

## Comparing the Effect of Intrathecal Injection of Pethidine with That of Bupivacaine on Hemodynamics in Hip Surgery: A Double Blinded Clinical Trial

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### ABSTRACT

**Background:** The use of regional anesthesia for lower limb orthopedic surgery is preferable to general anesthesia. In some studies comparing regional anesthesia and general anesthesia, the one-month mortality of patients undergoing regional surgery was significantly lower. Given the relative advantages observed about intrathecal injection of pethidine, including fewer side effects, and longer postoperative analgesia, in combination with effective sensory, motor, and sympathetic blocks, we sought to compare the influence of intrathecal injection of pethidine and bupivacaine on the hemodynamics of patients.

**Methods:** In this double blind randomized parallel trial, patients undergoing surgery with femoral and hip fractures, were divided into two groups. In the first group bupivacaine and in the second group pethidine were used for spinal anesthesia. Hemodynamic changes were examined and recorded during surgery. The results were analyzed by SPSS18 software

**Results:** 67 patients undergoing surgery with femoral and hip fractures, were divided into two groups of 30 and 37 individuals. The mean heart rate in patients with a high risk of surgery was higher in the group receiving pethidine compared to the group of bupivacaine, with a Cohen's effect size of 0.294. This effect size is evaluated as average, while the rate of mean arterial pressure with Cohen's effect size of 0.511 was evaluated as large.

**Conclusion:** Pethidine can be a good alternative to bupivacaine, especially in patients at high risk of surgery, given its hemodynamic stability.

### Introduction

From 1990 to 2004, the number of surgical operations for femur fractures increased by 158% [1-2]. Proximal femur fracture is a major problem and a common fracture in the elderly people around the

world. This issue is associated with high social and medical costs and significant debilitating complications [3]. Elderly people suffer from reduced capacity and limitation of performance due to degenerative changes caused by increasing age in most of the body systems. Choosing the best and safest method of anesthesia in these patients is usually difficult. This is because general

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anesthesia can increase incidence of morbidity and mortality in elderly patients with several coexisting diseases or suffering from a severe systemic disease (American Society of Anesthesiologists, ASA class 3 or higher) [4]. Hemodynamic changes and complications from anesthesia are important. Elderly patients are more at risk after orthopedic surgery compared to younger patients. [5] Treatment of hypotension caused by various types of anesthesia is not risk-free either and may be associated with complications [6-7]. Thus, it would be very useful to choose a drug that, in addition to the benefits of regional anesthesia, has minimal hemodynamic fluctuations [8]. Today, the use of new techniques and the reduction of drug doses to prevent higher block level as well as lowering incidence of poisoning caused by local anesthetics are new targets to reduce mortality due to regional anesthesia [9].

Opioids are the strongest analgesics available with central effects. For years and since the discovery of opioid receptors in the spinal cord, their use in the spinal canal in the clinic has been accepted with the aim of developing strong segmental analgesia without the complications and limitations of systemic use. All drugs prescribed as intrathecal create some degrees of analgesia. The main difference is the duration of effect, the rate of clearance, and the pathways in which the drugs reach their receptors in the brain [10]. Pethidine is a lipophilic drug that is 10 times less potent and 30 times more lipid soluble than morphine, and it has a faster onset of action. Pethidine is different from other opioids as it has local anesthetic properties and has motor and sensory fiber blocks [11]. Its intrathecal dose was used in various studies from 0.25 to 1 mg per kilogram of body weight, and its local anesthetic effects were comparable to those of cocaine [12]. Different doses were used in different studies, but in general, as a single anesthetic agent, it was recommended to use a dose of 1 mg per kilogram of body weight.

Pethidine has acted as a hyperbaric drug in CSF. Thus, according to the results of studies and the benefits of using intrathecal opioids and the need for further study, we decided to use pethidine alone and examine its effects plus side effects against local anesthetic, bupivacaine via subarachnoid method. The results of this study can be generalized to all patients who are candidates for surgery under spinal anesthesia. The David Williams survey also showed that according to the lower price of pethidine compared to bupivacaine, 60 cents (US) for 100 mg of pethidine compared to \$ 1.60 (US) for 4 ml of bupivacaine solution 0.5%, in developing countries, the use of pethidine given its safety and effectiveness is a good alternative for reducing treatments costs [13].

## Methods

This study was performed as double-blind clinical trial with two parallel randomized groups which was approved by the Ethics Committee of Golestan University of Medical Sciences (COA number: IR.GOUMS.REC.1397.017). And also, this clinical trial has been registered in <https://www.irct.ir/> with the code number IRCT20180603039966N1.

All patients who were hospitalized in 5 Azar Medical-Educational Center in Gorgan from September 2018 until September 2019, with hip and femoral fractures, and were candidates for surgery, were examined according to the inclusion criteria of the study. Inclusion criteria were patients with hip or femoral fractures, no history of allergy to local anesthetics and pethidine. On the other hand, the exclusion criteria of the study included coagulation disorders, absolute contraindications to neuraxial block (patient dissatisfaction and inability to hold the position, and lack of patient cooperation to perform the block, localized puncture site infection, high ICP). For all patients, the purpose of study and a summary of the methodology were described by an anesthesiologist, and informed written consent was taken from them to enter the study.

