Effect of methoxymine on prevention and treatment of myocardial injury and cardiac function in elderly patients with hypotension during intraspinal anesthesia

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Abstract. – OBJECTIVE: We aimed to investigate the effects of methoxamine to prevent hypotension in the elderly with intraspinal anesthesia (IA) on myocardial injury and cardiac function.

PATIENTS AND METHODS: A retrospective study was conducted by enrolling sixty elderly patients who underwent femoral head replacement (FHR) under IA in our hospital from August 2019 to August 2020. The patients were divided into two groups according to the random number table method. In the control group (CG) (30 patients), 5 mg of ephedrine was administered sedately when patients developed hypotension (20% below basal blood pressure). In the research group (RG) (30 cases), 2 μg/(kg·h) of methoxamine hydrochloride was given as a constant-rate pump before anesthesia, and 1 mg of methoxamine hydrochloride was administered intraoperatively if hypotension occurred. The hemodynamic [systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR)], myocardial injury indexes [cardiac troponin I (cTnI), creatine kinase isoenzyme MB (CK-MB), fatty acid binding protein (FABP), plasma amino-terminal brain natriuretic peptide precursor (NT-proBNP)], cardiac function indexes [systemic vascular resistance (SVR), stroke volume (SV), net percentage ejection time (ET)] were observed before anesthesia (T1), at the end of surgery (T2), and 6 h after surgery (T3) in both groups. The Bruggemann Comfort Score (BCS) and Visual Analog Scale (VAS) scores at T3, 12 h postoperatively (T4) and 24 h postoperatively (T5) in both groups were observed, and the incidence of adverse reactions to intralesional anesthesia in both groups was counted.

RESULTS: SBP, DBP and HR at T2 were lower than those at T1 in both groups, and SBP, DBP and HR at T3 were higher than those at T2, and SBP, DBP and HR at T2 and T3 in the RG were higher than those in the CG (p<0.05). In both groups, cTnI, CK-MB and FABP were higher at T2 and T3 than at T1, higher at T3 than at T2, and NT-proBNP was higher at T2 than at T1 and T3, and lower in the RG than in the CG (p<0.05). In both groups, SVR and SV at time point T2 were lower than at time point T1 and ET was higher than at time point T1, SVR and SV at time point T3 were higher than at time point T2 and ET was lower than at time point T2, SVR and SV in the RG were higher than in the CG and ET was lower than in the CG (p<0.05). VAS scores were higher in both groups at T4 and T5 than at T3, and lower in the RG than in the CG (p<0.05).

CONCLUSIONS: Methoxamine can effectively reduce the risk of hypotension in geriatric endotracheal anesthesia, which can reduce myocardial injury and stabilize cardiac function in patients.

Key Words:

Femoral head replacement, Intraspinal anesthesia, Myocardial injury, Cardiac function.

Introduction

Femoral neck fracture and femoral head necrosis are among the most common diseases in the elderly. Femoral Head Replacement (FHR) is an important way to treat these diseases, which can effectively restore the stability of the hip joint and relieve patients' clinical symptoms[1]. Due to the decrease in physical function and liver and kidney compensatory function, as well as the combination of hypertension, diabetes and other underlying diseases, the elderly have a reduced ability to biotransform and clear a variety of anesthetic drugs and are prone to respiratory depression, hypotension, and other adverse reactions, which threaten their lives. According to the results of related studies[2], the complication rate is about 95% in elderly people over 80 years of age. Therefore, elderly patients undergoing FHR need to be combined with effective anesthesia to improve surgical safety.

Intraspinal anesthesia (IA) belongs to the common anesthesia methods for clinical lower abdominal, lower limb, and perineal surgeries, which can effectively reduce the dose of anesthetic drugs used, alleviate the physical burden of patients, and

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reduce the risk of adverse reactions by injecting anesthetic drugs into the lumen of patients' spinal canal and blocking the nerve conduction function[3]. However, due to the degeneration of physical functions and reduced cardiovascular self-replacement in the elderly population, they are prone to a stronger stress response during anesthesia, causing hemodynamic fluctuations and making patients hypotensive[4]. Hahn and Drobin[5] found that the incidence of hypotension after intratubular anesthesia in elderly patients ranged from 25% to 82%, and hypotension can lead to a decrease in the amount of cardiac blood returned to patients, resulting in insufficient myocardial blood supply and myocardial injury, leading to a decrease in cardiac function. Methoxamine is a highly selective α1 agonist that excites α adrenergic receptors on peripheral blood vessels. Related studies[6] reveal that methotrexate promotes small vessel constriction, increases vascular resistance, improves coronary blood flow, and has a positive effect on myocardial protection, but it has not been studied under vertebral anesthesia. In view of this, the present study focused on analyzing the effects of methotrexate on myocardial injury and cardiac function in the prevention and treatment of hypotension in IA in the elderly.

