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Comparison of the Effect of Inhalational Isoflurane-Nitrous Oxide Anesthesia and Intravenous Propofol-Remifentanil Anesthesia on Postoperative Pain

Javad Nourian[1], Niloofar Khobestani[2], Pouneh Zolfaghari[3], Javad Khajemozafari[4], Mehdi Ebrahimi[5], Mohammad Bagher Sohrabi[6*]
[1] Department of Anesthesiology, Clinical Research Development Unit, Imam Hossain Hospital, Shahroud University of Medical Sciences, Shahroud, Iran.
[2] Student Research Committee, Shahroud University of Medical Sciences, Shahroud, Iran.
[3] Vice-chancellery of Health, Shahroud University of Medical Sciences, Shahroud, Iran.
[4] Department of Orthopedic, Imam Hossain Center for Education, Research and Treatment, Shahroud University of Medical Sciences, Shahroud, Iran.
[5] Department of Surgeon, Imam Hossain Center for Education, Research and Treatment, Shahroud University of Medical Sciences, Shahroud, Iran.
[6] School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.

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Abstract

Background: *The severity of postoperative pain varies widely in the different types of anesthesia. The aim of the present study was to compare the effect of isoflurane-nitrous oxide anesthesia and propofol-remifentanil anesthesia on postoperative pain after foot and ankle surgery.*
Methods: *In this double-blind clinical trial, 60 eligible patients were divided into two equal intervention and control groups; the first group inhaled anesthesia with isoflurane-nitrous oxide and the control group were given intravenous anesthesia with propofol-remifentanil using the quadruple random block model and postoperative pain intensity was measured and compared in the two groups. Data on pain severity were collected at different times and analyzed using SPSS statistical software and related tests. The significant level was set at 0.05.*
Results: *Of the 60 participants, 38 (52.4%) were male and 22 (47.6%) were female. The mean age of the participants was 33.9±15.1 years. The intensity of pain in the recovery room and up to 4 hours after surgery was significantly (Pvalue<0.001) lower in the intervention group but after 4 hours there was no significant difference between the two groups. So, it can be seen in the present study that there was a significant decrease (Pvalue<0.036) in the number of cases requiring analgesics prescribed in the recovery room and up to 4 hours after surgery in the intervention group.*
Conclusions: *According to the results, evaporation anesthetic isoflurane-nitrous oxide can be used in the stage of induction of anesthesia in orthopedic surgeries, and has achieved good results in reducing pain, especially during the first 4 hours, postoperative.*

Keywords: Isoflurane, Propofol, Inhaler anesthesia, IV anesthesia, Postoperative pain.
[*]**Corresponding to:** MB Sohrabi, **Email:** mb.sohrabi@yahoo.comhra
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Introduction

Endurance of pain is one of the problems that constantly causes people distress and entails many unpleasant side effects. Pain is a global health problem and the most common reason people refer to the health service is pain control. According to the international association for the study of pain (IASP), pain is an unpleasant emotional or sensory experience with potential or actual tissue damage or a description of such a condition.[1-2] In the meantime, one of the worst types of pain that humans have to tolerate is acute postoperative pain and the more severe the pain, the worse the hemodynamic and metabolic responses for patients.[2] About 80% of patients experience moderate to severe pain after surgery. The threshold for pain tolerance varies in different individuals, and some patients may feel more pain than others and need more medication to reduce pain.[3] Inadequate pain relief after surgery results in complications such as longer recovery time, longer hospital stay, and increased hospital costs, and decreased patient satisfaction. Pain after orthopedic surgeries is also considered to be the most common type.[3-4] Effective postoperative pain management is currently part of the surgical process and not only reduces patient suffering but also reduces mortality. It also results in faster recovery and early discharge from the hospital, improving patient quality of life and reducing costs.[5] Effective postoperative pain management involves a multimodal approach in which different drugs are used with different mechanisms and methods of administration.[5-6]

