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COMPARATIVE ANALYSIS OF THE ANALGESIC BENEFITS OF FENTANYL, REMIFENTANIL, AND MORPHINE WITH INTRAVENOUS PATIENT-CONTROLLED ANALGESIA FOLLOWING CARDIOVASCULAR SURGERY

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ABSTRACT

Background: This study compared the analgesic effects of morphine and fentanyl, two more opioid agents, with remifentanil following cardiac procedure.

Material and Methods: 75 adult patients scheduled for elective OPCABG procedure with adequate left ventricle function (ejection fraction >40%,left ventricular end-diastolic pressure [LVEDP] <18 mmHg) were studied.The following patients were excluded from the study: those who had an intraoperative intra-aortic balloon pump insertion, were older than 70 years old, had unstable angina, abnormal hepatic or renal function, had undergone a previous sternotomy, or were undergoing emergency surgery.

Result :Pain was assessed by using a visual analog scale (0-10), and sedation was assessed with the Ramsay sedation score (1-6) 30 minutes, 1, 2, 4, 12, and 24 hours after extubation. The number of boluses and demands, time to extubation, and side effects were analyzed. Visual analog scale, sedation scores, and mean extubation times were similar in all groups. Total number of boluses and demands were statistically more in the remifentanil group. Regarding the side effects, nausea and vomiting was higher in group M ($p < 0.05$), whereas itching was prominent in group F ($p < 0.05$).

Conclusion:Despite the different durations of these 3 opioid agents, the infusion dose of remifentanil was as effective as morphine and fentanyl after CABG surgery with fewer side effects.

Keywords: *cardiac procedure,postoperative analgesia,morphine, fentanyl, remifentanil*

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INTRODUCTION:

After cardiac procedure, wounds account for more than 50% of postoperative morbidity.1 Stainless steel wire sutures, costochondral separation, pain following sternotomy, intraoperative tissue retraction, and chest tubes are all related to pain. Myocardial ischemia can occur due to enhanced concentrations of stress hormones and increased myocardial oxygen demand when pain control following coronary artery surgery is inadequate. 2,3.Four, five Additionally, pain following a sternotomy makes it difficult to cough, which results in pulmonary dysfunction.6 Patients' discharge from the hospital and the intensive care unit may be delayed by any of these conditions.

Postoperative pain is now commonly managed with intravenous (IV) patient-controlled analgesia (PCA), which was first introduced by Sechzer7 in 1968. Patients using PCA are able to self- administer analgesic medication in small doses in accordance with physician-established limits to manage post-operative pain. Effective pain management is achieved by reducing blood fluctuations of analgesic medications through this technique. Quick titration and minimal body accumulation are key components of the perfect opioid for PCA.

Remifentanil is a new μ-selective opioid agonist with a very fastonset(half-life of equilibration between blood and brain= 1.3 minutes) and a short duration of action (3-4 minutes) because of rapid hydrolysis of the methyl ester linkage by nonspecific blood and tissue esterases.[8- 10]It does not accumulate in the body in contrast to other opioids.[10,11]Its short half-life, lack of accumulation after prolonged administration, and organ-independent metabolism should make it an ideal agent for postoperative analgesia.

Remifentanil and IV PCA following myocardial revascularization, however, have not been the subject of many studies. The authors of this study postulated that when remifentanil was given as a continuous infusion following off-pump coronary artery bypass graft (OPCABG) surgery, it would have fewer side effects and improved analgesia as assessed by the visual analog scale (VAS) in comparison to morphine and fentanyl.

MATERIALS AND METHODS:

After getting written informed consent, 75 adult patients scheduled for elective OPCABG surgery with adequate left ventricle function (ejection fraction >40%,left ventricular end-diastolic pressure [LVEDP] <18 mmHg) were studied.Patients with American Society of Anesthesiologists risk levelIV or V, abnormal hepatic or renal function, previous sternotomy, unstable angina, older than 70 years, intra operative insertion of an intra-aortic balloon pump, or undergoing emergency surgery were not included in the study. All patients were shown the relevant PCA handset at the

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preoperative visit and were instructed on its use the day before surgery.