Patients and Methods

General Data

A total of seventy elderly patients who underwent FHR under IA in our hospital from August 2019 to August 2020 were selected. According to the exclusion criteria, 10 patients were excluded, and eventually, 60 patients were included in this study. These sixty patients were divided into two groups of 30 patients each according to the random number table method. In the research group (RG): 16 males and 14 females, aged 61-78 years, mean age (68.70±3.06) years; body mass index (BMI) 20-27 kg/m^2, mean BMI (23.60±1.04) kg/m^2. Reasons for surgery: 11 cases of femoral neck fracture, 12 of intertrochanteric fracture, and 7 of aseptic femoral head necrosis. In the control group (CG): 17 males and 13 females, aged 62-79 years, mean age (69.10±3.24) years; BMI 20-28 kg/m^2, mean BMI (23.90±1.17) kg/m^2. Reasons for surgery: 13 cases of femoral neck fracture, 11 of intertrochanteric fracture, and 6 of aseptic femoral head necrosis. The above information was well balanced between both groups ($p>0.05$) and comparable. The study was approved by the Ethical Committee of Danzhou People's Hospital and participants gave written informed consent.

Selection Criteria

(1) Inclusion criteria: 1. All participants were treated with FHR; 2. All received IA; 3. Age ≥60 years; 4. Those with well-controlled underlying disease.
(2) Exclusion criteria: 1. Subjects with previous cardiovascular diseases such as myocardial infarction and cerebral infarction; 2. Those who were allergic to the study drug; 3. Those with co-morbid autoimmune diseases; 4. Subjects with co-morbid mental illness. 5. Those combined with malignant tumors.

Methods

Anesthesia methods

After the patient was admitted to the room, the upper limb vein was opened and hydroxyethyl starch 130/0.4 sodium chloride injection (Harbin Medisan Pharmaceutical Co., Ltd., Beijing, China; specification: 250 mL/bottle, SFDA Approval No. H20067462) 500 mL was administered within 20-30 min, followed by infusion of Sodium Lactate Ringer's Injection (Sichuan Kelun Pharmaceutical Co., Ltd., Chengdu, China; specification: 500 mL/bottle, SFDA Approval No. H20055488) with a gum: crystal ratio of 1:1. The patient was placed in a flexed knee position on the healthy side, and a puncture was performed between L_{3-4} ridges, and 3 mL of 0.75% ropivacaine hydrochloride injection (Aspen Pharmacare Australia Pty Ltd, Sydney, Australia; SFDA Approval No. H20140765) was injected in 3 fractions after 5 min, with a total dose of less than 1.5 mg/kg at each interval of 5 min.

RG

Before anesthesia, 2 μg/(kg·h) of methoxyamine hydrochloride (specification: 1 ml:10 mg, SFDA Approval No. H42021934; Yuanda Pharmaceutical Co., Ltd., Haerbin, China) was given as a constant-rate pump, and 1 mg of methoxyamine hydrochloride was given intraoperatively if hypotension occurred.

CG

5 mg of ephedrine (specification: 30 mg/branch, SFDA Approval No. H11020598; Beijing Yookon Pharmaceutical Co., Ltd., Beijing, China) was administered by sedation when the patient developed hypotension (20% below basal blood pressure).

Outcome Measures

(1) Hemodynamics: patients' Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Heart Rate (HR) levels were detected before anesthesia (T1), at the end of surgery (T2), and 6 h after surgery (T3) using a patient monitor BSM-6301C (Nihon Kohden Corporation, National Instrument No. 20163072540; Tokyo, Japan).