Shrestha BR's study [14] was used to determine the sample size which was determined 37 in the pethidine group and 30 in the bupivacaine group at the confidence level 0.95, with power test 0.80, and by applying different variance ratios. Random allocation was performed based on the number of heartbeats in the pre-intervention phase, with the heart rate of eligible individuals measured and arranged in a descending order and placed in one of two groups according to the stratified randomization method and based on applying two-group block randomization. Accidental allocation concealment was performed using sequentially numbered, sealed, opaque envelopes. For blinding the statistical evaluator, the data were given to them as coded.

All patients were under combined epidural spinal anesthesia with the Arrow® Combined spinal epidural tray. Before starting the procedure, all patients were given 5 ml per kilogram of body weight of isotonic crystalloid solution. Patients in group 1 were anesthetized with intrathecal injection of 1 mg/kg of pethidine solution (50 mg/mL) at room temperature with addition of normal saline to reach to 2 mL. The group 2 patients were anesthetized with 2 mL of bupivacaine 0.5% solution at room temperature. The patients underwent aseptic spinal anesthesia at the L2-L3 level, and epidural catheter was embedded for them. The anesthesia procedure and recording of vital signs as well as possible side effects of the drugs were performed by a skilled anesthetist (in this project, the resident of anesthesiology in companionship of the assistant professor) who was unaware of the drug content in the syringe.

Blood pressure in patients with NIBP was measured from the moment of entering the operating room to the end of surgery. To monitor blood pressure in patients at high risk for surgery (ASA III, IV), arterial line was initially embedded for patients. The patients' vital signs (mean arterial pressure, pulse rate) were recorded every three minutes for the first 15 minutes of the surgery, then every 5 minutes until 1 hour, and then every 15 minutes. The sensory block onset was evaluated by the Pin Prick test. The motor block onset was evaluated and recorded by Modified Bromage Scales of grade II.

In case of hypotension of more than 30% of baseline level for that patient, intravenous injection of phenylephrine 0.2 mg every 10 to 15 minutes was used. In the case of moderate to severe pruritus, which causes discomfort to the patient, 10 mg bolus dose of propofol was injected intravenously to allow the patient to tolerate pruritus and not to cause respiratory depression and apnea. In severe bradycardia, intravenous atropine 0.02 mg per kg body weight was used. During the surgery, supplemental oxygen with nasal cannula was used for all patients.

Normality was investigated using Shapiro-Wilks test. Independent t and paired t-tests and Mann-Whitney and Wilcoxon tests were used to analyze the data. Also, the rate of change was calculated to adjust on non-identical base values in the two groups, and its average was compared between the two groups.

**Table 1- Average rate of change in the heart rate according to the type of drug used (Values are expressed as mean of the Rate of Change (ROC±SD). HR: Heart Rate, ROC= ((previous value/current value)-1) \*100**

Drug Type	Average rate of change in the HR (standard deviation)	P value	Cohen's d.
Bupivacaine	-0.0468(±0.08)	0.539	0.15
Pethidine	-0.0323(±0.09)		

**Table 2- Average rate of change in MAP according to the type of drug used (Values are expressed as mean of the Rate of Change (ROC±SD). MAP: Mean Arterial Pressure. ROC= ((previous value/current value)-1) \*100**

Drug Type	Average rate of change in MAP (standard deviation)	P value	Cohen's d.
Bupivacaine	-0.2112(±0.14)	0.532	0.19
Pethidine	-0.1866(±0.17)		

(Table 1) reports the average rate of changes in the heart rate in the first 30 minutes regardless of the risk of anesthesia (ASA Classification) and only according to the type of drug used. The results show that the difference was not statistically significant and Cohen's effect size was calculated to be 0.15, suggesting a small effect size. (Table 2) outlines the average rate of changes in MAP in the first 30 minutes, irrespective of the risk of anesthesia (ASA Classification) and only according to the type of drug used. The results reveal that the difference was not statistically significant and the Cohen's size effect was calculated to be 0.19, indicating a small effect size (P value: 0.532).

The patients were also divided into three classes regarding their age: less than 40 years, 41 to 64 years, and

## Results

A total of 67 patients entered our study. In 37 patients, pethidine and in 30 patients bupivacaine were used for the spinal anesthesia. The age of patients ranged from 28 to 93 years, the mean age of patients in the pethidine group was 62.94±17.43, and the mean age of patients in bupivacaine group was 72±13.91 years. There were 36 male and 31 female patients. Patients' weight ranged from 45 to 100 kg, the mean weight of patients in the pethidine group was 73.78±13.61 kg and in the bupivacaine group was 64.73±10.74. The number of opium addicted patients was 29. In the bupivacaine group, 10 patients were addicted to opium, and in the pethidine group, 19 patients had opium addiction.