After the surgery is over and the effect of anesthetic drugs is eliminated, the pain at the surgical site is felt and naturally it hurts the patient.[7] The severity of this pain is especially severe in the first few hours and days after surgery and usually requires pain medication.[8-9] Different anesthesia drugs are used for different patients and the anesthesia methods vary. Medications used during anesthesia can also affect the severity and duration of postoperative pain. The most common anesthetic agents that can be mentioned are inhaled Isoflurane-Nitrous Oxide (INO) and Propofol-Remifentanil (PR) intravenously.[10] Propofol is one of the most common anesthetic drugs which has potential to induce and maintain anesthesia. The patient wakes soon after anesthesia and the postoperative complications are minimal.[11-12] Isoflurane is a very good inhaler anesthesia in maintaining anesthesia and controlling intraoperative stress responses and recovery rate in isoflurane is much faster than other inhalers.[13] Nitrous Oxide is one of the weakest anesthetic gases with a MAC of 104% at atmospheric pressure (sea level). That is, even with the maximum permissible prescription (70%) it cannot be a complete anesthetic and should be combined with other inhaled or intravenous anesthetics. Its mechanism of analgesia is mediated by the release of endogenous endorphins at the supra spinal level and the inhibition of specific receptors at the spinal cord.[14-15]

Given the importance of the topic and the frequency of orthopedic patients requiring surgery and the lack of similar studies at the regional level, the purpose of this study was to

compare isoflurane-nitrous oxide inhalation anesthesia with propofol-remifentanil intravenous anesthesia after an open leg and ankle surgery in Imam Hossain hospital in Shahroud in 2018.

Materials and Methods

This retrospective double-blind clinical trial was performed on 60 patients with open fractures of the leg or foot ankle in open surgery and internal fixation of fracture (ORIF) referred to Imam Hossain hospital, Shahroud, Iran from May 2018 to August 2018 who were randomly divided into two equal groups.

Inclusion criteria: aged between 18-60 years; ASA class 1 & 2 anesthesia, fractures of the leg or foot ankle, taking anticonvulsant drugs, sedative and antidepressant drugs, and satisfaction in research.

Exclusion criteria: unstable hemodynamic status; any complications that could alter the procedure and anesthesia; sensitivity to any of the anesthetic drugs; use of opium within 48 hours before surgery; use of any analgesics drugs 48 hours before surgery, and dissatisfaction in research.

Blinding description: In this study, patients, and the person responsible for the severity of the pain and the analyzer were blinded. All patients were examined for hemodynamic and cardiovascular status before being split up into the intervention and control groups.

The division of patients into two groups of intervention and control was done by a qualified nurse who had no knowledge of the actions to be performed in the two groups. Measuring the severity of pain at different times and results recorder was carried out by a qualified nurse without any knowledge of the type of intervention and control patients.

Patients who were entered into the study were divided into intervention and control groups based on a randomized design based on four randomized blocks. The researcher first identified 60 series A and B cards based on a 4-block random pattern and placed A and B cards in separate envelopes and provided the envelope to the treating physician in the order specified in the pattern. Patients in both groups fasted for at least 8 hours and were administered intravenously before anesthesia (fentanyl 1 µg/kg). The onset of anesthesia was Propofol 2 mg/kg and muscle relaxation was induced by atracurium 0.5 mg/kg. Then endotracheal intubation was performed.

In the intervention group, anesthesia was induced as follows: remifentanil 0.25 µg/kg/min+Propofol 150 µg/kg/min, which was equivalent to 60 ml of Propofol 1% per hour and 20 ml of remifentanil (50 µg/ml). The patient was ventilated with 50% oxygen. In the control group anesthesia with Nitrous Oxide with oxygen (50% O_2+50% N_2O) and isoflurane (1.2%-1.5%) was administered. Cardiovascular and respiratory monitoring was performed in both groups and the depth of anesthesia was adjusted according to clinical symptoms. Muscle relaxation was repeated in both groups (if necessary).

In the recovery ward, if there was pain, pethidine 20 mg was administered. After moving to the orthopedic section, if there was pain, pethidine 20 mg per 6 hours was administered.