(2) Myocardial injury: 5 ml of elbow venous blood was collected from patients at T1, T2 and T3, centrifuged (speed 3,000 r/min, centrifugation 15 min, centrifugation radius 6 cm) to separate serum and plasma into two test tubes. Serum was collected, and levels of cardiac troponin I (cTnI) and plasma amino-terminal brain natriuretic peptide precursor (NT-proBNP) were measured by chemiluminescence, creatine kinase isoenzyme MB (CK-MB) by enzymatic immunosuppression, and fatty acid binding protein (FABP) by immunoturbidimetric assay. The kits were provided by Roche Diagnostics (Basel, Switzerland) and were operated in strict accordance with the kit instructions.

(3) Cardiac function: Systemic Vascular Resistance (SVR), Stroke Volume (SV), and net percentage Ejection Time (ET) levels were measured at T1, T2, and T3 time points using a noninvasive cardiac output measurement device C3 (Osypka Medical GmbH, National Instrument No. 20172217113; Berlin, Germany).

(4) Pain: patients' pain levels were assessed using Visual Analog Scoring (VAS)[7] at time points T3, 12 h postoperatively (T4), and 24 h postoperatively (T5), with a total VAS score of 10, with higher scores being more painful.

(5) Comfort: patient comfort was assessed at time points T3, T4, and T5 using the Bruggemann Comfort Score (BCS)[8], with a total BCS score of 4; the higher the score, the higher the comfort level.

(6) Adverse reactions.

The flow diagram of this study is shown in Figure 1.

Statistical Analysis

SPSS 25.0 software (IBM Corp., Armonk, NY, USA) was used for data processing, and the measurement data were all tested for normality by the Shapiro-Wilk normality test, and those meeting the normal distribution were expressed as $\bar{x}\pm s$ using the independent samples *t*-test between groups. The counting data were represented as % ratio, using χ^2 test. Generalized estimating equations were used to analyze the multi-temporal measures; $p<0.05$ was considered statistically significant.

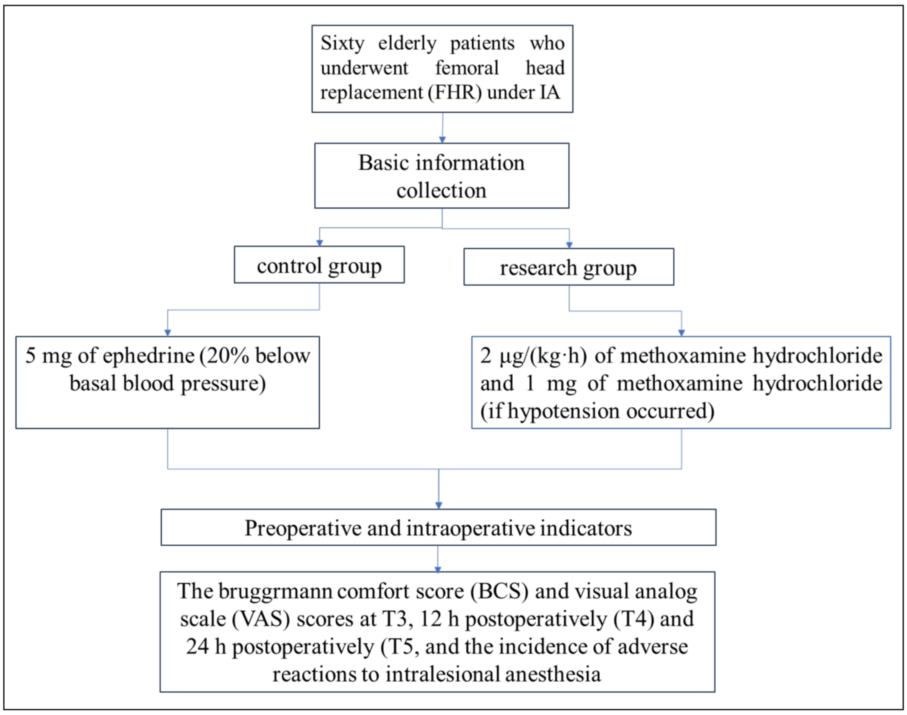

Figure 1. The flow diagram of this study.

Results

Hemodynamics at Different Time Points

SBP, DBP, and HR at T2 were lower than those at T1 in both groups, and SBP, DBP, and HR at T3 were higher than those at T2, and SBP, DBP, and HR at T2 and T3 in the RG were higher than those in the CG ($p<0.05$) (Figures 2-4).

