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Comparison of Intraoperative Infusion of Remifentanil Versus Fentanyl on Pain Management in Patients Undergoing Spine Surgery: A Double Blinded Randomized Clinical Trial

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Abstract

Background: Remifentanil is an ultra-short-acting opioid which facilitates hemodynamic management. However, there are concerns about postoperative Remifentanil hyperalgesia because of its potent fast onset and offset.

Objectives: The aim of this study was to determine visual analog scale (VAS), postoperative pain, and morphine used in two groups after spine surgery.

Methods: In this randomized clinical trial study, 60 patients aged 18 - 60 years old, according to the American Society of Anesthesiology (ASA) I - II, who underwent spinal canal stenosis or scoliosis surgery, were divided into two groups. In the control group, patients received 0.07 - 0.1 μg/kg/h intraoperative Fentanyl infusion, and in the intervention group 0.1 - 0.2 μg/kg/min remifentanil was infused during the surgery. Both groups received 15 mg/kg intravenous Acetaminophen 20 minutes before the end of the surgery. Postoperative pain score and morphine consumption were measured 6, 12, 24, and 48 hours after discharge from the post-anesthesia care unit (PACU).

Results: During the first 12 hours, VAS and morphine consumption were significantly higher in remifentanil group ($P < 0.001$). However, no significant difference was found between the two groups in morphine consumption 12 - 48 hours after surgery.

Conclusions: These findings suggest that Remifentanil infusion during surgery may increase postoperative pain. Also, VAS and morphine consumption were higher during the first 12 hours.

Keywords: Remifentanil, Fentanyl, Postoperative pain, Spine surgery

1. Background

In medicine, pain is a prevailing sign, and its characterization is very important in diagnosis and choice of treatment (1, 2). Opioids are analgesics used for treating perioperative pain (3). Experimental studies have reported that opioids may induce hyperalgesia and allodynia (4, 5). Opioid-induced hyperalgesia (OIH) is characterized by an increase in pain severity, distribution, or sensitivity in patients receiving high doses or long periods of opioids for the treatment of pain (6). Pharmacokinetic characteristics of opiates affect the intensity of OIH. Remifentanil is an ultra-short-acting agonist of the mu-opioid receptor; it has a rapid onset and offset compared with long-acting opiates and may cause noticeable hyperalgesia (7-9). Remifentanil has an ester link that is sensitive to methyl ester hydrolysis by non-specific esterases in blood and other tissues. This makes the key to its pharmacokinetic and pharmacodynamic profile available (10). Among the possible mechanisms leading to OIH and antinociceptive tolerance, N-methyl-d-aspartate (NMDA) pain facilitator processes seem to play an important role (3, 11, 12). Some studies proposed that intense and constant contact with opioids can be associated with the advancement of hyperalgesia and NMDA receptors within the beginning of opioid-related hyperalgesia by pain facilitating framework (13, 14).

Several reports have demonstrated that the continuous infusion of remifentanil also induces hyperalgesia, which is similar to the findings related to some other opioids. OIH after intense opioid use in people has been a subject of argument; whereas studies in healthy volunteers have reliably appeared auxiliary hyperalgesia after intense opioid implantation frameworks (12, 13, 15-18).

2. Objectives

This study aimed to evaluate a better perioperative pain management strategy in older patients with spine canal stenosis and younger patients undergoing scoliosis surgery, that are challengeable in postoperative pain control. We determined postoperative pain, visual analogue scale (VAS), and morphine utilization in two groups undergoing spine surgery to compare the effects of remifentanil to fentanyl in patients.

3. Methods

3.1. Design

This double-blinded randomized clinical trial study was conducted in 2015 at Sina Hospital in Tehran, Iran. The study was approved by the Ethics Committee and Institutional Review Board (IRB) of Tehran University of Medical Sciences (ethics code: 92-04-30-27234-132500) and registered at the Iranian Registry of Clinical Trials (IRCT) website as "IRCT2014072618597N1".

