Comparative study of the effect of two different doses of remifentanil on bleeding control in lumbar fusion surgery: A randomized clinical trial☆

Seyedeh Hamideh Hashemiyazdi a,b, Mehrdad Masoudifar a, Zahra Rahimi c, Azim Honarmand a, Mohamad Aryafar d,*

a Department of Anesthesiology, School of Medicine, Anesthesiology and Critical Care Research Center, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
b Department of Anesthesiology, School of Medicine, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
c Department of Anesthesiology, School of Medicine, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
d Department of Anesthesiology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

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ABSTRACT

Objectives: Spinal fusion surgery completely prevents movement or friction between the two vertebrae. Remifentanil, a selective drug agonist, suppresses and decreases the vasomotor system upon release of histamine. In this study, the efficacy of remifentanil infusion at doses of 0.1 and 0.3 μg/kg/min in the control of low blood pressure was compared.

Methods: In this randomized clinical trial, 110 candidates for selective spinal fusion surgery were entered and randomized into 2 groups. The first group received 0.1 μg/kg/min and in the second group 0.3 μg/kg/min remifentanil. The systolic and diastolic blood pressure, pulse rate, SPO2, and surgeon’s satisfaction were measured and compared between groups.

Results: the systolic blood pressure was significantly lower in patients receiving 0.3 μg of remifentanil by the time 30, 45, 60, and 90 min during the surgeries (P < 0.05). No significant difference was observed in terms of PR (P = 0.19) and SPO2 (P = 0.41) between the two groups. We also observed significantly higher duration of surgeries (P = 0.002), duration of anesthesia (P = 0.009), significantly higher bleeding volume (P < 0.001), higher fluid intake (P = 0.01) and higher transfused blood (P = 0.01) in patients that received 0.1 μg remifentanil compared to other patients.

Conclusion: Here we showed that administration of 0.3 μg/kg/min remifentanil was associated with significantly lower systolic blood pressure during the surgeries. On the other hand, patients that received 0.1 μg/kg/min remifentanil had significantly higher duration of surgeries, duration of anesthesia, significantly higher bleeding volume, higher fluid intake, and also higher transfused blood.

1. Introduction

Spinal fusion surgery is a surgical procedure that causes a permanent connection between two or more vertebrae [1]. This procedure prevents movement or friction between the vertebrae and is often performed on the lumbar spine [2]. Spinal fusion could also be performed on other spinal levels such as cervical and thoracic [3,4]. Selective fusion surgery is performed in adolescents in cases of curvature [5]. The benefit of this surgery is the limitation of fusion levels, therefore decreasing the limitation of motion [6]. Three types of surgical procedures are performed for spinal fusion, which are posterior, anterior, and posterior-anterior fusion. Indications for spinal fusion include spinal deformity due to cerebral palsy, neuromuscular disease, scoliosis, trauma, vertebral tumors [7], and mechanical injuries due to spinal instability, and some reoperations [8,9].

Bleeding is known as an important intraoperative complication during spinal fusion that interferes with the success of the operation and increases the complications during and after the operation [10]. This

☆ The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1399.1025, Iranian registry of clinical trials (IRCT) code: IRCT20200217046523N12).

* Corresponding author. Islamic Azad University, Tehran, Iran.
E-mail address: md.m.aryafar@gmail.com (M. Aryafar).

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complication depends on various factors such as the type of anesthesia, the type of injury, the type of fusion, the skill of the surgeon, and the patient’s characteristics [11,12]. Excessive bleeding during surgery is one of the most important problems during lumbar fusion surgery [13].

By defining a reduction in blood pressure and heart rate, the goal of clearing the surgical field can be achieved [14]. Excessive bleeding during surgery, in addition to reducing the surgeon’s view of the surgical field, causes more trauma to the surrounding tissues, and the longer the period, the better the recovery period [15]. Controlled hypotension reduces bleeding from the surgical incision, thereby providing technical freedom and better vision for the surgeon in terms of operating more accurately [16,17]. In controlling hypotension, drugs such as Trimetaphan and pentolium, vascular wall muscle relaxants such as hydralazine, sodium nitroprusside, and beta-blockers including propranolol [18-20].