Myocardial Injury at Different Time Points

In both groups, cTnI, CK-MB, and FABP were higher at T2 and T3 than at T1, higher at T3 than at T2, and NT-proBNP was higher at T2 than at T1 and T3, and lower in the RG than in the CG ($p<0.05$) (Figures 5-8).

Cardiac Function at Different Time Points

In both groups, SVR and SV were lower than the T1 time point, and ET was higher than the T1 time point at the T2 time point; SVR and SV were higher than the T2 time point, and ET was lower than the T2 time point at the T3 time point. SVR and SV were higher, and ET was lower than CG in the RG ($p<0.05$) (Figures 9-11).

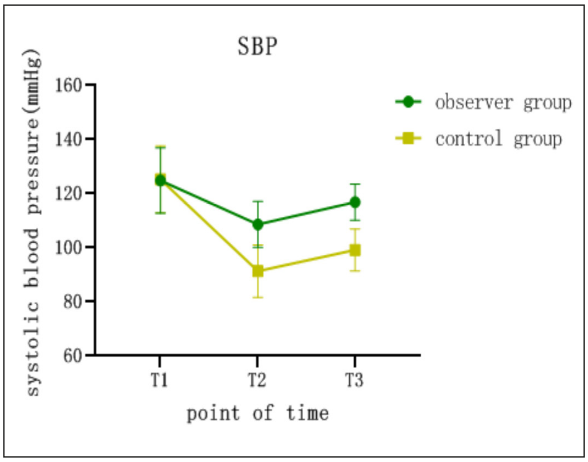

Figure 2. Horizontal line graph of SBP at two different sets of time points.

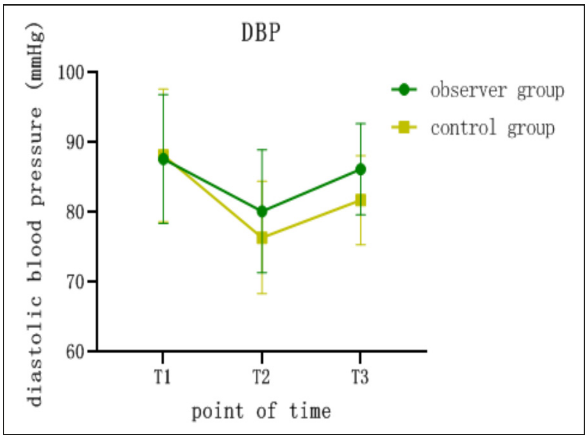

Figure 3. Horizontal line graph of DBP at two different sets of time points.

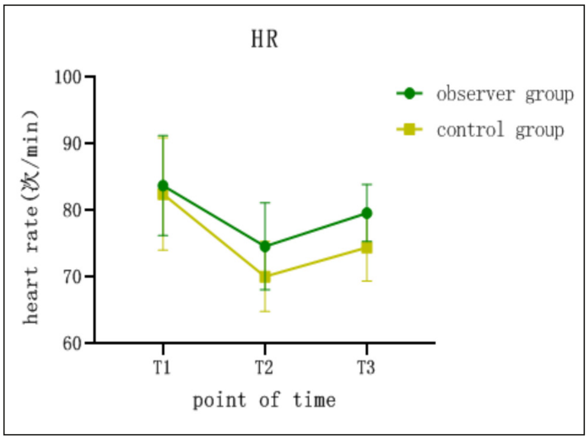

Figure 4. Two sets of horizontal folded HR plots at different time points.

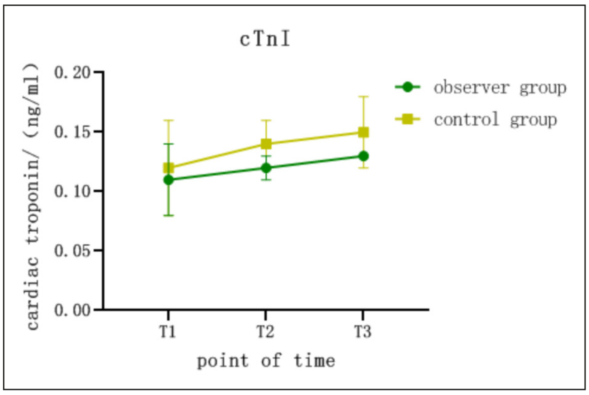

Figure 5. Horizontal line graph of cTnI at two different sets of time points.