The mean arterial pressure (MAP) and the number of heart beats per minute measured were almost the same in both groups. The baseline mean arterial pressure was 109.21±18.89 mmHg in the pethidine group and 110.06±15.90 mmHg in the bupivacaine group. The mean baseline heart rate was 88.97±15.25 beats per minute in the pethidine group and 88±14.51 beats per minute in the bupivacaine group. To compare the effects of the two drugs, the average rate of changes of the measured variables in the first thirty minutes was used. Decrease in MAP and heart rate of more than 30% compared to baseline measurements were considered to be hypotension or bradycardia.

65 to 93 years. In each age group, patients were classified according to the type of drug used for spinal anesthesia and their risk of anesthesia. despite the differences between low risk and high-risk patients in the last two age groups, there was no significant difference between low risk and high-risk patients according to the P values.

In (Table 3), according to the average rate of changes in the heart rate in the first thirty minutes compared to baseline, in low-risk patients, the Cohen's number calculated for heart rate was 0.034, which means that the effect Size was small. In high-risk patients, the Cohen's number calculated for the heart rate was 0.294, demonstrating that the effect size is moderate.

In (Table 4), in the case of MAP, in low-risk patients, there was no significant difference between the two

drugs, pethidine and bupivacaine (P value: 0.31), but the Cohen number in the low-risk group was calculated 0.41, which means that the effect size was moderate. In high-risk patients, the difference between the two groups was not statistically significant (P value: 0.12), but Cohen's

number was calculated 0.511 in high-risk patients, which means that the effect size is large.

The mean duration of sensory block in 30 patients undergoing anesthesia with bupivacaine was 118.16±19.97 minutes and in 37 patients undergoing anesthesia with pethidine was 97.16±21.55 minutes.

**Table 3- Average rate of changes in the heart rate according to the type of drug used and ASA classification (Values are expressed as mean of the Rate of Change (ROC±SD). ROC= ((previous value/current value)-1) \*100**

Risk of Anesthesia	Drug Type	Average rate of changes in the heart rate	P value	Cohen's d.
Low Risk	Bupivacaine	-0.0479(±0.10)	0.928	0.034
	Pethidine	-0.0443(±0.10)		
High Risk	Bupivacaine	-0.0461(±0.07)	0.376	0.294
	Pethidine	-0.0197(±0.09)		

**Table 4- Average rate of changes in MAP according to the type of drug used and ASA classification (Values are expressed as mean of the Rate of Change (±SD). MAP: Mean Arterial Pressure. ROC= ((previous value/current value)-1) \*100**

Risk of Anesthesia	Drug Type	Average rate of changes in MAP	P value	Cohen's d.
Low Risk	Bupivacaine	-0.1591(±0.11)	0.319	0.41
	Pethidine	-0.2153(±0.16)		
High Risk	Bupivacaine	-0.2413(±0.14)	0.128	0.511
	Pethidine	-0.1564(±0.18)		

## Discussion

Regional anesthesia is usually preferred in elderly patients due to its various benefits [15].

The results also showed that in patients at a high risk of surgery, pethidine is a better option. For example, in patients with a high risk of surgery, the average rate of change in the heart beat reduction, was lower than in patients with bupivacaine, and although it was not statistically significant, it had a moderate effect on patients according to the Cohen's number. Although the rate of MAP did not differ significantly between the two groups, the effect size was large and therefore it could be clinically effective and provide good hemodynamic stability for the patient during surgery. Nevertheless, the statistical non-significance of our findings (P value> 0.05) may have occurred due to the limited number of cases and it is recommended to conduct more extensive studies to investigate the effects of these drugs.

In Cozian's study, the hemodynamic changes caused by the intrathecal injection of pethidine were investigated, and a very small change was observed in the heart rate, which was not statistically significant, which is similar to our results. Bradycardia was reported to require treatment with atropine in a limited number of patients in a Conway's study, in which intravenous fluid was not prescribed before spinal and only in patients with block levels of T7 and higher.

Pethidine is a reliable and useful drug when used as an intrathecal anesthetic for lower limb surgery. Its motor blockade is not very deep and it has a short duration of

action, with aspect being very useful in early ambulation of patients in the postoperative period. Pethidine can cause long-term analgesia in the postoperative period, which also reduces the need for more analgesics. The greatest logical reason behind using intrathecal pethidine is hemodynamic stability [16]. The results of some studies suggest that the use of intrathecal pethidine is beneficial for high-risk patients. [17] In our study, we found that in patients with a high risk of surgery, pethidine had a better and more beneficial effect.

Also, Ebru Canakci's (2017) study showed that the use of intrathecal pethidine in TURP surgery in patients with ASA classification of 1 to 3 was associated with hemodynamic stability during surgery, no observed respiratory depression, better postoperative pain control, and ultimately greater patient comfort [18], which is very consistent with our results.

This drug can be used as a single agent in spinal anesthesia. Nevertheless, its use has not been expanded for this purpose, such as bupivacaine, and its effects and recovery parameters are not yet widely available in anesthesia texts and more studies are required to investigate the significant side effects of drug use [19-21].

Overall, given that the patients with a high risk of surgery should bear many risks during surgery, hemodynamic stability has a particular importance to the anesthesiologist, and patients who received pethidine had lower incidence of bradycardia or hypotension episodes.

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