Measured patient-related variables including age, sex, history of smoking, substance abuse and the duration of the fracture and the variables associated with the fracture, including the type of fracture and the site of the fracture. Also, pain severity and analgesic dose used in the ward; measurable pain intensity variable was determined and charted by the justified sampler at 2, 4, 6 hours after entering the orthopedic ward and then every 6 hours for 24 hours. numeric rating scale (NRS) was used to measure pain, with zero score meaning no pain, score 2 meaning mild pain, score 2 to 4 moderate pain, score 4 to 6 severe pain, score 6 to 8 very severe pain and a score above 8 meant the most severe pain imaginable.[2] The flow diagram of the study is shown in figure 1.

Questionnaires were collected and analyzed by SPSS 16 software using descriptive statistics, chi-square, and independent t-test. Descriptive statistics, mean, absolute and relative frequency were also used. Sample size using G. Power 3.0.10 at a significant level of 5% and a power of 80%, equal to 30 people in each group and a total of 60 people. This study has an ethics code number (IR.SHMU.REC.1395.122) from the research deputy of Shahroud university of medical sciences. This research IRCT20170130032313N1 was coded in the Iranian clinical trial system. The essential information and objectives of the study were explained to the patients, and written consent was obtained for participation in the study.

Results

Of the 60 patients, 38(52.4%) were male and the remainder were female. The mean age of the participants was 33.9±15.1 years and the age group of 20-40 years old with 35.8% had the highest frequency. There was no significant difference between mean age in intervention and control groups (Pvalue<0.05). Furthermore, in 36 patients (67.9%), the fracture site was related to the leg (tibia & fibula) region. The results of demographic and clinical information of patients are shown in table 1. Postoperative pain assessment in the two groups showed that intensity of pain in the recovery room and up to 4 hours after surgery was significantly lower (Pvalue<0.001) in the intervention group but after 4 hours there was no significant difference between the two groups. The average severity of postoperative pain in patients in the two groups at different hours is shown in table 2. The findings of the study also showed that there was a significant decrease (Pvalue<0.036) in the number of cases requiring prescribed analgesics in the recovery room and up to 4 hours after surgery in the intervention group. The results of the number of cases requiring analgesia in the two groups at different times are shown in table 3.