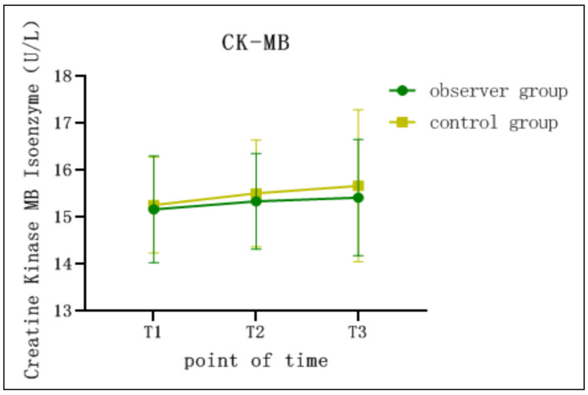

Figure 6. Horizontal line graph of CK-MB at two different sets of time points.

Pain Levels at Different Time Points

The VAS scores at T4 and T5 were higher than those at T1 in both groups and were lower in the RG than in the CG, with statistically significant differences ($p<0.05$) (Figure 12).

Comfort Scores at Different Time Points

No statistically remarkable difference was found in BCS scores at the T3 time point between both groups ($p>0.05$). The BCS scores at T4 and T5 were lower than those at T3 in both groups and were higher in the RG than in the CG, with statistically remarkable differences ($p<0.05$) (Figure 13).

Generalized Equation Analysis of VAS at Different Time Points

Interpretation of bias regression coefficients: RG: $\hat{\beta}$=-0.675, $p<0.001$, indicated a 0.675 reduction in VAS scores in the RG compared to the CG. T4 and T5 time points $\hat{\beta}$=0.975 and 1.036, $p<0.001$, indicated an increase in VAS scores of 0.975 and 1.036 in the RG compared to the T3 time point. RG *T4 and T5 time points $\hat{\beta}$=-0.627 and -1.057, $p<0.001$, indicated that the difference between the

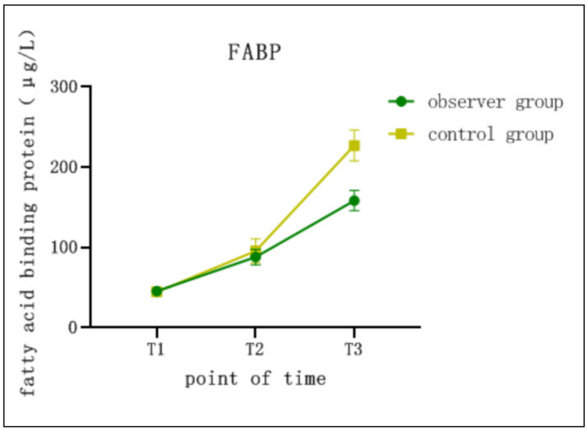

Figure 7. Horizontal line graph of FABP at two different sets of time points.

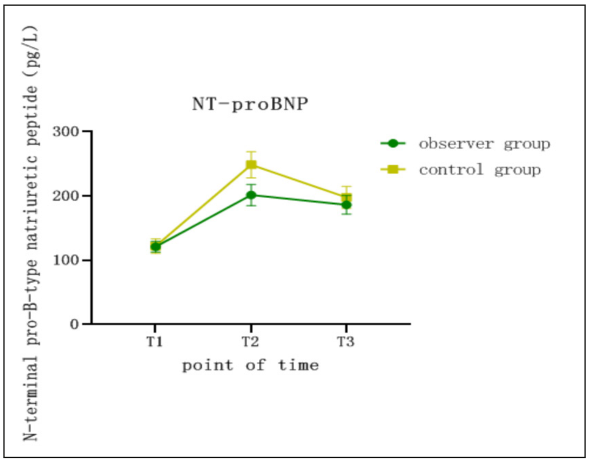

Figure 8. Horizontal line graph of NT-proBNP at two different sets of time points.

