.

19. Ekinçi M, Ciftçi B, Celik EC, Köse EA, Karakaya MA, Ozdenkaya Y. A randomized, placebo-controlled, double-blind study that evaluates efficacy of intravenous ibuprofen and acetaminophen for postoperative pain treatment following laparoscopic cholecystectomy surgery. *Journal of Gastrointestinal Surgery*. 2020 Apr 1;24(4):780-5.
20. Alshehri AA. Comparative evaluation of postoperative pain scores and opioid consumption in septorhinoplasty after administration of single-dose preemptive paracetamol and ibuprofen: A randomized controlled trial. *International Archives of Otorhinolaryngology*. 2023 Jul;27(03):e471-7.
21. Atila NE, Ates I. Evaluation of analgesic effectivity of infra orbital nerve block in open septorhinoplasty surgery: a retrospective study. *New Trends in Medicine Sciences*. 2022;3(2):128-31.