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Effect of Intraoperative Remifentanil on Postoperative Pain and Analgesic Requirements in Colorectal Surgery: A Cohort Study

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Abstract

Background: Remifentanil is an ultra-short-acting, high-potency opioid. Short-acting drugs such as Remifentanil can cause acute drug tolerance or opioid-induced hyperalgesia, thereby affecting postoperative pain.

Objective: This study aimed to compare postoperative pain in patients receiving propofol-remifentanil anesthesia versus Propofol alone.

Methods & Materials: This cohort study was performed on 35 patients admitted to the central operating room of Ghaem Hospital. Samples were selected from among the patients for two groups: those receiving Remifentanil plus Propofol and those receiving Propofol alone during surgery. The amount of analgesia received was recorded at 0, 30, 60, 120 minutes, and 6 and 12 hours after surgery. The patient's pain was also assessed using the VAS questionnaire at the same time. Data were analyzed using SPSS software version 23.

Results: In total, 60% (21 patients) were male, and 40% (14 patients) were female, with a mean age of 56.88 ± 17.88 years. The two groups were homogeneous in terms of age, sex, and weight. The two groups were also not statistically different in surgery duration, duration of anesthesia, or propofol dose. No significant difference was observed between the two groups in terms of intravenous Acetaminophen and meperidine intake at 0, 30, 60, 120 minutes, 6 hours, and 12 hours. There was no significant difference between the two groups in terms of ketorolac 30 mg and methadone. Although VAS scores in the Remifentanil + propofol group were lower than those in the propofol group at the final time points of 2, 6, and 12 hours, group (Propofol only or Remifentanil + propofol) did not affect VAS scores.

Conclusion: The study results showed that when an intermediate dose of Remifentanil (0.1 µg/kg/min) was combined with Propofol, no evidence of post-operative hyperalgesia was observed. Therefore, it is recommended that Remifentanil be preferably used in combination with Propofol.

Keywords: Hyperalgesia, Remifentanil, Propofol, pain.

1. Introduction

Remifentanil is an ultra-short-acting opioid anesthetic widely used in surgical procedures due to its potent analgesic properties and ease of titration. It is approximately twice as potent as fentanyl and 200 times more potent than morphine, acting primarily as a µ-opioid receptor agonist to provide effective analgesia during surgery (1). These properties make it highly desirable for use in operating rooms, as it ensures rapid onset and offset, facilitating smooth transitions in patient care during and after procedures. Despite its advantages, the use of short-acting opioids like Remifentanil has been associated with significant postoperative challenges, including acute opioid dependence and opioid-induced hyperalgesia (1, 2). Hyperalgesia, a state of increased sensitivity to pain, can complicate postoperative pain management, requiring higher opioid doses and alternative strategies for adequate pain control. This phenomenon is believed to occur due to sensitization via pronociceptive mechanisms, such as the “wind-up phenomenon,” which exacerbates pain perception (3).

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Studies in animal models and human volunteers have demonstrated that acute tolerance to the analgesic effects of Remifentanil can develop within just two hours of continuous infusion, raising concerns about its implications for postoperative pain control (4). Although nausea and constipation are common opioid-related adverse effects, they are less clinically relevant during general anesthesia. Instead, the primary concerns include acute tolerance and hyperalgesia, which may compromise patient recovery and comfort following surgery. (2)

Hyperalgesia in surgical contexts poses a significant challenge, as it complicates the differentiation between opioid-induced hyperalgesia and unmanaged pain (5). Patients experiencing hyperalgesia often exhibit heightened sensitivity to stimuli, even generalized pain (allodynia). The management of opioid-induced hyperalgesia involves strategies such as dose reduction, adjunctive non-opioid analgesics, and the use of NMDA receptor antagonists like ketamine, which help mitigate pronociceptive sensitization (3). Although most studies focus on hyperalgesia arising postoperatively, there is growing evidence that intraoperative administration of high doses of opioids, including Remifentanil, may trigger this phenomenon.