Remifentanil suppresses and decreases the vasomotor system upon release of histamine [21]. Compared to other narcotic drugs such as fentanyl and alfentanil, remifentanil can provide better hemodynamic stability in stressful surgical events and alter cerebral blood flow changes. On the other hand, such treatment should be performed with great care because there is a possibility of heart failure or bronchoconstriction [22]. Controlled hypotension should be used with caution to minimize the risk of damage to vital organs. Important risks of controlled hypotension include the possibility of coronary, cerebral, or renal circulatory failure [23,24]. Previous studies have shown the effectiveness of remifentanil in controlled hypotension but different dosages have been reported [25]. To date, no previous studies have compared the effects of 0.1 and 0.3 μg/kg/min dosages of remifentanil in reducing bleeding. As a result, using the optimized dosage of remifentanil has great importance, especially in patients undergoing special surgeries including selective fusion. Therefore, in this study, the efficacy of remifentanil infusion at doses of 0.1 and 0.3 μg/kg/min in the control of low blood pressure in patients undergoing dual lumbar fusion surgery was compared.

Methods and material.

This is a triple-blinded randomized clinical trial that was performed in 2020 in Al-Zahra hospital affiliated to Isfahan University of Medical Science. The current study was conducted on patients that were candidates for posterior spinal fusion surgery under general anesthesia. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR. MUL.MED.REC.1399.1025, Iranian registry of clinical trials (IRCT) code: IRCT2020021704652N12).

The inclusion criteria were age between 16 and 70 years, candidates for posterior spinal fusion surgery at the level of 1 and 2, American Society of Anesthesiologists (ASA) classification equal to 1 or 2 and signing the written informed consent to participate in this study. The exclusion criteria the use of hypotensive induction anesthesia, the occurrence of unwanted hemodynamic complications due to surgical technique, having severe cardiovascular diseases and patients with the history of hypertension.

Required Sample size was calculated with using the sample size estimation formula to compare the means with considering the 95% confidence level, 80% test power, standard deviation of mean blood pressure above 140 mm Hg), tachycardia (heart rate greater than 100 beats per minute), and bradycardia (heart rate lower than 45 times per minute) during operation and recovery. In case of hypotension, 5–10 mg of ephedrine, and in case of bradycardia, atropine in the amount of 0.5 mg was injected. The volume of bleeding during the operation was calculated by the weight of gauze used and the amount of suctioned blood during the operation. Other required information such as duration of operation (from the time of surgical incision to the time of the last suture), duration of anesthesia (from the start of injection to discontinuation of anesthesia), time of extubation (from time to closure of anesthesia to the exit of the tube Chip) and the length of stay in recovery were determined and recorded in all patients. After the operations, the patients were discharged from the recovery according to the modified Aldrete criteria [28]. If morphine was needed, the dose and frequency of injections were recorded.

To remove the bias, all surgeries were performed by a single neurosurgeon. Surgeon satisfaction at the end of the operation was measured using the 5-point Likert scale. The above criterion is a 5-part criterion that divides satisfaction from 1 to 5, which included completely satisfied [5], satisfied [3], dissatisfied [1], and completely dissatisfied [2]. The occurrence of postoperative complications such as nausea and vomiting was monitored and recorded. The severity of nausea in patients was classified from zero to 3 using the Apfel criterion, which was zero as no nausea, 1: as mild nausea, 2, as moderate nausea, and 3 as severe and persistent nausea. If the patient had a complication, he was not excluded from the study.

