Norepinephrine in Goal-Directed Fluid Therapy During General Anesthesia in Elderly Patients Undergoing Spinal Operation: Determining Effective Infusion Rate to Enhance Postoperative Functions

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Abstract: Background and Objective: Intraoperative hypotension is a common complication in general anesthesia that could result in different serious complications particularly in elderly patients. This Randomized Clinical Trial (RCT) aims to determine effective continuous infusion rate of norepinephrine to prevent intraoperative hypotension during spinal surgery under general anesthesia in elderly patients.

Methods: This RCT was conducted on elderly patients (n=108) undergoing general anesthesia for posterior lumbar spinal fusion. The patients were randomly divided into 0.030, 0.060, and 0.090 μg·kg·min⁻¹ groups of norepinephrine infusion rates. The outcomes were assessed at entrance to operation room (T0), 15 mins after anesthesia induction (T1), 60 mins following surgery (T2), and immediately after surgery (T3). The intraoperative and postoperative complications and rehabilitation outcomes were comparatively assessed.

Results: All three groups significantly reduced the incidence of delayed wound healing (0.030 vs. 0.060 vs. 0.090 μg·kg·min⁻¹; 33.3% vs. 10% vs. 10%, P=0.024) and wound infection (26.7% vs. 6.7% vs. 6.7%, P=0.031). Intraoperative total fluid volume and colloids volume in the 0.030 group were significantly higher than 0.060 and 0.090 groups (P=0.005, P=0.003, and P=0.01, respectively). The 0.060 and 0.090 groups significantly increased mean-arterial-pressure than the 0.030 group at T2 and T3. Both 0.060 and 0.090 infusion rates significantly reduced intraoperative hypotension than 0.030 dosage (P=0.01 and P=0.003, respectively). The bradycardia incidence in the 0.090 group was significantly higher than the 0.030 (P=0.026) and 0.060 groups (P=0.038). The 0.060 group decreased the first intake by 1.4 hours (P=0.008) and first flatus by 1.1 hours (P=0.004) and postoperative hospital stay by 1 day (P=0.066).

Conclusion: The 0.060 μg·kg⁻¹·min⁻¹ norepinephrine infusion combined with goal-directed fluid therapy exhibited adequate intraoperative management and postoperative outcomes.

Clinical Trial Registration: www.chictr.org.cn, identifier ChiCTR-1900021309.

Keywords: Spinal fusion, prophylactic infusion, norepinephrine, general anesthesia, elderly patients, postoperative outcomes.

1. INTRODUCTION

Spine degenerative disease affects a diverse population particularly older adult patients (age range: 65 to 80 years old) [1, 2]. Recent population-based cohort and longitudinal studies have demonstrated that those patients who present with three to four comorbid conditions have significantly improved symptoms and quality of life with low perioperative morbidity and hospital length of stays of 2 to 4 days on average [3-5]. The surgical intervention is a common treatment option to ameliorate symptoms and improve the quality of life [6-8]. General anesthesia is the common route of anesthesia in elderly patients for spinal surgery [9-12]. Intraoperative hypotension is a common complication after general anesthesia, which could result in different serious complications [13, 14]. Research is ongoing to develop effective method for the prevention and management of intraoperative hypotension particularly for elderly populations [15-18]. Findings on the efficacy and usefulness of fluid therapy or vasopressors for the management of intraoperative hypotension induced by general anesthesia in elderly are controversial and the ideal regimen has not been determined [13, 16, 19]. Long operative duration, increased intraoperative blood loss, and increased volumes of crystalloid fluid resuscitation...
have been reported to be not conducive to early rapid recovery of patients [20]. The goals of intraoperative fluid management are to maintain central euvoolemia and to minimize excess salt and water [21]. Excessive fluid loading in elderly patients has been reported to disrupt glycocalyx. Glycocalyx is a carbohydrate-rich layer lining the endothelium that plays a crucial role in maintaining endothelial integrity. Destruction of endothelial glycocalyx can cause periorbital edema and affect prognosis [22]. Pulse pressure variation (PPV) is used as an accurate position indicator on the Frank–Starling curve. The arterial PPV induced by mechanical ventilation has been reported as a reliable and accurate predictor of fluid responsiveness in patients under anesthesia without cardiac arrhythmia. This indicator is a useful measure to predict the adverse hemodynamic effects of fluid depletion as well as the beneficial effects of fluid loading [23]. Norepinephrine is characterized by α-adrenergic agonistic activity in addition to a weak β-adrenergic agonistic activity [24]. This compound does not reduce the heart rate and cardiac output as much as phenylephrine. The prophylactic administration of norepinephrine to prevent and control hypotension during general anesthesia for spinal surgery in elderly patients is a new idea and few studies and data in the literature are scarce. Therefore, this study aims to investigate the effectiveness of prophylactic norepinephrine continuous infusion in preventing hypotension during general anesthesia for spinal surgery in elderly patients using a sequential allocation trial. The main objective is to determine the optimum continuous infusion rate of norepinephrine (0.030, 0.060, and 0.090 μg.kg⁻¹.min⁻¹) against intraoperative hypotension during spinal surgery in elderly patients.