Given these challenges, this study aims to compare the incidence and severity of postoperative hyperalgesia in patients receiving Remifentanil and Propofol during surgery to those receiving plain Propofol. Understanding the impact of Remifentanil on postoperative pain and hyperalgesia will help guide better pain management strategies in colorectal cancer surgery.

2. Materials and Method

2.1. Participants

This cohort study was conducted on patients undergoing colorectal surgery for rectal cancer at Qaem Hospital. A convenience sampling method was employed. Eligible participants were patients aged >20 years with an American Society of Anesthesiologists (ASA) physical status of I–III who were scheduled for colorectal surgery under general anesthesia. During the procedure, patients received either Propofol alone or Propofol combined with Remifentanil, and no other anesthetic or analgesic agents were administered intraoperatively. Patients with chronic inflammatory diseases, preoperative chronic pain, psychiatric disorders, diabetic neuropathy, substance or alcohol abuse, those who had taken an analgesic within 24 hours prior to the procedure, or those who withdrew from the study were excluded.

A baseline questionnaire including age, gender, weight, past medical history, and drugs was completed for all patients scheduled for colorectal surgery upon admission to the operating room. The selection of anesthetic agents (Propofol alone or Propofol + Remifentanil) for general anesthesia was determined by the attending anesthesiologist according to routine clinical practice and individual clinical judgment. The investigators did not participate in or influence this decision. Subsequently, patients were screened based on the anesthetic technique and intraoperative medications administered. Those who met the predefined inclusion criteria were enrolled in the study and assigned to one of the two study groups according to the anesthetic regimen received: Group A (remifentanil group) and Group B (non-remifentanil group). All patients received premedication with midazolam (1–2 mg) and fentanyl (2 µg/kg), followed by induction with propofol (2 mg/kg) and atracurium (0.5 mg/kg). During surgery, Group A received Propofol (100 µg/kg/min) and Remifentanil (0.1 µg/kg/min) for anesthesia maintenance. In comparison, Group B received Propofol (100 µg/kg/min) alone.

Postoperative pain was assessed using the Visual Analog Scale (VAS) immediately after regaining consciousness and at 30, 60, and 120 minutes post-surgery. Postoperative analgesia was administered according to a standardized institutional protocol. VAS scores guided analgesic administration: no medication for scores <4, intravenous Acetaminophen for scores 5–6, and opioids for scores 7–9. Additional parameters recorded included surgery duration, anesthesia time, total doses of Remifentanil and Propofol, and post-operative total analgesic use.

2.2. Sample Size and Statistical Analysis

According to the data obtained from the prior study (6), the mean Morphine use after 30 min in the Remifentanil and non-Remifentanil groups was reported as about 5 (3.5) and 2(1.1), respectively. Considering α=0.05 and β=0.2, the minimum sample size was calculated to 15 in each study group using G*power software.

Data analysis was conducted using SPSS v23. Descriptive statistics were expressed as frequency, percentage, mean, and standard deviation. Chi-square or Fisher's exact test was used for qualitative variables. In contrast, independent t-tests or Mann-Whitney tests were employed for quantitative variables, depending on data normality. To investigate the effect of time measurements (repeated variable) and the time * group interaction, the generalized estimating equation (GEE) method was used.

3. Results

The present study was conducted on 35 patients admitted to the central operating room of Qaem Hospital, Mashhad, Iran. The patients were allocated into two groups: those who received Remifentanil plus Propofol (18 patients) and those who received only Propofol during surgery (17 patients). The mean age of participants was 56.88 ± 17.88 years, ranging from 20 to 83 years. The mean age of the participants by group is shown in Table 1. According to these data, there was no significant difference in age, weight, or gender between the two groups, indicating that the groups were homogeneous.