Data analysis: The obtained data were entered into the Statistical Package for Social Sciences (SPSS) version 24. We used independent t-test and repeated measure tests to compare data between different timelines and also different groups. P-value < 0.05 was considered a significant threshold.

Unique identifying number (UIN) of your study: Researchregistry7111.

The work has been reported in line with the CONSORT criteria [29].

2. Results

A total number of 114 patients entered this study and were...
randomized into 2 groups of 57 patients. 4 patients (2 patients in each group) were excluded due to changes in the surgical plan. Data are indicated in Fig. 1. The primary analysis of demographic data showed no significant differences between the two groups regarding age, weight, and ASA classification, level of surgeries, gender, and past medical histories (P > 0.05 for all items). These data are indicated in Table 1.

Further analysis showed that the systolic blood pressure was significantly lower in patients receiving 0.3 μg of remifentanil by the time 30, 45, 60, and 90 min during the surgeries (P < 0.05) but no significant differences could be observed among patients regarding diastolic blood pressure and MAP (Table 2).

According to Table 3, no significant difference was observed in terms of PR (P = 0.19) and SPO2 (P = 0.41) between the two groups. We also evaluated further variables among groups. These data showed a significantly higher duration of surgeries (P = 0.002), duration of anesthesia (P = 0.009), significantly higher bleeding volume (P < 0.001), higher fluid intake (P = 0.01), and higher transfused blood (P = 0.01) in patients that received 0.1 μg remifentanil compared to other patients. We also showed that the surgeon’s satisfaction was significantly higher in patients that received 0.3 μg remifentanil (P = 0.001). There were also no significant differences between groups regarding other variables. These data are indicated in Table 4.

No significant differences could also be observed between the two groups regarding nausea and vomiting.

3. Discussion

A comparison of two different dosages of remifentanil in patients undergoing spinal surgeries with the possibility of massive bleeding was associated with decreased amounts of bleeding. In this study, the efficacy of remifentanil infusion at doses of 0.1 and 0.3 μg/kg/min in the control of low blood pressure in patients undergoing dual lumbar fusion surgery was compared. Here we showed that the patients that received 0.3 μg/kg/min remifentanil had significantly lower systolic blood pressure by the time of 30, 45, 60, and 90 min during the surgeries. On the other hand, patients that received 0.1 μg/kg/min remifentanil had significantly higher duration of surgeries, duration of anesthesia, significantly higher bleeding volume, higher fluid intake, and also higher transfused blood. Similar findings are reported in our study.

In a study by Hadi and colleagues in 2010, 30 candidates for spinal fusion surgery were divided into two groups and received 0.2 μg/kg/min remifentanil with or without ketamine and were evaluated for 24 h in the post-anesthesia care unit. It was reported that patients that received only remifentanil had significantly lower blood pressure and heart rate. The patients had also lower bleeding volumes which led to better hemodynamic stability [30]. Rahimzadeh and colleagues also compared the results of remifentanil and dexmedetomidine injections among patients undergoing posterior spinal fusion surgery. They evaluated 60 patients and explained that patients that received remifentanil with the dosage of 0.1 μg/kg/min had decreased blood pressure but the patients receiving dexmedetomidine had lower hemodynamic indexes at 30, 60, 120, and 360 min after extubation [31]. The findings of our study were in line with these results showing the effectiveness of remifentanil injection. An important point of the current study was that we compared two different dosages of remifentanil and the clinical outcomes of patients undergoing spine surgery. It was declared that injection of 0.25 μg/kg per minute of remifentanil was associated with a significant reduction in blood pressure and bleeding volume during the 5 h of post-anesthesia care. The study recommended that higher dosages could have better effects on patients [32]. These data are also in line with our findings.

