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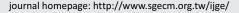
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Original Article

# Comparison of the Clinical Effects of Ibuprofen and Paracetamol Used for Analgesic Purposes in Endoscopic Retrograde Cholangiopancreatography in Geriatric Patients

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| ARTICLE INFO | SUMMARY |
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| | *Background:* Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure that is used to visualize the biliary pancreatic ductal system following the intravenous (IV) injection of an opaque contrast medium. Ibuprofen, a propionic acid derivative, has analgesic, anti-inflammatory, and antipyretic features similar to a non-selective cyclooxygenase inhibitor. In this study, we aimed to evaluate the effect of ibuprofen on geriatric patients with ERCP.<br>*Methods:* A total of 80 patients and age > 65 years, were included in the study. Participants were divided into three groups: group P (n = 27) was administered a 1000 mg/100 ml paracetamol infusion 30 minutes (min) before the procedure; group I (n = 28) was administered a 400 mg/100 ml ibuprofen IV infusion 30 min before the procedure; and group C (n = 25), a control group, was not administered analgesics before the procedure.<br>*Results:* Group I was found to have a significantly lower intraoperative fentanyl dose than group P and C. The intraoperative propofol dose was lowest in group I and highest in group C. While visual analog scale (VAS) scores demonstrated no significant differences among the groups in the first 15 min after the procedure; group I was found to have significantly lower VAS levels in 30 min after the procedure.<br>*Conclusion:* The present study compared the effects of ibuprofen and paracetamol administered prior to the ERCP procedure with results demonstrating a reduction in the dose of intraoperative narcotics with intravenous ibuprofen. |

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## 1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure that is used to visualize the biliary pancreatic ductal system after an injection of an opaque contrast medium.[1] ERCP procedure is a painful and stressful procedure, necessitating the need for general anesthesia or deep sedation during the procedure.[2] Geriatric patients constitute a considerable proportion of the patient population that undergoes ERCP and are at risk for adverse effects related to sedation by sedative agents such as apnea, arrhythmia, hypertension, bradycardia, and oxygen desaturation.[3] The purpose of preemptive analgesics is to prevent or minimize the memory of pain and thereby reduce the need for analgesia and analgesic medicine complications.[4]

Ibuprofen, a propionic acid derivative, has analgesic, anti-inflammatory, and antipyretic features similar to a non-selective cyclooxygenase (COX) inhibitor.[5] Intravenous (IV) ibuprofen first came into use in 2009 and is suitable for preemptive analgesia. Previous studies have shown that IV ibuprofen decreases postoperative pain and the need for opioids.[6] The central anti nociceptive-analgesic effect of paracetamol due to the inhibition of COX-3, a variant of COX-1.[7] Studies on the parenteral formulation of paracetamol have reported that it reduces post operative opioid use; reduces the incidence of vomiting and nausea; improves sleep quality; and causes less sedation.[8,9] Studies conducted in recent years have reported that IV ibuprofen and paracetamol can decrease the need for narcotic analgesia and sedative agents.[10] We hypothesized that the use of IV ibuprofen prior to ERCP procedure would reduce opioid consumption and the associated side effects. Therefore, in this study designed to test this hypothesis, IV paracetamol and IV ibuprofen were used for analgesic premedication purposes in ERCP and comparisons were made between them regarding intraoperative hemodynamics, need for additional narcotic analgesics, and recovery period in geriatric patients.

## 2. Material and methods

Prior to the study, approval was obtained from the Hitit University local ethics committee, and informed consent was obtained from each patient. The study involved 80 patients, aged > 65 years, classified as American Society of Anesthesiologists (ASA) physical status I–III who would undergo ERCP with sedoanalgesia under elective conditions in the gastroenterology clinic. Patients were screened for mental, pulmonary or heart diseases; liver and/or renal failure; gastrointestinal surgery history; prior use of sedative–hyp-

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notic or centrally acting medicine; and known sensitivity to benzo-diazepine, local anesthetics, propofol, and opioid group drugs and were excluded from the study when one of these conditions was present.