Table 1. Comparison of demographic data of two groups of Propofol and Remifentanil + Propofol

Variable		Propofol Group	Remifentanil + Propofol Group	P-value
Age (years)		60.88 ± 17.95 64 (50, 77)	53.11 ± 17.47 52 (39, 69)	0.18 *
Weight (kg)		65.52 ± 6.40 65 (62, 70)	68.11 ± 7.92 68.5 (61, 75)	0.35 *
Gender	**Female**	7 (41.2%)	7 (38.9%)	0.89 **
	Male	10 (58.8%)	11 (61.1%)	

Data presented as mean ± standard deviation or median (interquartile range). The qualitative variable was reported as frequency (percentage). (*Mann-Whitney U test; **Chi-square test)

The mean duration of surgery was 4.3 ± 1.58 hours (ranging from 1.45 to 7.3 hours), and the mean duration of anesthesia was 4.64 ± 1.55 hours (ranging from 2 to 7.5 hours). The mean duration of surgery and anesthesia for each group is shown in Table 2. According to this data, there was no significant difference between the groups concerning the duration of surgery (P = 0.44) or the duration of anesthesia (P = 0.37), indicating that the groups were homogeneous in terms of these variables.

Table 2. Comparison of average duration of surgery and duration of anesthesia in two groups of Propofol and Remifentanil

Variable	Propofol Group		Remifentanil + Propofol		P-value
	Mean	SD	Mean	SD	
Surgery Duration (hours)	4.49	1.34	4.12	1.79	0.44
Anesthesia Duration (hours)	4.85	1.33	4.45	1.75	0.37
Propofol Dose	1838.82	728.56	1616.66	618.58	0.34

* Mann-Whitney test

The mean dose of Propofol in both groups was estimated at 1724.57 ± 673.65 (ranging from 110 to 3000 mg), and the mean dose of Remifentanil was 1.06 ± 2.05 (ranging from 1 to 4 µg). Table2 shows the mean Propofol dose for the two groups. According to the data in this table, no significant difference was observed between the two groups regarding the Propofol dose, and the two groups were homogeneous (P = 0.34).

Assessment of patients regarding the presence of underlying diseases showed that 68.6% (24 individuals) of the patients had no underlying diseases. The frequency of underlying diseases among the studied individuals is displayed in Table3. Based on the data in this table, no significant differences were observed between the two groups regarding the incidence of diabetes (P = 0.603), hypertension (P = 0.402), hyperlipidemia (P = 0.22), asthma (P > 0.99), and ischemic heart diseases (P = 0.104). Therefore, the two groups were also homogeneous regarding the occurrence of underlying diseases. Epilepsy, hyperthyroidism, and hypothyroidism were not reported in any of the studied patients.

Table 3. Frequency of underlying diseases in the propofol and remifentanil groups

Underlying Diseases	Propofol N (%)	Remifentanil + Propofol N (%)	Total Frequency	P-value
Diabetes	15 (88.2%)	17 (94.4%)	32 (91.4%)	0.603
Hypertension	13 (76.5%)	16 (88.9%)	29 (82.9%)	0.402
Hyperlipidemia	15 (88.2%)	18 (100%)	33 (94.3%)	0.22
Asthma	17 (100%)	17 (94.4%)	34 (97.1%)	0.99
Ischemic Heart Disease	14 (82.4%)	18 (100%)	32 (91.4%)	0.104

*Fisher's exact test

** Percentages exceed 100% because patients could have multiple comorbidities

Based on the obtained data, the majority of patients did not receive analgesics at the zero-time point (immediately after regaining consciousness in the recovery room). Additionally, 20%, 37.2%, and 17.1% of patients did not receive analgesics at minutes 30, 60, and 120, respectively. At the sixth postoperative hour, only 25.7% of patients did not require analgesics, while approximately 63% did not receive analgesics at the twelfth hour. The findings indicate that at zero, intravenous Acetaminophen was administered more than other analgesics (20%), whereas 25 mg of meperidine was