| Table 1: Comparison of demographic data between groups. |
|-------------|---------|---------|----------|--------|
|              |         | Mean    | Std. Deviation | p-value |
| Age          | 0.1 μg  | 55      | 41.56     | 14.29  | 0.23   |
|              | 0.3 μg  | 55      | 44.57     | 11.64  |        |
| Weight       | 0.1 μg  | 54      | 70.77     | 9.74   | 0.06   |
|              | 0.3 μg  | 54      | 74.24     | 9.11   |        |
| ASA          | 0.1 μg  | 48      | 5         | 53     | 0.07   |
|              | μg      | Percent | 90.6%     | 9.4%   | 100.0% |
|              | 0.3 μg  | 39      | 11        | 50     |        |
|              | μg      | Percent | 78.0%     | 22.0%  | 100.0% |
|              | 0.3 μg  | 5       | 44        | 53     | 0.26   |
|              | μg      | Percent | 17.0%     | 83.0%  | 100.0% |
| Level of      | 0.1 μg  | 9       | 4        | 53     |        |
| surgery      | μg      | Percent | 9.3%      | 90.7%  | 100.0% |
|              | 0.3 μg  | 5       | 49        | 54     |        |
| Gender       | 0.1 μg  | 30      | 25        | 55     | 0.84   |
|              | μg      | Percent | 54.5%     | 45.5%  | 100.0% |
|              | 0.3 μg  | 28      | 27        | 55     |        |
|              | μg      | Percent | 50.9%     | 49.1%  | 100.0% |
| past medical | 0.1 μg  | 45      | 10        | 55     | 0.81   |
| histories    | μg      | Percent | 81.8%     | 18.2%  | 100.0% |
|              | 0.3 μg  | 43      | 12        | 55     |        |
|              | μg      | Percent | 78.2%     | 21.8%  | 100.0% |

Using independent t-test and chi-square tests.

Fig. 1. Evaluation of blood pressures between groups.
### Table 2
Evaluation of blood pressure changes by time and group therapy.

| group | T = pre | T = 0 | T = 30min | T = 45min | T = 60min | T = 90min | T = 120min | T = 150min | T = 180min | T = 210min | T = recovery 30 | T = recovery 45 | T = recovery 60 | T = recovery 90 | P1 | P2 | P3 |
|-------|---------|-------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------------|---------------|---------------|---------------|----|----|----|
| SIS   | Mean    | 138.7091 | 120.8364 | 122.4000  | 98.7455   | 100.9181  | 102.3922  | 102.4894  | 103.1522  | 117.2909  | 126.7455     | 116.6566     | 118.3662     | 0.001         | 0.15 | 0.63 |
| µg    | Mean    | 141.6364 | 121.7273 | 123.1363  | 96.7363   | 111.3818  | 108.6182  | 98.8399   | 101.7455  | 105.7000  | 120.4545     | 117.8438     | 112.3842     | 0.001         | 0.04 | 0.01 |
| 30min | 90min   | 120.8364 | 122.4000  | 98.7455   | 100.9181  | 102.3922  | 102.4894  | 103.1522  | 117.2909  | 126.7455  | 116.6566     | 118.3662     | 112.3842     | 0.001         | 0.04 | 0.01 |