3.2. Population

The population of this study included 60 patients scheduled to undergo elective lumbar spinal canal stenosis and scoliosis surgery. The inclusion criteria were patients aged 18 - 60 years; no history of substance abuse, and all had American Society of Anesthesiologists (ASA) status of I or II such as treated hypertension, obesity with BMI under 35. Exclusion criteria were irregular heart rhythm; prolonged corrected QT interval in electrocardiogram; severe valvular heart disease; acute or chronic renal failure; liver failure; nerve paralysis (hemiplegia); spinal nerve injury; patient's dissatisfaction to participate in the study; allergy to egg; history of using drugs, opioid, or alcohol abuse; psychiatric disorders; delayed extubation; obesity (BMI > 30); and surgical duration less than 2 hours. A written informed consent was obtained from all eligible patients. Patients were taught how to use the VAS for evaluating postoperative pain (0 = no pain, 10 = the worst pain).

3.3. Study Groups and Randomization

Using a computer-generated (Microsoft excel) table of random numbers, 30 patients were allocated to each group (intervention/control) (total sample size = 60). While the patients in the control group received intraoperative infusion of 0.07 - 0.1 μg/kg/h fentanyl (Caspian Pharmaceutical Company, Tehran, Iran), the patients in the intervention group received intraoperative infusion of 0.1 - 0.2 μg/kg/min remifentanil (Abureihan Pharmaceutical Company, Tehran, Iran). If the patients met the inclusion criteria, they were assigned into control and intervention groups according to a randomization table used in the surgery room. Intraoperative remifentanil and fentanyl infusions were adjusted to keep mean arterial blood pressure (MAP) and heart rate (HR) within 20% of baseline. All patients received intravenous (IV) Acetaminophen (15 mg/kg) 20 minutes before the end of the surgery. Blinding was done in such a way that patients, outcome assessors, and statistical analyzers were not aware of the study groups.

3.4. Anesthesia Method

After routine monitoring and establishment of IV access, we performed anesthesia induction with IV Midazolam (0.05 mg/kg), Fentanyl (2 μg/kg), Propofol (2 mg/kg), Atracurium (0.5 mg/kg), and Lidocaine (1 mg/kg). Anesthesia was maintained using Propofol (100 - 150 μg/kg/h), and intraoperative infusion of Propofol changed more or less to keep bispectral index (BIS) between 40 and 60. Neuromuscular blockades were maintained by Atracurium (0.1 mg/kg) every 20 minutes. Primarily, patients were ventilated as follows: (1) respiratory rate (RR): 10; (2) tidal volume (TV): 10c c/kg; (3) inspiratory/expiratory (I/E) ratio: 1/2; and (4) PaCO2 between 35 and 45. RR and TV were adjusted according to arterial blood gas (ABG) results. Intraoperative monitoring was performed by EKG, noninvasive blood pressure cuff (NIBP), invasive blood pressure (IBP), pulse oximeter, end-tidal carbon dioxide (ETCO2) monitoring, BIS, and RR.

3.5. Objectives and Measurements

Our primary outcome was to compare postoperative pain between the groups. Meanwhile, the secondary outcomes included evaluating postoperative opioid consumption, postoperative nausea and vomiting (PONV), and the time needed to start eating solids.

Postoperative pain was evaluated using VAS by a nurse who was unaware of the patient's group after arrival to the Post-Anesthesia Care Unit (PACU) (15 minutes after extubation) and 6, 12, 24, and 48 hours after discharge from PACU. Pain control was considered adequate if the score on the VAS was 3 and less and the patient had no complaints about pain. Rescue analgesia was maintained using IV morphine. Morphine was administered on-demand as analgesia with a dose of 2.5 mg as needed with respiratory monitoring. Total morphine consumption was recorded. The level of sedation by using Ramsay sedation scale (RSS)