given more than other analgesics at minutes 30, 60, and 120. Furthermore, intravenous Acetaminophen was administered more than other analgesics at hour 6 (25.7%). No significant difference was observed between the two groups regarding the administration of 1000mg of intravenous Acetaminophen at zero time point (P = 0.104), minute 30 (P > 0.99), minute 60 (P = 0.22), minute 120 (P > 0.99), hour 6 (P = 0.32), and hour 12 (P = 0.603). Additionally, no significant differences were found between the two groups in terms of receiving 25 mg of meperidine at zero (P > 0.99), 30 (P = 0.35), 60 (P = 0.17), 120 (P > 0.71) minutes, and 6 (P = 0.08), 12 (P > 0.99) hours postoperatively. Likewise, no significant difference was observed between the two groups regarding the administration of 30 mg of ketorolac and methadone.

The mean VAS scores of patients at different times for the two groups were presented in Table4. Although the VAS scores in the Remifentanil + propofol group were lower than those in the propofol group at the final time points of 2, 6, and 12 hours, the group (Propofol only or Remifentanil + Propofol) did not have any effect on VAS score.

Table 4. The average VAS score of patients at different times by two study groups

VAS Score	Propofol	Remifentanil + Propofol	P-value (time)	P-value (group)	P-value (time*group)
Minute 0	4.23 ± 1.25	4.88 ± 2.21	0.84	0.46	0.116
Minute 30	7.29 ± 1.96	6.22 ± 2.28			
Minute 60	5.47 ± 1.58	6.05 ± 2.28			
Minute 120	6.47 ± 1.17	5.94 ± 1.73			
6 Hours	5.52 ± 1.58	4.83 ± 1.09			
12 Hours	4.94 ± 1.47	3.77 ± 1.66			

Data presented as mean standard deviation. Generalized estimating equation (GEE) was used.

Finally, the progression of VAS scores over time was examined in both groups. The data indicated no significant difference in the progression of VAS scores at different time points between the two groups (P = 0.24). Figure1 illustrates the progression of VAS scores over time in the two groups.

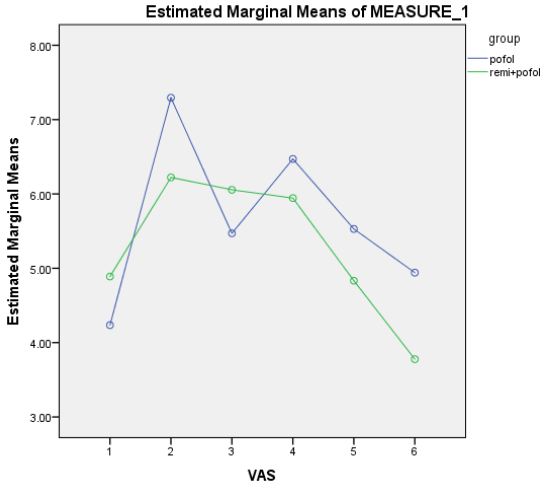

Figure 1. Progression of VAS Scores over time in both groups

4. Discussion

Since pain is a common complication that most patients with rectal cancer suffer after surgery, managing hyperalgesia in these patients can play a critical role in their treatment and recovery. The findings show that intravenous Acetaminophen was administered more frequently than other analgesics at minute zero and hour 6. In contrast, meperidine was administered more frequently at minutes 30, 60, and 120. Additionally, methadone was the most administered analgesic at hour 12. According to the obtained data, there was no significant difference between the two groups (those receiving Remifentanil with Propofol and those receiving only Propofol) in terms of intravenous Acetaminophen and meperidine administration at minute zero, 30, 60, 120, hour 6, and hour 12. Similarly, no significant difference was observed between the two groups regarding the administration of 30 mg of ketorolac and methadone. Regarding the VAS score, there was no significant difference between the two groups at minutes 0, 30, 60, and 120.