### Table 3
Comparison of PR and SPO2 among patients.

| group | T = pre | T = 0 | T = 30min | T = 45min | T = 60min | T = 90min | T = 120min | T = 150min | T = 180min | T = recovery 0 | T = recovery 30 | T = recovery 45 | T = recovery 60 | T = recovery 90 | P1 | P2 | P3 |
|-------|---------|-------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------------|---------------|---------------|---------------|---------------|----|----|----|
| PR    | Mean    | 91.1091 | 88.9636  | 81.5636   | 82.0991   | 80.6909   | 78.0000   | 79.2727   | 78.0592   | 79.0490       | 77.9149       | 81.2373       | 79.6111       | 75.2069       | 68.3551       | 69.2481      | <0.001 | 0.19 |
| µg    | Mean    | 13.1144 | 14.5894  | 17.05847  | 11.9124   | 12.9356   | 11.73949  | 11.60352  | 12.6167   | 12.23630      | 12.75496      | 13.78412      | 12.61978      | 10.37641      | 13.22540      | 12.36724     |              |      |
| 0.3 µg| Mean    | 95.0182 | 90.0727  | 85.4909   | 81.4272   | 80.3819   | 82.8545   | 77.2182   | 75.8182   | 77.2778       | 78.7800       | 81.4000       | 80.2909       | 80.6000       | 67.7421       | 68.2360      | 0.001        |      |
| SPO2  | Mean    | 97.8900 | 98.7091  | 98.8545   | 99.2182   | 98.8909   | 98.8349   | 98.5849   | 98.5490   | 98.5102       | 98.4231       | 98.3017       | 97.8584       | 97.8721       | 97.8734       | 0.001        | 0.099 | 0.41 |
| µg    | Mean    | 15.47099| 13.91753 | 12.65332  | 12.75837  | 12.27556  | 45.31239  | 12.67206  | 15.0294    | 12.80211      | 13.16503      | 14.87429      | 13.95639      | 15.79332      | 11.25740      | 11.30870     |              |      |
| 0.3 µg| Mean    | 97.6000 | 98.5455  | 98.8182   | 99.0182   | 98.7636   | 98.7636   | 98.6182   | 98.6182   | 98.5268       | 98.3148       | 98.1915       | 98.4474       | 98.4526       | 98.4723       | 0.001        |      |
| P4    | Mean    | 90.3338 | 1.9491   | 1.09021   | 1.17837   | 1.10493   | 1.10493   | 1.12655   | 1.16255   | 1.17837       | 2.23036       | 2.23255       | 1.87007       | 1.96387       | 1.25387       |              |      |

P1 (Time), P2 (interaction), P3 (intervention) at a significant level of repeated measure test. P4 at the 5% level of independent t-test.
μg/kg/min remifentanil injections with the dosage of 0.1 μg/kg/min during spinal surgeries is associated with significant positive results compared to other patients.

### Availability of data and materials
All relevant data and materials are provided in the manuscript.

### Ethical approval
All procedures performed in this study involving human participants 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.

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No funding was secured for this study.

### Author statement
Dr. Seyyedeh Hamideh Hashemiyazdi and Dr. Mohammad Aryafar: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Mehrdad Masoudifar and Dr. Azim Honarmand: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Zahra Rahimi: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

### Registration of research studies
Name of the registry: IRT202002017046523N12. Unique Identifying number or registration ID: IR. MUI.MED.REC.1399.1025.

Hyperlink to the registration (must be publicly accessible): https://en.irct.ir/trial/54856.

### Guarantor
Dr. Seyyedeh Hamideh Hashemiyazdi.

### Consent
Not applicable.

### Provenance and peer review
Not commissioned, externally peer-reviewed.

### Human and animal rights
No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

### Declaration of competing interest
The authors deny any conflict of interest in any terms or by any means during the study.

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### Table 4
Evaluation of surgical duration, anesthesia duration, recovery duration, bleeding volume and fluid intake and other variables.