Using a computer generated sequence of numbers and a sealed envelope technique, patients were randomly divided into three groups: group P (n = 27) patients were administered a 1000 mg/100 ml paracetamol infusion 30 minutes (min) before the procedure; group I (n = 28) patients were administered a 400 mg/100 ml IV ibuprofen infusion 30 min before the procedure; and group C (n = 25), a control group, patients were not administered analgesics before the procedure.

Thirty minutes after paracetamol or ibuprofen administration, patients were taken to the ERCP unit where mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SpO2) were monitored. Sedation depth was assessed using the Ramsey Sedation Scale (RSS) (RSS scores:1 point = awake and restless; 2 points = awake and cooperative, 3 points = asleep and responds to verbal stimulus; 4 points = asleep, brisk response to painful stimulus; 5 points = asleep, sluggish response to painful stimulus; and 6 points = asleep and no response to painful stimulus). The study was completed in a double blind manner by ensuring that patients as well as the researcher evaluating the patients were not aware of the medication used. Prior to and throughout ERCP procedure, MAP, HR, SpO2, respiratory rate, and procedure durations were recorded starting at baseline (values before the medicine was administered), 1 and 5 min after the medicine was administered, and at 5 min intervals until an hour after the procedure. Patients were positioned facedown, with head turned toward the endoscopist (right), and oxygen support was applied via nasal cannula at a rate of 4 L/min.

Prior to the start of ERCP, patients were administered an IV injection of midazolam (0.02 mg/kg), an IV loading dose of propofol (1 mg/kg), and additional doses of infused propofol (1–3 mg/kg/h) to maintain a sedation level of RSS score > 4. When the patients had pain (wriggle, a 30% increase in HR and MAP), they were administered 0.5 μg/kg of fentanyl in repeated doses, with each doses recorded as an additional analgesic dose. Any adverse effects during the procedure were recorded, which included hypoventilation (respiratory rate < 8 breaths/min [BPM], and superficial abdominal respiration observation), apnea (lack of respiration for 30 s), hypoxia (SpO2 < 90%), hypotension (30% decrease from baseline), hypertension (30% increase from baseline), arrhythmia, and bradycardia (< 50 BPM). For patients exhibiting an SpO2 below 90%, interventions included increasing oxygen delivery via nasal cannula to 6 L/min, stimulating patients with a verbal and/or tactile stimulus, providing respiratory support, and decreasing or ending the infusion when necessary. For patients who developed hypotension, fluid infusion was increased, and if the condition remained unresolved, they were administered with 5 mg IV ephedrine. For bradycardia, 0.5 mg IV atropine was administered. Patients who continued to have hypoventilation, apnea, hypotension, hypertension, arrhythmia, and bradycardia despite the initiated treatment plan were excluded from the study.

After ERCP procedure, patients with an RSS score < 4 were taken from the ERCP room to the recovery room, and their MAP, HR, SpO2, visual analog scale (VAS) score, and Modified Aldrete Score (MAS) were recorded at 5 min intervals for 30 min with time recover to MAS:9 recorded. Patients with MAS:9 and greater received a medical recommendation, and were referred, and then medically escorted to the appropriate department. After ERCP, the endoscopist evaluated the outcome of the procedure and the patients' status (bad, moderate, good, very good).
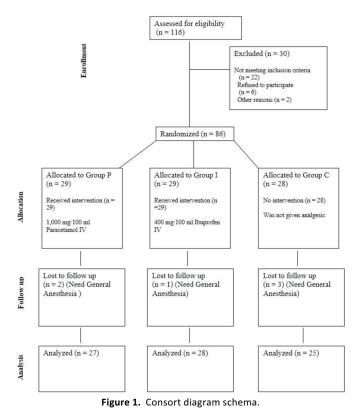
## 2.1. Statistical analysis

Data were analyzed using SPSS 22 (SPSS Inc., Chicago, II, USA). The mean ± standard deviation, median, minimum, and maximum were assessed for quantitative data across subjects. Categorical variables were presented numerically and in percentages. Normality was tested using the Shapiro–Wilks test, and one-way analysis of variance (ANOVA) test was performed for group comparisons for normally distributed data. For non-normally distributed data, group comparisons were performed using Kruskal-Wallis test by ranks. Post hoc pairwise multiple comparisons tests were performed to determine significant differences between groups. Comparisons of the categorical data were performed using chi-square or Fisher exact test. Significance level was set at a p value of 0.05.