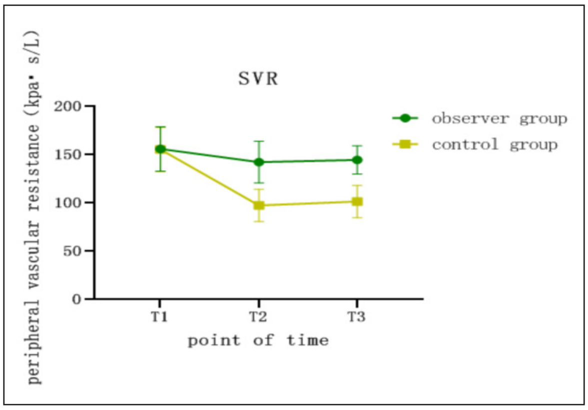

Figure 9. Horizontal line graph of SVR at two different sets of time points.

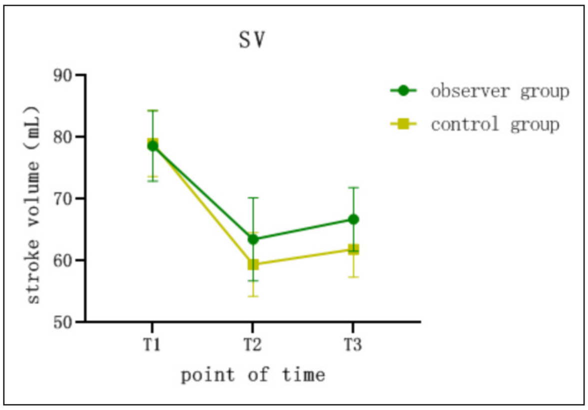

Figure 10. Horizontal line graph of SV at two different sets of time points.

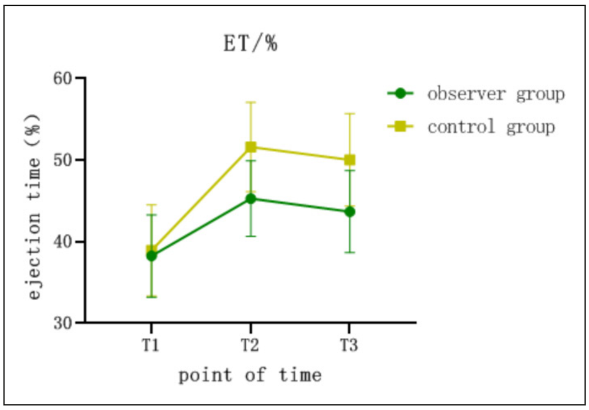

Figure 11. Horizontal line graph of SBP at two different sets of time points.

RG *T4 and T5 time points and T3 time points was 0.627 and 1.057 lower than the CG (Table I).

Generalized Equation Analysis of BCS at Different Time Points

Interpretation of the partial regression coefficient: $\hat{\beta}$=0.527, p<0.001, indicated an increase of 0.527 in BCS scores in the RG compared to the CG. T4 and T5 time points $\hat{\beta}$=0.627 and 1.927, p<0.001, indicated an increase in BCS scores of 0.627 and 1.927 in the RG compared to the T3 time point. RG *T4 and T5 time points $\hat{\beta}$=-1.092 and -1.329, p<0.001, indicated that the difference between RG *T4 and T5 time points and T3 time points was 1.092 and 1.329 lower than that of the CG (Table II).

Adverse Reactions

The incidence of adverse reactions in the RG was 4.41% (3/68), including one case of hypotension, one of bradycardia, and one of nausea, while

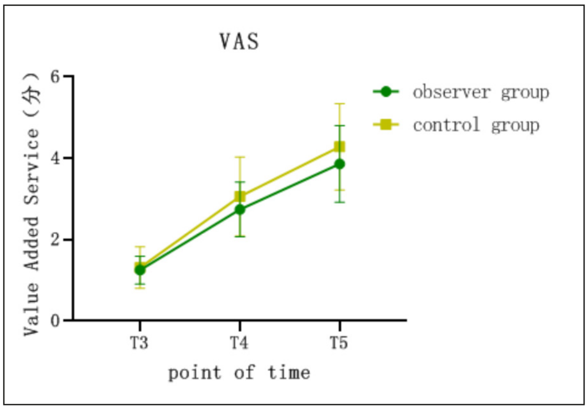

Figure 12. Horizontal line graph of pain at two different sets of time points.