|                         | N  | Mean   | Std. Deviation | P-VALUE |
|-------------------------|----|--------|----------------|---------|
| Surgical duration (hour)| 0.1 μg | 50  | 3.6382        | .58280  | 0.06 |
|                         | 0.3 μg | 51  | 3.8700        | .67620  |       |
| Anesthesia duration (hour) | 0.1 μg | 55  | 4.5000        | .75768  | 0.009 |
|                         | 0.3 μg | 55  | 4.8473        | .69975  |       |
| Extubation duration (hour) | 0.1 μg | 51  | 39.1176       | 12.23544 | 0.11 |
|                         | 0.3 μg | 50  | 35.3000       | 12.13908 |       |
| Recovery duration (hour) | 0.1 μg | 51  | 1.3333        | .43205  | 0.42  |
|                         | 0.3 μg | 50  | 1.2700        | .35297  |       |
| Bleeding volume (ml)    | 0.1 μg | 52  | 536.5385      | 223.19327 | <0.001 |
|                         | 0.3 μg | 55  | 372.7273      | 201.11223 |       |
| Fluid intake (L)        | 0.1 μg | 52  | 2.4904        | 1.51622  | 0.01  |
|                         | 0.3 μg | 54  | 1.7037        | 1.70050  |       |
| Transfused blood (L)    | 0.1 μg | 51  | .5294         | .85681   | 0.01  |
|                         | 0.3 μg | 47  | .1702         | .43335   |       |
| Atropine (mg)           | 0.1 μg | 7   | 1.2500        | 1.86474  | 0.28  |
|                         | 0.3 μg | 12  | .4429         | .45408   |       |
| Ephedrine (mg)          | 0.1 μg | 13  | 2.3889        | 3.08486  | 0.41  |
|                         | 0.3 μg | 18  | 3.3846        | 3.65897  |       |
| Propofol (mg)           | 0.1 μg | 50  | 301.7105      | 255.93569 | 0.72 |
|                         | 0.3 μg | 51  | 337.9688      | 580.74182 |       |
| Remifentanil (mg)       | 0.1 μg | 53  | 5.3395        | 2.41141  | 0.01  |
|                         | 0.3 μg | 53  | 4.0154        | 1.67778  |       |
| Extra morphine (mg)     | 0.1 μg | 25  | 7.0853        | 6.20056  | 0.33  |
| Extra labetalol (mg)    | 0.1 μg | 18  | 4.1667        | 4.91596  |       |
|                         | 0.3 μg | 6   | 3.37291       | 0.21405  |       |
| Surgeon’s satisfaction   | 0.1 μg | 55  | 2.2000        | .91084   | 0.001 |
|                         | 0.3 μg | 54  | 1.4815        | .77071   |       |

Using independent t-test and chi-square tests.

Some other previous studies have also declared the effectiveness of remifentanil injections with the dosage of 0.1 μg/kg/min during spinal surgeries [33–35] and reported lower blood pressure, lower bleeding, lower surgery and recovery, and also limited fluid intake compared to other agents. In the present study, we showed that administration of 0.3 μg/kg/min is associated with better results during and after surgical operations and also with no difference in complications.

In 2008, a study was conducted by Kim and colleagues in Korea on 60 patients that were candidates for endotracheal intubation and reported that 1 μg/kg/min remifentanil followed by an infusion of 0.1 μg/kg/min is more effective than 1.5 mg/kg esmolol for inhibiting the cardiovascular responses following endotracheal intubation during the induction of general anesthesia. They also explained that higher dosages of remifentanil might have better results. However, the study evaluated these parameters from 1 to 5 min before intubation and 1–5 min after intubation [36]. We believe that administration of 0.3 μg/kg/min remifentanil could have significant clinical outcomes in other medical interventions.

Our study is the first one to provide evidence regarding two different doses of remifentanil for managing bleeding among spinal surgery patients along with intraoperative and postoperative parameters. It can also be deduced that 0.1 μg/kg/min may be less to achieve the desirable results. The limitations of the current study were restricted number of patients and also not evaluating the hemoglobin levels of patients and also the amounts of administered muscle-relaxants in patients. Therefore, we suggest that further studies on larger populations should be performed with evaluating the mentioned factors.

### 4. Conclusion
Here we showed that administration of 0.3 μg/kg/min remifentanil was associated with significantly lower systolic blood pressure by the time of 30, 45, 60 and 90 min during the surgeries. These data indicate the effectiveness and beneficial outcomes of 0.3 μg/kg/min remifentanil injection in patients undergoing posterior spinal fusion surgery under general anesthesia. These data show that administration of 0.3 μg/kg/min remifentanil during surgeries is associated with significant positive results compared to other patients.
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