The sample size was calculated using G-power (Version 3.1) package programming. It was calculated for ANOVA, which was used for testing the main hypothesis of the present study. As a result of the sample size analysis, it was found that minimum 75 individuals, 25 in three different groups, needed to be enrolled in the study in order to reveal significant differences among the groups using 80% power (1-$\beta$ = 0.80), $\alpha$ = 0.05 error (95% confidence interval), and 0.37 effect size with a one-sided hypothesis.

## 3. Results

Data obtained from 86 out of 116 patients who met the inclusion criteria were used in this study. Six out of 86 patients were excluded from the study due to the need for general anesthesia (Figure 1). The remaining patients were aged between 65 and 103 years. Of all the patients, 55% (n = 44) were female and 44% (n = 36) were male. No significant differences were observed among the groups in terms of age, weight, indication, and duration of ERCP, ASA scores, and gender distributions (p > 0.05) (Table 1).

Significant differences were onserved among groups in terms of additional sedation medication dose. Group I was found to have a



**Figure 1.** Consort diagram schema.

significantly lower intraoperative fentanyl dose than group P and group C. However, no significant differences were found between the groups P and C in terms of intraoperative fentanyl use. No significant differences were found among the groups in terms of the administration of additional propofol dose (Table 2). While VAS scores demonstrated no significant differences among groups at 1 min and 15 min after the procedure, group I was found to have significantly lower VAS scores 30 min after the procedure. While the recovery times did not show significant differences for MAS:9, among the groups, group I had the shortest MAS:9 time (Table 3).

There were no significant differences among the groups when comparing adverse effects to the procedure. While postoperative apnea and nausea were highest in group C, they were higher in group P than in group I. Intraoperative hypertension was highest in group C and lowest in group I. No significant differences were found among the groups in terms of patient and endoscopist satisfaction (Table 4). HR and MAP were not significantly among the groups (Figure 2).

## 4. Discussion

The purpose of sedoanalgesia is to ensure patient comfort and cooperative during ERCP, with cardiac and respiratory stability. However, differences in pharmacokinetic and pharmacodynamic responses to sedative and analgesic agents can lead to vomiting and nausea or adverse events on an individual by individual basis requiring different sedation levels based on the severity of the response.[11–13] Today, barbiturates, benzodiazepines, hypnotics and opioids are frequently used for sedation purposes. However, geriatric patients are more sensitive to the negative effects of the medications used for sedation. Thus, efforts should be made to minimize the doses of sedative drugs to reduce adverse effects.[14,15]

Despite the use of a general analgesic regimen, there is still a need for opioids in order to relieve severe pain. In addition, there is a consensus to reduce opioid consumption in procedures that require analgesics due to their systemic adverse effects.[16] The latest approach for reducing opioid consumption is using opioids, analgesics, and/or anti-inflammatory drugs before, during and/or after the procedure. Ibuprofen and paracetamol are among the most frequently used analgesics due to their lower potential of adverse effects than

**Table 1**
Patients characteristics.

|  | Group P (n = 27) | Group I (n = 28) | Group C (n = 25) | p |
|---|---|---|---|---|
| Age | 75.52 ± 9.39 | 77.75 ± 9.20 | 72.26 ± 5.75 | 0.068 [a] |
| Weight (kg) | 80.19 ± 10.14 | 78.00 ± 10.77 | 73.72 ± 6.96 | 0.051 [b] |
| Operation time (min) | 36.78 ± 10.97 | 36.61 ± 10.37 | 32.20 ± 10.11 | 0.214 [b] |
| ERCP indication |  |  |  | 1.000 [d] |
| Pancreatitis | 5 | 5 | 4 |  |
| Cholangitis | 4 | 5 | 4 |  |
| CBD stone | 14 | 15 | 13 |  |
| Other | 4 | 3 | 4 |  |
| ERCP procedure |  |  |  | 0.994 [d] |
| Sphincterotomy | 16 | 17 | 15 |  |
| Balloon dilatation | 3 | 4 | 3 |  |
| Biliary stent | 5 | 4 | 3 |  |
| Other | 3 | 3 | 4 |  |
| Sex |  |  |  | 0.815 [c] |
| Female | 16 | 14 | 14 |  |
| Male | 11 | 14 | 11 |  |
| ASA |  |  |  | 0.761 [c] |
| ASA 1 | 4 | 7 | 7 |  |
| ASA 2 | 11 | 12 | 9 |  |
| ASA 3 | 12 | 9 | 9 |  |