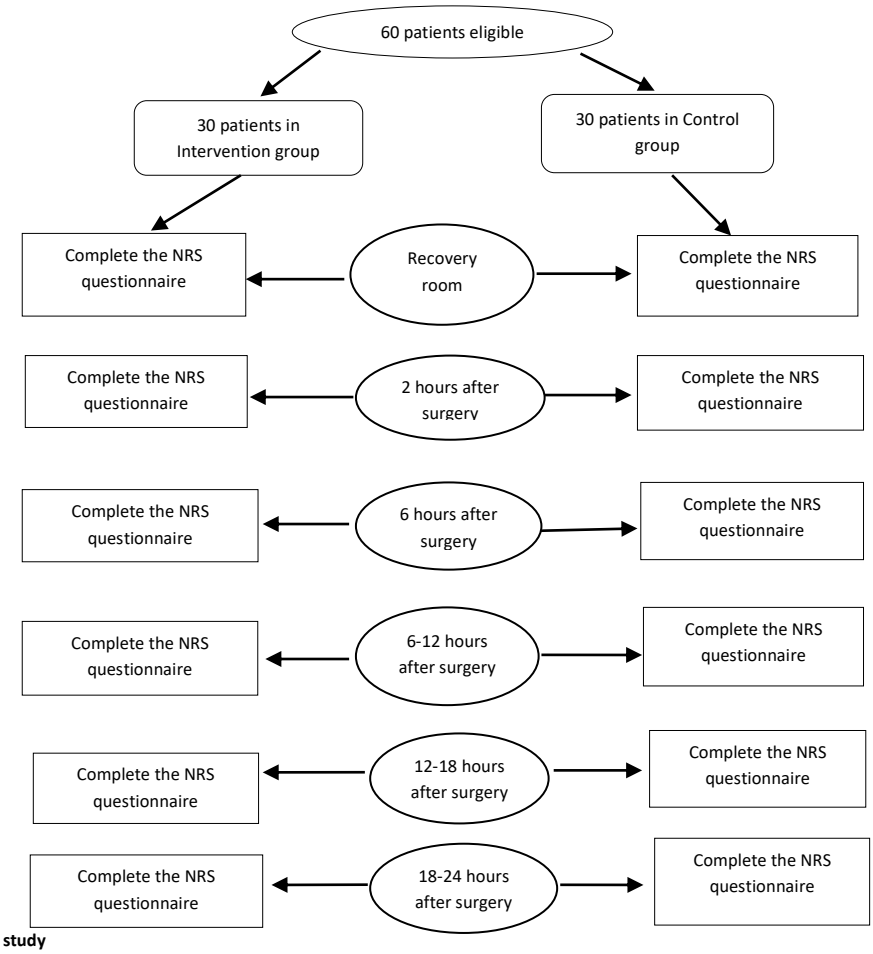

Figure 1. The flow-diagram of the study

Table 1. The demographic and clinical information of patients

Demographic & clinical information	Intervention group Mean±SD/Number (%)	Control group Mean±SD/Number (%)	Total Mean±SD/Number (%)	Pvalue
Age (year)	33.9±15.2	34.1±15.1	33.9±15.1	0.118
Age category				
– < 20 years	7(23.3)	5(16.7)	12(20.0)	
– 20- 40 years	12(40.0)	11(36.7)	23(38.3)	
– 40-60 years	8(26.7)	10(33.3)	18(30.0)	0.325
– > 60 years	3(10.0)	4(13.3)	7(11.7)	
Sex				
– Male	21(70.0)	22(73.3)	41(68.3)	0.501
– Female	9(30.0)	8(26.7)	17(31.7)	
Previous disease history				
– Positive	9(30.0)	6(20.0)	15(25.0)	0.091
– Negative	21(70.0)	24(80.0)	45(75.0)	
History of drug use				
– Positive	8(26.7)	5(16.7)	13(21.7)	0.146
– Negative	22(73.3)	25(83.3)	47(78.3)	
Place of fracture				
– Wrist and toe of foot	9(30.0)	5(16.7)	14(23.3)	0.057
– Tibia and fibula	21(70.0)	25(83.3)	46(76.7)	
Type of fracture				
– Closed	11(36.7)	13(43.3)	24(40.0)	0.068
– Open	19(63.3)	17(56.7)	36(60.0)	
Cause of trauma				
– Traffic accidents	21(70.0)	25(83.3)	46(76.7)	
– Fall	3(10.0)	1(3.3)	4(6.7)	0.079
– Others	6(20.0)	4(13.4)	10(16.6)	
Previous surgical history				
– Positive	14(46.7)	19(63.3)	33(55.0)	0.053
– Negative	16(53.3)	11(36.7)	27(45.0)	
History of anesthesia				
– Positive	13(43.3)	12(40.0)	25(41.7)	0.143
– Negative	17(56.7)	18(60.0)	35(58.3)	

Table 2. Frequency distribution of patients according to pain intensity at different times after surgery

pain intensity/different times	Intervention group Mean±SD	Control group Mean±SD	Pvalue
Recovery room	6.6±3.7	7.4±4.4	0.001
2 hours after surgery	6.1±2.7	6.7±3.5	0.001
4 hours after surgery	5.4±3.1	5.9±3.7	0.017
6 hours after surgery	4.7±3.4	5.1±3.8	0.095
6-12 hours after surgery	4.4±3.3	4.6±3.5	0.124
12-18 hours after surgery	3.5±3.3	3.7±3.5	0.254
18-24 hours after surgery	2.8±2.7	2.9±2.3	0.341

Table 3: Frequency distribution of patients in need of analgesia at different hours after surgery

Need of analgesia/different times	Intervention group Number (%)	Control group Number (%)	Total Number (%)	Pvalue
Recovery room	0(0)	3(10)	3(5.0)	0.036
4 hours after surgery	3(10.0)	7(23.3)	10(16.7)	0.047
6-12 hours after surgery	10(33.3)	12(40.0)	22(36.7)	0.104
18-24 hours after surgery	17(56.7)	17(56.7)	34(56.7)	0.341