Opioid-induced hyperalgesia (OIH) has been clearly demonstrated in both animal and human models (7). In postoperative patients, OIH has mainly been studied following opioid-based anesthesia and during postoperative analgesia. These findings have mostly been used to highlight hyperalgesia as a pathophysiological phenomenon; however, the true clinical impact of OIH has not yet been accurately estimated. Previous experimental studies have shown that the administration of Remifentanil induces OIH and tolerance (8). Ishida and colleagues reported that Remifentanil causes temporary hyperalgesia, which is strongly associated with the duration of exposure to Remifentanil (9). However, the occurrence of OIH in patients receiving Remifentanil intraoperatively remains controversial. The most likely explanation for this discrepancy between experimental and clinical results may lie in the difference in pain conditions, as pain during opioid administration may delay tolerance and reduce surgical pain (10).

In a 2016 study conducted in Hong Kong, Yu et al. demonstrated that, due to variations in drug administration methods, infusion duration, anesthesia duration, cumulative remifentanil doses, and pain measurement methods, it was not possible to reach a definitive conclusion regarding the effect of Remifentanil on hyperalgesia (1). Many studies have compared the effects of high-dose Remifentanil to lower doses or to a control group, with a wide variety of surgeries, including major procedures such as abdominal surgery (16), gynecology, breast surgery (11), thyroid surgery (12), orthopedic surgery (13), and cardiac surgery (6). Overall, there is significant heterogeneity. Studies have used various infusion regimens, infusion durations, anesthesia maintenance, cumulative remifentanil doses, and pain measurement outcomes. Overall, two main factors—remifentanil dose and method of administration along with anesthesia maintenance—are cited as influential in the development of hyperalgesia. Previous research has indicated that OIH may occur when Remifentanil is administered at doses exceeding 2 $\mu g.kg^{-1}.min^{-1}$. Generally, high-dose remifentanil infusions have led to increased postoperative analgesic requirements. Previous studies have shown that higher doses of Remifentanil may induce acute opioid-induced hyperalgesia. Comparing studies involving various surgeries may be challenging due to differences in postoperative pain intensity, which could lead to varying analgesic needs.

It has been suggested that OIH could contribute to chronic pain development (1). In a 2005 study in Manchester, Rauf and colleagues evaluated the effects of Remifentanil on morphine requirements during the first postoperative hour following

coronary artery bypass surgery under propofol-fentanyl-based anesthesia. Twenty patients undergoing coronary artery bypass surgery received either remifentanil 0.1 µg/kg or saline, randomly assigned, with Propofol and the study drug maintained until patients were ready to wake after surgery. Postoperative analgesia was provided immediately with morphine. Results indicated that, within the first hour after stopping Propofol, morphine requirements were significantly higher in the remifentanil group than in the saline group. There was no difference in total morphine administered over the entire postoperative period or in total requirements within the first 12 hours. Pain scores and stimulation scores also did not significantly differ between the two groups, suggesting that remifentanil use is associated with increased opioid requirements in the first hour after discontinuation (6).

In a 2013 study in Germany, Welzing and colleagues investigated fentanyl and remifentanil doses, along with low-dose midazolam, in 46 mechanically ventilated children. Results showed that Remifentanil had to be increased by 24% and fentanyl by 47% to achieve adequate sedation during mechanical ventilation. After extubation, only one infant from each group required methadone for withdrawal symptoms. None of the infants exhibited signs of OIH in either group, suggesting that Remifentanil, combined with low-dose midazolam, does not cause hyperalgesia (14).

Wang and colleagues observed that Remifentanil, a short-acting opioid, is more prone to inducing hyperalgesia, which can lead to increased postoperative pain, morphine consumption, and pain sensitivity. They found that a 0.3 µg/kg/min Remifentanil dose reduced patients' mechanical pain threshold, resulting in hyperalgesia (15). Xiaohu and colleagues noted a significant difference in morphine requirements in the first postoperative hour. However, no significant difference was found at 12 hours. The greatest difference in absolute morphine doses occurred between 15 and 30 minutes, aligning with the pharmacokinetics of Remifentanil and morphine (Remifentanil has a tissue-sensitive half-life of 8 minutes, while morphine's onset of action is around 20 minutes after IV administration) (16).