[a] Kruskal–Wallis test, [b] ANOVA test, [c] Chi-square test, [d] Fisher exact test.
ASA: American Society of Anesthesiologist; CBD: common bile duct; ERCP: Endoscopic Retrograde Cholangiopancreatography.

**Table 2**
Additional drug table (median (min–max)).

|  | Group P (n = 27) | Group I (n = 28) | Group C (n = 25) | p | Post hoc p value |
|---|---|---|---|---|---|
| Drug |  |  |  |  |  |
| Propofol (mg) | 90 (0–200) | 70 (0–200) | 110 (0–200) | 0.076 [a] | - |
| Fentanil (μg) | 32.5 (0–50) | 12.5 (0–50) | 37.5 (0–50) | 0.005 [a] | P-I: 0.016 P-C: 0.189 I-C: 0.004 |

[a] Kruskal–Wallis test.
mg: milligram, μg: microgram.

**Table 3**
Visual Analog Scale and Modified Aldrete Score values.

|  | Group P Median (min–max) | Group I Median (min–max) | Group C Median (min–max) | p | Multiple comparison p |
|---|---|---|---|---|---|
| VAS |  |  |  |  |  |
| 1.dk | 2 (0–3) | 1 (0–3) | 3 (0–5) | 0.516 [a] | - |
| 15.dk | 5 (1–7) | 4 (0–5) | 6 (1–8) | 0.114 [a] | - |
| 30.dk | 7 (1–9) | 4 (0–5) | 9 (2–10) | < 0.001 [a] | P-C: 0.286 I-C: < 0.001 P-I: 0.001 |
| MAS 9 time | 9.56 ± 0.51 (10) | 8.71 ± 0.53 (10) | 9.64 ± 0.70(9) | 0.656 [b] | - |

[a] Kruskal–Wallis test, [b] ANOVA test.
VAS: Visual Analog Scale, MAS: Modified Aldrete Score.

**Table 4**
Side effect and satisfaction.

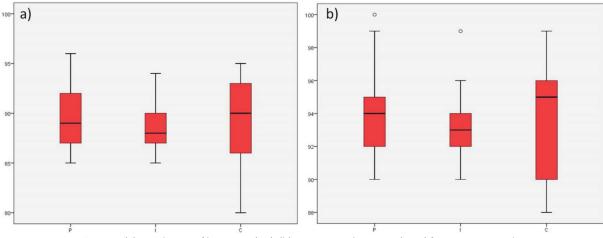|  | Group P n (%) | Group I n (%) | Group C n (%) | p |
|---|---|---|---|---|
| Side effect |  |  |  | 0.750 [b] |
| Apnea | 6 (22.2) | 4 (14.2) | 8 (32.0) |  |
| Nausea | 7 (25.9) | 4 (14.2) | 9 (36.0) |  |
| Vomiting | 2 (7.4) | 1 (3.5) | 1 (4.0) |  |
| Hypotension |  |  |  | 0.092 [b] |
| Yes | 7 (25.9) | 3 (10.7) | 9 (36.0) |  |
| Patient satisfaction |  |  |  | 0.609 [a] |
| Very good | 2 (7.4) | 5 (17.8) | 1 (4.0) |  |
| Good | 18 (66.6) | 20 (71.4) | 19 (76.0) |  |
| Moderate | 5 (18.5) | 2 (7.1) | 4 (16.0) |  |
| Bad | 2 (7.4) | 1 (3.5) | 1 (4.0) |  |
| Endoscopist satisfaction |  |  |  | 0.315 [b] |
| Very good | 19 (70.3) | 23 (82.2) | 21 (84.0) |  |
| Good | 5 (18.5) | 5 (17.8) | 4 (16.0) |  |
| Moderate | 3 (11.1) | 0 | 0 |  |
| Bad | 0 | 0 | 0 |  |

[a] Chi-square test, [b] Fisher exact test.