was assessed on a 6-point scale (1 = anxious, restless, agitated; 2 = co-operative, oriented, tranquil; 3 = responding to commands, sleeping; 4 = brisk response to a light glabellar tap or loud noise; 5 = a sluggish response to a light glabellar tap or loud noise; and 6 = no response to a light glabellar tap or loud noise). Duration of anesthesia was also recorded. Postoperative pain, PONV, the time needed to start eating solids, RSS, NIBP, and HR were measured from arrival to the PACU and then 6, 12, 24, and 48 hours after discharge from PACU; and the patients were treated if necessary. Every single patient received IV Acetaminophen (15 mg/kg) after discharge from PACU every 6 hours. All patients received IV ondansetron (4 mg) for PONV prophylaxis at the end of surgery.

3.6. Statistical Analysis

Statistical data analysis was carried out using the Statistical Package for Social Sciences 20 (SPSS) software (SPSS Inc., Chicago, IL, USA). Descriptive indices and univariate analysis were done for baseline and outcome variables according to each study group. Comparison of the study's outcome variables over time was done by using repeated measures analysis of variance (ANOVA). P-values less than 0.05 were considered statistically significant. The correlation between observations on the same subject is 0.3, and the Alpha level is 0.05.

4. Results

There were 30 patients in each group. The two groups did not have significant differences in baseline characteristics (Table 1). Duration of surgery and anesthesia were almost similar in both groups (P-value > 0.05; Table 1).

In the PACU, VAS and morphine consumption were significantly higher in the remifentanil group at the first visit after surgery (0 - 1 h) (P-value < 0.001). VAS and morphine consumption were also higher in the Remifentanil group 6 hours after discharge from PACU (P-value < 0.001). After 12, 24, and 48 hours of discharge from PACU, the VAS, and morphine consumption were not significantly different between the two groups (P-value > 0.05) (Tables 2 and 3). PONV was not significantly different between the two groups, but the time to eat solid food was significantly different (Table 1).

VAS scores were significantly higher in the Remifentanil group compared to the fentanyl group during the first 24 hours (P-value < 0.001). However, there was no significant difference between the two groups during the second 24 hours (P-value > 0.05) (Table 4).

Regarding RSS, patients in the remifentanil group were more aware than the fentanyl group (Table 4).

5. Discussion

According to our results, morphine consumption and VAS scores were higher in the remifentanil group compared to fentanyl group after spine surgery only in the first 12 hours. The time to eat solid food was significantly lower in the Fentanyl group. Some studies evaluated hyperalgesia followed by remifentanil infusion 24 hours after surgery (16, 17, 19). In this study, VAS and morphine consumption were measured 48 hours after surgery. Although we administered IV Acetaminophen for all patients, the remifentanil group showed greater cumulative morphine consumption during the first 12 hours after discharge from PACU; however, no more consumption of morphine was recorded during 12 - 48 hours. Remifentanil was used for the intervention group since remifentanil is an ultra-short-acting and potent drug, patients in this group were more oriented than the control group during the PACU time; consequently, they revealed more pain. In the control group, fentanyl infusion was used during the operation, and patients were less aware than the intervention group due to the residual effect of fentanyl, which could be confirmed by RSS measurement, and they had minor pain in comparison with the remifentanil group. Several studies compared the low and high doses of remifentanil infusion, while this study compared the low dose of remifentanil (0.1 - 0.2 μg/kg/min) vs. Fentanyl (0.07 - 0.1 μg/kg/h) and remifentanil was co-administered with Propofol. Findings from a systematic review also suggested that Propofol may have a preventative effect on the development of remifentanil-induced hyperalgesia; therefore, our results may not relate to OIH (20, 21). The total morphine consumption 48 hours after surgery was lower in comparison with other studies, which could be justified by administration of IV Acetaminophen (15 mg/kg) after discharge from PACU every 6 hours. Remifentanil is an ultra-short-acting opioid that facilitates hemodynamic and neurologic management. Since the half-life of remifentanil is short, it is better to use it as an infusion (22, 23). The main problem of remifentanil-based anesthesia is the rapid disappearance of its analgesic effect after the end of infusion, which may cause the development of acute opioid tolerance (AOT); because of the pharmacokinetic properties of remifentanil, the incidence of AOT would be predictable (24, 25). Recent studies showed different consequences and there is still