Three groups of 25 patients each were created through preoperative randomization of the patient population. Patients in group F received fentanyl (50 µg/mL) with an infusion rate of 1 µg/kg/h and a 10-µg bolus; patients in group R received remifentanil (50 µ/mL) with an infusion rate of 0.05-µg/kg/min and 0.5-µg/kg bolus, with a 5-minute lockout period for all groups. Patients in group M received morphine (1 mg/mL) with an infusion rate of 0.3 mg/h and 1-mg bolus doses. Fentanyl bolus doses were stopped about half an hour before the surgery was supposed to end.

After surgery, a special infusion set (Life Care Provider Set; Abbott Laboratories, Donegal, Ireland) was used to start PCA infusions through a peripheral vein right away. Postoperative data were recorded in the cardiac intensive care unit at 30 minutes, 1hour,2hours,4hours,12hours,and24hoursafterextubationbyapainclinic nurse who had no knowledge about the infusion solutions.

RESULTS:

Demographic characteristics of the patients, duration of sugery, and fentanyl quantities used during the intraoperative period were similar in the 3 groups (Table 1). There were no significant difference of VAS among the study groups(Fig1). The mean VAS scores in 24 hours in groups M, F, and R were 1.6, 1.5, and 1.4, respectively. Total PCA demands and bolus numbers were significantly higher in the remifentanil group compared with the others in the 24-hour period (Table 2) ($p < 0.05$). Also, Ramsay sedation scores were similar in the 3 groups, without any significant differences (Table 3).

Number of PCA Demands and Boluses

	TOTAL DEMAND	TOTAL BOLUS
GroupM	22.5±6.9	17.3±5.66
GroupF	23.4±7.23	18.5±5.84
GroupR	37.4*±9.45	29.2†±7.97

NOTE.Resultsaregivenasmean±SD.Abbreviations:M,morphine;F,fentanyl;R,remifentanil.
*p<0.05,groupRversusgroupMandFintotaldemands.
†p<0.05,groupRversusgroupMandFintotalbolusnumbers

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Postoperative SideEffects and Characteristics

	NAUSEA	VOMITING	ITCHING	RESCUE ANALGESICS
GroupM	13*	9†	6	2
GroupF	8	5	10‡	2
GroupR	5	2	2	3

NOTE.Resultsaregivenasnumber(n)ofpatients in each groupexperiencing the side effects.

Abbreviations:M,morphine;F,fentanyl;R,remifentanil.

*p<0.05,groupMversusR

The incidence of nausea and vomiting in the morphine group was significantly higher than in the remifentanil group ($p < 0.05$) (Table 4). In the morphine group, nausea was seen in 13 (52%) patients, whereas it was seen in 8 (32%) patients in the fentanyl group and 5 (20%) patients in the remifentanil group. Vomiting occurred in 9(36%),5(20%),and2(8% patients in the morphine, fentanyl, and remifentanil groups, respectively. In addition, itching was significantly higher in the fentanyl group than in the remifentanil group(p<0.05);observedin10 (40%) patients in the fentanyl group, 6 (24%) in the morphine group, and 2 (8%) patients in the remifentanil group. Further- more,there were nostatistical differences in the additional oral analgesic used among the groups. The authors did not find any respiratory side effects such as respiratory depression (<10 breaths/min), decreases in SpO_2 or apnea in any of the study groups.

Time to extubation was not different among groups. The mean durations were 308 ± 26, 318

± 13, and 339 ± 16 minutes in groups M, F, and R, respectively.

DISCUSSION:

In this study, PCA remifentanil after OPCABG surgery produced less side effects and similarly effective pain control, as measured by VAS, when compared to morphine and fentanyl. Remifentanil's pharmacokinetic and pharmacodynamic profiles make it appropriate for use in PCA systems.