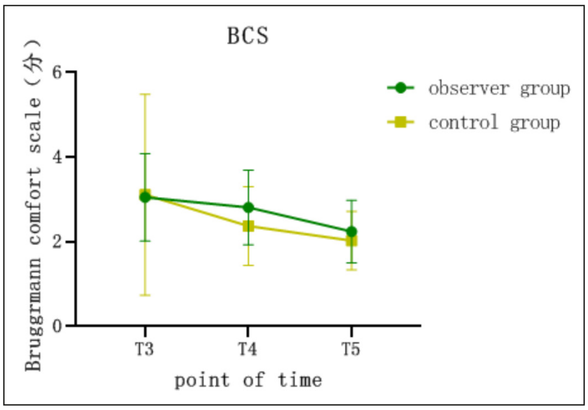

Figure 13. Line graph of comfort scores at different time points for both groups.

Table I. VAS generalized equation analysis for two different sets of time points.

Variables	B	S.E.	Wald 95% CI	Wald χ^2	p
Intercept	19.274	0.668	18.836 - 20.774	24.667	<0.001
RG	-0.675	1.057	3.067 - 8.704	5.114	<0.001
CG	-	-	-	-	-
T3	-	-	-	-	-
T4	0.975	0.869	-11.468 – -8.039	25.674	<0.001
T5	1.036	0.814	-4.857 – -1.724	13.649	<0.001
RG*T3	-	-	-	-	-
RG*T4	-0.627	2.759	-7.305 - 1.024	4.174	<0.001
RG*T5	-1.057	2.069	-14.784 – -6.339	14.052	<0.001

RG: research group, CG: control group; 6 h after surgery (T3), 12 h postoperatively (T4), 24 h postoperatively (T5).

Table II. Table II. Analysis of BCS generalized equations for two different sets of time points.

Variables	B	S.E.	Wald 95% CI	Wald χ^2	p
Intercept	72.165	0.933	70.395 - 74.054	60.274	<0.001
RG	0.527	1.298	-2.015 - 3.084	3.834	<0.001
CG	-	-	-	-	-
T3	-	-	-	-	-
T4	0.627	1.415	8.143 - 13.679	29.774	<0.001
T5	1.927	1.264	2.186 - 6.474	13.175	<0.001
RG*T3	-	-	-	-	-
RG*T4	-1.092	1.975	-10.05 – -2.847	12.639	<0.001
RG*T5	-1.329	1.624	-8.127 – -0.574	4.395	<0.001

RG: research group, CG: control group; 6 h after surgery (T3), 12 h postoperatively (T4), 24 h postoperatively (T5).

the incidence of adverse reactions in the CG was 13.46% (8/52), including six cases of hypotension, one of bradycardia, and one of nausea. The difference was statistically remarkable between both groups (χ^2=4.106, p=0.043).

Discussion

The use of IA for lower abdominal and lower extremity surgery can achieve better analgesia and muscle relaxation with less impact on respiration and circulation. However, most patients undergoing FHR are elderly people, who may have intervertebral foramen occlusion, spinal stenosis and dramatically reduced intracorporeal volume, resulting in less easy extravasation of anesthetic drugs and faster up and down diffusion. It can easily lead to too wide anesthetic plane or incomplete block, making hemodynamic instability during surgery, resulting in hypotension or difficulty in completing surgery, and seriously threatening the safety of patients[9]. Therefore, there is still a clinical need to find more effective anesthesia. From the results of this study, methoxamine can effectively reduce the risk of hypotension in geriatric endotracheal anesthesia, which can reduce myocardial injury and stabilize cardiac function in patients.

After IA, due to the blockade of sympathetic nerve fibers, the vasodilatation of the innervated area leads to a decrease in patients' return blood volume and lower blood pressure, increasing the risk of hypotension[10]. At the same time, due to the degenerative lesions of the autonomic nervous system in elderly patients, the cardiovascular system is less able to regulate stress and adaptability, and the sympathetic and vagal nerves are prone to disorders in the process of regulating HR, leading to a decrease in cardiac function, resulting in cardiovascular events such as myocardial infarction and arrhythmias, which seriously threaten patients' life safety. Thus, it is important for patients to know how to reduce the incidence of hypotension and stabilize cardiac function in elderly patients undergoing FHR. Methoxamine is a highly selective α agonist that excites α-receptors, which in turn induces sustained constriction of fine arteries throughout the body, increasing vascular resistance and thus improving myocardial blood flow[11]. It is hypothesized that the application of methoxamine in elderly patients with IA has a positive effect on stabilizing blood pressure and reducing myocardial injury.