Table 1. Demographic Characteristics of the Patients, Surgery, and Anesthesia Duration [a]

Demographic Characteristics	Remifentanil	Fentanyl	P-Value
Age (y)	38.57 ± 19.22	38.37 ± 20.32	0.99
Sex			0.14
Male	14 (46.67)	7 (23.33)	
Female	16 (53.33)	23 (76.67)	
Weight (kg)	66.5 ± 13	65.3 ± 20.7	0.1
Surgery duration (h)	3.96 ± 0.83	3.76 ± 0.88	0.517
Anesthesia duration (h)	4.15 ± 0.90	3.80 ± 0.83	0.512
PONV (h)	3.2 ± 0.83	2.1 ± 0.7	0.23
Starting solids (h)	9.2 ± 0.43	4.1 ± 0.41	< 0.05 [b]

[a] Values are expressed as mean ± SD.
[b] Significant after adjustment for multiple comparison.

Table 2. Postoperative VAS During 48 Hours

VAS (h)	Group; Mean ± SD		P-Value
	Fentanyl	Remifentanil	
VAS_PACU	2.70 ± 1.20	4.96 ± 1.47	< 0.001 [a]
VAS_6	3.16 ± 1.11	4.60 ± 1.35	< 0.001 [a]
VAS_12	3.43 ± 1.38	3.83 ± 1.46	0.284
VAS_24	2.66 ± 1.84	2.83 ± 1.44	0.691
VAS_48	2.10 ± 1.26	2.16 ± 0.94	0.835

[a] Significant after adjustment for multiple comparison.

Table 3. Postoperative Morphine Consumption

Morphine (h)	Group; Mean ± SD		P-Value
	Fentanyl	Remifentanil	
Morphine_PACU	0.20 ± 0.61	1.30 ± 1.46	< 0.001 [a]
Morphine_6	0.00 ± 0.00	0.73 ± 0.98	< 0.001 [a]
Morphine_12	0.20 ± 0.61	0.26 ± 0.69	0.722
Morphine_24	0.26 ± 0.69	0.13 ± 0.50	0.406
Morphine_48	0.06 ± 0.36	0.00 ± 0.00	0.365

[a] Significant after adjustment for multiple comparison.

Table 4. RSS and VAS Scores During the First and Second 24 Hours

RSS (h) and VAS (h)	Group	
	Fentanyl	Remifentanil
PACU RSS	1 (3.3)	2 (6.7)
0-24 (RSS/VAS)	17 (56.7)/2.99 ± 0.76*	26 (86.7)/4.05 ± 0.92 [a]
24-48 (RSS/VAS)	12 (40.0)/2.10 ± 1.26	2 (6.7)/2.16 ± 0.94

[a] Significant after adjustment for multiple comparison.

controversy about whether remifentanil could induce hyperalgesia.

Fentanyl requirement and pain scores were measured 1, 24, and 48 hours after surgery. A meta-analysis of 865 patients enrolled in four clinical trials addressing the impact of the addition of IV Acetaminophen to analgesia after total hip and knee arthroplasty concluded that there was a significant decrease in pain score and opioid consumption on post-operative days 1 to 3. Nausea and vomiting were decreased in the groups who received IV Acetaminophen (22, 26).

Cortinez et al. also suggested that during 24 hours postoperatively there was no development of AOT after remifentanil-based anesthesia on 60 patients who underwent elective gynecological surgery randomly receiving sevoflurane (1.75 MAC) or remifentanil (0.1 μg/kg/min) (16, 27).