Moderately intense pain is experienced after a sternotomy. A clinical study13 found that in patients having sternotomy for heart surgery, the majority of pain occurred in the first and second postoperative days. For this reason, intense coughing and breathing following a sternotomy require pain management during the first 48 hours. Incisional pain restricts deep breathing, makes it difficult to cough up secretions from the airway, and

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contributes to the development of pulmonary a telectasis in patients for whom effective pharmacological analgesia is not administered.14, 15, The risk of thromboembolic complications during the postoperative period may also rise with late mobilization due to intense pain.16-18

The present data show that all groups experienced mild-to- moderate pain at rest. VAS values were similar for all groups. The auth or observed that the mean VAS scores decreased after extubation during the 24-hour study period. The mean VAS scoreswere2.9,2.4,and2.0forgroupsM,F,andR30minutes after extubation, and 0.5, 0.7, and
0.8 after 24 hours, respectively, with no significant differences. These results are inconsistent with those of Roelants et al.[19]They reported a good quality of analgesia with remifentanil PCA by continuous in- fusion and bolus dosages. In another clinical study, Guillen et al[20]determined lower VAS values with fentanyl compared with remifentanil by PCA bolus after cardiac surgery. The authors suggest that this discrepancy may be explained by the possible underutilization of the PCA bolus doses in the Guillen study thatcouldhaveledtoinadequateanalgesiafortheremifentanil group. Therefore, a low-dose continuous background infusion may be important for sustained analgesia when using ultra- short-acting opioids by PCA. Even with a continuous back- ground infusion, patients receiving remifentanil in the present study had significantly more PCA demands and bolus admin- istration compared with morphine and fentanyl. Patients in the remifentanil group made 37.4 demands and received 29.2 boluses on average in the 24-hour study period. This may be related to remifentanil's ultrashort duration of action and lack of accumulation in the body. There were no differences among the groups regarding these dation scores,and these findings are consistent with recent studies.[19-22]The measured sedation scores were mostly 3 in the fentanyl and morphine groups and 2 in the remifentanil group.

Regarding the side effects,itching was significantly higher in the fentanyl group when compared with the morphine and remifentanil groups ($p < 0.05$). In a similar way, the nausea and vomiting incidences were found to be significantly higher in the morphine group

compared with the fentanyl and remifentanil groups ($p < 0.05$). The incidence of nausea and vomiting is highly variable among studies. There was as similar frequency of nausea and vomiting in the present study compared with that of Schraag et al[21]who reported a 26% and 10% nausea incidence in patients receiving remifentanil.Schuttleretal,[23]how- ever, reported a 47% incidence of nausea for remifentanil, which is more than twice that seen in the present study (20%). This suggests a dose-dependent adverse effect that may be aggravated by incremental manual bolus doses and also total dose infused.

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In the literature, some of the studies using remifentanil for postoperative analgesia have found a high incidence of respiratory depression. In one of these, Bowdle et al,[22]in a multi- center evaluation, compared different infusion rates of remifetanil and reported that the range of 0.05 to 0.15 µg/kg/min provides adequate analgesia for 78% of patients. They also recorded adverse respiratory effects (29%) and apnea (7%) in higher doses as a notable problem. Of the patients with respiratory depression, 73% had thoracic and spine surgery. They suggest that differences in patient characteristics and types of operations probably had an influence on the incidence of respiratory depression. In contrast, Schragg et al[21]and Guillen et al[20]did not report any respiratory side effects using remifentanil infusions for postoperative analgesia. Schraag et al used remifentanil in PCA for orthopedic surgery, and Guillen et al used it after cardiac surgery. In the present study, the authors did not determine any respiratory side effects like respiratory depression or apnea with remifentanil (50 µg/mL) with a infusion rate of 0.05 µg/kg/min and 0.5-µg/kg bolus doses, with a 5-minute lockout time.

There were no significant differences in the time to extubation among the 3 groups. This suggests that remifentanil with IVPCA doesnot prolong the time to extubation after OPCABG compared with morphine and fentanyl. Also,the present results were similar to those of Guillen et al[20]and Paris et al.[24]

CONCLUSION:

The study's findings demonstrate that, when compared to the administration of morphine and fentanyl, the IV PCA technique employing remifentanil offers comparable and sufficient pain relief as assessed by the VAS. Additionally, the continuous infusion plus bolus dose regimen did not result in side effects or an incidence of apnea. Further controlled trials are needed to determine whether IV PCA can be used by patients undergoing heart surgery to relieve postoperative pain while on remifentanil.

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CONFLICTS OF INTEREST:

There are no conflicts of interest.

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