Additional studies have provided evidence supporting the concept of hyperalgesia. Ruíz-López and colleagues measured pain tolerance in patients receiving Remifentanil at 0.1 µg/kg per minute over 4 hours, noting that after reaching peak pain between 60-90 minutes, Remifentanil's analgesic effect began to diminish (17). Kim and colleagues conducted a study on 198 patients undergoing gastrectomy, receiving intraoperative Remifentanil at 2, 4, 8, or 12 ng/mL, concluding that intraoperative Remifentanil at 12 ng/mL accelerated postoperative opioid requirements (18). A simple pharmacokinetic difference between various opioid receptor agonists cannot explain these findings. Results from the present study indicate that patients received higher amounts of intravenous Acetaminophen in the zero minute and at 6 hours postoperatively and higher doses of meperidine at 30, 60, and 120 minutes, while methadone use was highest at 12 hours. Consistent with previous studies, analgesic requirements were higher an hour after remifentanil use. However, no significant differences in intravenous Acetaminophen and meperidine requirements were observed between groups that received Propofol and Remifentanil and those that received only Propofol at 0, 30, 60, and 120 minutes and at 6 and 12 hours.

Various pharmacological methods have been tested to prevent remifentanil-induced hyperalgesia in postoperative patients, including preoperative ketamine (19), magnesium (20), Propofol (21), and nitrous

oxide (22). Propofol-based anesthesia appears to have a preventive effect against remifentanil-induced hyperalgesia. Studies using propofol-based anesthesia have not shown a difference in morphine consumption with high-dose Remifentanil. Similarly, no difference in pain levels during the first 24 hours post-surgery has been observed, possibly due to sensitivity resulting from pain intensity, as all patients used controlled analgesia. Shin et al. demonstrated that Propofol could prevent remifentanil-induced hyperalgesia in postoperative patients (11). Most studies have not reported hyperalgesia associated with Propofol (23). However, Drdla and colleagues concluded that OIH occurred in the high-dose remifentanil group with Propofol, likely due to the high dose of Remifentanil. No significant findings were reported in the Propofol groups regardless of remifentanil dosage. A systematic review suggests that Propofol may have a preventive effect against remifentanil-induced hyperalgesia (24).

The results of this study do not support the occurrence of hyperalgesia during short-term intraoperative use. Considering that surgery duration, anesthesia duration, and propofol dosage were statistically similar and homogeneous, we recommend that Remifentanil should still be used intraoperatively.

Limitation: In this study, fentanyl was used for anesthesia induction in both groups, which can be considered a limitation of the study. Additionally, larger studies with more participants may provide more accurate results.

5. Conclusion

In this cohort study, an intermediate dose of Remifentanil (0.1 µg/kg/min) combined with Propofol was not associated with increased postoperative pain or analgesic consumption compared to Propofol alone. However, due to the non-randomized design, use of fentanyl in both groups, and multiple statistical comparisons, these findings should be interpreted as preliminary. A well-powered randomized controlled trial is needed to assess OIH risk definitively.

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Ethical Considerations: All procedures were conducted in accordance with the Declaration of Helsinki. This study was reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences with the approval code IR.MUMS.MEDICAL.REC.1398.325. Informed consent was obtained from all patients before they participated in the study. Patients were assured that their information would remain confidential.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

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Consent for Publication: Not applicable.

Author Contributions: **S.J.P.F.**: Conceptualization, study design, data collection, and manuscript preparation.**B.E.**: Methodology, data collection, and investigation.**M.E.**: Statistical analysis, data interpretation, and manuscript review.**M.S.M.**: Supervision, critical revision of the manuscript, and final approval of the version to be published. All authors

contributed to the study, critically reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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