Lahtinen et al. reported that when remifentanil (0.3 μg/kg/min) was infused 3 hours in cardiac surgery patients who underwent sufentanil/Propofol-based anesthesia, there was no increase in postoperative pain and opioid requirement (28).

In a study by Gustorff et al., low dose of Remifentanil (0.08 μg/kg/min) was infused for 3 hours into 20 healthy volunteers at a constant concentration, and the study showed the absence of AOT (29).

In the study by Guignard et al., 50 patients who underwent major abdominal surgery were divided into two groups. In the first group, Desflurane was kept at 0.5 MAC, and remifentanil infusion was titrated. In the second group, 0.1 μg/kg/min remifentanil was infused, and desflurane was titrated. In conclusion, a large dose (0.3 μg/kg/min) of intraoperative remifentanil significantly increased postoperative pain and morphine consumption; the researchers reported that remifentanil caused AOT and hyperalgesia (17). While Guignard et al. recorded postoperative pain and morphine requirement for 24 hours, we measured the variables 48 hours postoperatively.

In a study by Joly et al., 75 patients experiencing major abdominal surgery were evaluated. Results showed that high-dose remifentanil group (0.4 mg/kg/min) needed more morphine than low-dose group (0.05 mg/kg/min) (30). Similar to our study, pain scores and morphine consumption were measured for 48 hours. However, the circumstance causing differences in results could be high doses of remifentanil (0.4 mg/kg/min vs. 0.1 - 0.2 μg/kg/min).

Although several studies demonstrated that OIH or AOT occurs more in cases of high-dose remifentanil infusion, a small dose of remifentanil infusion of effect-site target concentration 2 ng/mL (an infusion rate of 0.1 μg/kg/min) could cause initial postoperative pain rise (31).

The conditions under which OIH may occur are not thoroughly understood, but may consist of high doses, long-term treatment, or sudden changes in concentrations (32).

Regardless of the dose of remifentanil administered and duration of infusion, the mentioned discrepancies could be explained by the effects of co-administrated anesthetic drugs such as Propofol, Sevoflurane, and nitrous oxide (33). Fodale et al. suggested that while remifentanil was co-administered with Propofol or sevoflurane, AOT was not induced, which created an inhibiting effect at NMDA receptors neutralizing the remifentanil stimulation on these receptors (33).

In summary, we found that intraoperative infusion of remifentanil (0.1 - 0.2 μg/kg/min) vs. Fentanyl (0.07 - 0.1 μg/kg/h) can increase postoperative pain and morphine consumption during the first 12 hours after surgery.

One limitation of this study is that we did not use quantitative sensory testing (QST) to assess OIH. However, we believe that it could be rare because we used remifentanil and Propofol infusion together during surgery. Further multicenter studies with assessment of OIH and long-term follow-up of patients who show signs of postoperative hyperalgesia would be useful to assess whether chronic pain is a significant clinical consequence. Also, use of NMDA receptor antagonists to prevent probable OIH and AOT and using multimodal analgesia for controlling postoperative pain are recommended.

5.1. Conclusion

Our findings suggested that intraoperative remifentanil administration may not induce OIH or AOT, especially when remifentanil and Propofol are co-administrated. Also, this study demonstrated the usefulness of paracetamol as an adjuvant to an opioid-like morphine for the treatment of postoperative pain in patients who have had spine surgery.

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Footnotes

Authors' Contribution: Study concept and design, Reza Shariat Moharari and Negin Saeedi; Critical revision of the manuscript for important intellectual content, Shervin Shahinpour and Farhad Etezadi; Statistical analysis, Ayat Ahmadi and Mohammad Reza Khajavi; Designing the evaluation, performing parts of the statistical analysis, and helping to draft the manuscript, Atabak Najafi and Pejman Pourfakhr.

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Informed Consent: A written informed consent was obtained from all eligible patients.

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