Discussion

The results of this study showed that pain intensity in the recovery room, 2 and 4 hours after surgery in the Isoflurane-Nitroxide inhalation anesthesia group was significantly lower than the control group but after 4 hours of surgery, there was no difference between the two groups. It was also found that the need for analgesic drugs was significantly lower in the intervention group than the control group within the first 4 hours after surgery. Complete intravenous anesthesia (total IV anesthesia=TIVA) has several advantages over inhaled anesthesia.[16] The most important benefits being the ability to deepen anesthesia more quickly than evaporative anesthetics for surgery, faster recovery, non-air pollution, operating room space, damage to the ozone layer caused by evaporative anesthetics, failure to produce cardio depression using evaporative drugs, and the development of systolic and cardiac output hypotension.[17-19] On the other hand, inhaled anesthetics provide faster and lighter anesthesia.[20] Also, the use of new anesthetics, such as isoflurane, had no significant effect on the depth of anesthesia and on vital signs, and it is more acceptable and easier for the patient to accept when it is time for the needle to be inflamed.[21-22] Drugs, classified as intravenous anesthetics, are often used to induce anesthesia quickly with better relief. These medications may also be used in combination with inhaled anesthetics to maintain anesthesia by alternate or single-dose intravenous administration or fixed intravenous infusion.[23]

Pascal et al., in their study comparing the analgesic effect of isoflurane and Propofol in abdominal surgery, concluded that sedative scores were higher in the isoflurane group in the early hours (2 and 4 hours postoperatively) but they did not differ in the rest hours. It was also found that the need for narcotic analgesics such as Nalbuphine was lower in the isoflurane group within the first 6 hours.[24] These findings are largely consistent with the present study, but the important difference is the timing of postoperative pain assimilation in the two studies. In the present study, it is related to the first four hours after the operation, but in the Pascal study, it is related to the first twenty-four hours after the operation. Perhaps the most important reason for this difference is the age of the two patients and the cause of their trauma.

In the Mohaghegh study, it was found that inhaled anesthesia could reduce the severity of postoperative pain after intravenous anesthesia, but it was not statistically significant.[25] These findings are somewhat similar to the present study but are different with regards to the need for postoperative analgesics.

In the Yoon study, it was found that there was no difference between different anesthetic drugs and postoperative pain and the rate of pain was similar in inhaled and intravenous drugs.[26] This may be due to the type of surgery, the gender of the patients or the extent and time of surgery. This finding contradicts the results of the current study, the most important causes of which may be related to the age of the patients, the severity of the bone damage, as well as the sex of the patients in the above two studies.

In Chan's study, it was found that with increasing age, female sex, increased surgical time and increased number of surgeries, the palliative effect of Propofol and Isoflurane decreased, and the need for opiate analgesics was likely to increase. These findings also contradict the results of the present study. The cause of this difference may be related to the type of surgery, the duration and extent of the surgical site, as well as genetic differences.[27]

Peng et al., showed that the incidence of postoperative pain was significantly correlated with time and extent of surgery, and the more these two variables increased, the greater the severity of postoperative pain. They also stated that the amount of additional analgesic needed, significantly increased after 6 hours of surgery and this finding is fully consistent with our results.[28]

In the present study, there was no difference between the two sexes in terms of the severity of pain and the need for postoperative analgesics between the two groups, which is in contrast to Tallant, Guo and Kim studies.[29-31] One of the most important reasons for this difference is the gender distribution of patients in these studies. In the present study, a significant number of patients were male, but in other studies, patients of the same sex were almost equal.

In addition, in the present study, the highest rate of postoperative pain was in patients with open fractures of the

legs, which is probably due to the extent of the injury and longer surgery. These findings are consistent with the results of Mikuni and Kim studies.[32-33]

Regarding the findings of this study and comparing it with other studies, despite some limitations such as isoflurane-nitro oxide anesthesia and the need for an assistant to perform it, this evaporative anesthetic can be used in the induction of anesthesia in different age groups and in various surgical procedures, especially orthopedic surgeries and good results were achieved with respect to reducing pain, especially in the first 4 hours after surgery.

The limitations of this study were the shortage of eligible patients (due to the high opium use among patients) and the lack of full cooperation when determining the severity of the patients' pain. This restriction was also controlled with complete patient justification and patience.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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