**Figure 2.** (a) Distribution of heart rate (HR). (b) Mean arterial pressure (MAP) for groups P, I, and C.

that of other medications.[5] To date, no studies have compared the effects of IV ibuprofen or paracetamol for preemptive purposes prior to ERCP, especially in geriatric patients.

Viswanath et al. compared the effects of preemptively administered IV ibuprofen and paracetamol infusions prior to dental surgery on postoperative pain and consumption of narcotic analgesics and reported that ibuprofen had an important preemptive analgesic effect that resulted in a decreased use of postoperative opioids.[17] Celik et al. investigated the effects of preemptively administered ibuprofen and paracetamol before septorhinoplasty operations on postoperative pain and opioid consumption and highlighted the significant effect of ibuprofen overparacetamol in reducing the postoperative opioid consumption.[18] Mutlu et al. reported that IV ibuprofen administered before thyroid surgery decreased postoperative opioid consumption.[19] The present study results also showed that preemptively used ibuprofen prior to ERCP significantly decreased intraoperative fentanyl consumption.

Despite the fact that propofol is commonly used for sedoanalgesia and general anesthesia, its property of causing intraoperative hypotension is well known. Intraoperative hypotension might result in negative outcomes such as myocardial damage, stroke, acute renal damage, and death.[20] Hannam et al. investigated the hemodynamic effects of intraoperative propofol and etomidate in a patient group that underwent cardiac surgery and found that propofol decreased MAP more after the induction.[21] In the present study, three patients in group C, two patients in group P, and one patient in group I (6 patients) developed intraoperative hypotension. Each of these patients received a 5 mg IV ephedrine once to counteract this hypotensive effect considered to be linked to the use of intraoperative propofol.

Ulusoy et al. compared the effect of midazolam and tramadol on early cognitive functions after ERCP, and found no significant differences in MAS between the two groups.[22] Akıncı et al. compared groups that were administered dexketoprofen and paracetamol for analgesic purposes in ERCP; the three groups exhibited no significant differences in MAS.[23] In the present study, there was no significant difference among the three groups regarding MAS:9 time; but group I was found to have the shortest MAS:9 time. We suspect that the shortened MAS:9 time for group I was due to a lower dose of intraoperative fentanyl and propofol used in this group than that in the other two gropus. Kelly et al. found that ibuprofen did not increase bleeding in plastic surgery operations.[24] We also found that participating patients did not experienc any problems related to non-steroidal anti-inflammatory medicine-related coagulation and bleeding.

Nausea and vomiting, one of the most important postoperative issues, are related to the type and duration of surgery, the type of anesthesia, and the dose of opioid.[8] Gulhas et al., in their study of 120 total abdominal hysterectomy patients, reported that paracetamol, lornoxicam and trometamol decreased the adverse effects such as nausea, vomiting, and constipation by decreasing the dose of postoperative fentanyl.[25] In our study, there was no significant difference among the groups in terms of side effects.

One of the limitations of the present study is that we could not use the Bispectral Index (BIS), which is a more objective method for evaluationing sedation depth. However, the relationship between RSS and BIS has been reported in the related literature.[26,27] Another limitation of the study is that we did not monitor postoperative early and late period cognitive function and discharge time.

**5. Conclusion**

In conclusion, IV ibuprofen results in lower pain scores than paracetamol and control group by reducing intraoperative opioid use in patients undergoing ERCP. It also reduces opioid related adverse events such as nausea and apnea. We believe that ibuprofen is a valuable option in geriatric patients who are at a risk of experiencing adverse effects of narcotic medications. Larger studies are needed to evaluate the efficacy and use of ibuprofen in patients undergoing ERCP procedures.

**Conflict of interest statement**

Author 1 has nothing to disclose.
Author 2 has nothing to disclose.

**Ethical approval**

All procedures performed in studies in volving human par-

ticipants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

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