In this study, SBP, DBP, and HR at T2 and T3 time points were higher in the RG than in the CG, indicating that methoxamine can effectively stabilize hemodynamics in elderly patients undergoing IA. The reason for this analysis is that IA can extensively block sympathetic nerve fibers, causing vasodilatation in the nerve-controlled area, which results in a drop in blood pressure and slowed HR. When the blood pressure drops to a certain level, it can lead to nausea and vomiting in patients. Methotrexate is a direct-acting sympathomimetic amine drug that agonizes α-adrenergic receptors in the peripheral vasculature and constricts blood vessels, thereby elevating patients' blood pressure levels and stabilizing their hemodynamics[12]. Meanwhile, Guo et al[13] found that high doses of methoxamine were able to locally increase vascular resistance by 54%, directly constrict blood vessels, increase blood pressure levels, and stabilize hemodynamics.

cTnI belongs to the myocardial muscle contraction regulatory protein. Under normal conditions, the level of cTnI in the blood is low, but when a myocardial injury occurs, its small molecular weight can be rapidly released into the blood and increase the level of cTnI[14]. FABP is present in multiple tissues, and is most abundant in the myocardium and skeletal muscle; it is one of the early indicators for the diagnosis of acute myocardial infarction, which can be elevated within 30 min to 3 h when myocardial injury occurs[15]. NT-proBNP is mainly synthesized and secreted by cardiomyocytes, and when ventricular load and ventricular wall tension are altered, it can lead to an increase in its level, which can effectively reflect left ventricular contraction. Moreover, it is an important indicator for assessing myocardial injury[16].

In this study, cTnI, FABP, and NT-proBNP were lower in the RG than in the CG at all time points, while SVR and SV were higher in the RG and ET was lower than in the CG, indicating that methoxamine can effectively reduce myocardial injury and have a protective effect on cardiac function in elderly patients with IA. The reason for this analysis is that the dramatic intraoperative changes in hemodynamics and cardiac work done can cause different degrees of myocardial injury, promote the expression and secretion of the apoptotic molecule Caspase-3, which initiates myocardial cell apoptosis, causing myocardial injury and affecting the cardiac function of patients[17]. The CG used ephedrine to improve patients' blood pressure levels. Ephedrine can act as a vasoconstrictor and elevate blood pressure by agonizing α- and β-receptors. Relevant studies[18] showed that the β-receptor dilating effect of ephedrine can counteract the vasoconstrictive effect of its α-receptors, thus affecting the blood pressure level of patients, while β-receptor excitation can increase the HR level, exacerbating myocardial oxygen consumption in elderly patients and further increasing the risk of myocardial injury, which is not conducive to the recovery of cardiac function. Methoxamine not only consistently elevates aortic diastolic pressure, increases coronary perfusion pressure, and increases myocardial blood flow, but also has a little excitatory effect on the myocardium, does not dramatically increase elevated myocardial oxygen consumption, and has a protective effect on the heart[19]. In terms of safety, only one case of hypotension, one of bradycardia, and one of nausea were observed, indicating that methoxamine can reduce the risk of adverse reactions in elderly patients undergoing IA. The reason is that methotrexate reduces the risk of adverse effects in elderly patients by raising blood pressure, stimulating the auricular sinus, lowering patients' HR, reducing myocardial effects, and decreasing myocardial injury[20]. Also, Khammy et al[21] confirmed that methoxamine also alleviated immunosuppression caused by stress reactions during anesthesia and surgery in elderly patients, boosting their immunity and thus reducing the risk of adverse reactions, which is consistent with the findings of this study.

Conclusions

To sum up, methoxamine can effectively reduce the risk of hypotension in geriatric endotracheal anesthesia and can reduce myocardial injury and stabilize cardiac function in patients. The biotransformation and clearance ability of various anesthetic drugs decreased after FHR in the elderly, and adverse reactions such as respiratory depression and hypotension were easy to occur, which threatened the life of patients. The results of this study suggest methoxamine can be used in FHR in the elderly to improve the therapeutic effect.

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Ethics Approval

The study was approved by the Ethical Committee of Danzhou People's Hospital.

Informed Consent

Participants were involved in this study after they signed informed consent.

Conflict of Interest

The authors declare no competing interests.

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