2. MATERIALS AND METHODS

2.1. Research Design

This was a single center prospective double blind RCT with parallel group design conducted in the affiliated Hospital of Inner Mongolia Medical University (AHIMMU) (Hohhot, China) from September, 2018 to April, 2019. All experimental procedures of the study were approved by local ethics committee of IHIMMU, Hohhot, China (ethic code: KY2018022), which were in accordance with the ethical standards and regulations of human studies of Helsinki declaration (2014). The study was registered in the Chinese Clinical Trial Registry (website: www.chictr.org.cn, ChiCTR-1900021309) and adhered to CONSORT guidelines. After explaining the experimental procedures and objectives and possible risks and benefits of the study to them, all patients filled and signed written consent form for participation in the study.

2.2. Patients

Elderly patients with lumbar disk herniation or lumbar spondylolisthesis candidates of elective lumbar spinal fusion and with American Society of Anesthesiologists (ASA) physical status of I/II/III were included in the study. The experimental procedures of the study including surgeries, preoperative and postoperative assessments and follow ups were performed in the department of anesthesiaology, AHIMMU, Hohhot, China. Patients with cardiac morbidities, hypertensive disorders, severe hepatic and renal dysfunction, hyperthyroidism, vascular diseases, and digestive ulcer were excluded from the study.

The surgery was posterior lumbar discectomy combined with pedicle screw fixation and intertransverse fusion. The inclusion criteria were the elderly patients with ASA grade less than III and aged 60 to 85 years old. The exclusion criteria were patients with bradycardia (heart rate < 50 beat per minute), cardiac morbidities, heart block greater than the first degree, abnormal liver or renal function, hyperthyroidism, vascular diseases and bowel disease (e.g. ulcerative colitis, Crohn’s disease, and irritable bowel syndrome). During the study at any time, patients were free to discontinue the study. Randomization was performed using an online random number generator. All surgeons, patients, attending anaesthesiologists, nurses and follow-up anaesthesiologists were blinded to the group assignments.  

2.3. Interventions

At the holding area, an IV line was established with an18-gauge IV cannula in the forearm, and an infusion of lactated Ringer’s (LR) solution was started at a minimal rate to keep the vein open. A baseline mean arterial pressure (MAP) was measured in the supine position three times and then averaged. Readings were performed 1 minute apart using an automated device for noninvasive blood pressure assessment. Patients were divided into one of three groups:

Ninety patients were randomly divided into three groups (n=30). The 0.030 group (n = 30) who received 0.030 μg.kg⁻¹.min⁻¹ continuous norepinephrine infusion; the 0.060 group (n = 30) who received 0.060 μg.kg⁻¹.min⁻¹ continuous norepinephrine infusion; the 0.090 group (n = 30) who received 0.090 μg.kg⁻¹.min⁻¹ continuous norepinephrine infusion. All patients received continuous norepinephrine infusion before the initiation of general anesthesia.

In the operating room, standard monitoring processes were performed for ECG, heart rate, noninvasive blood pressure, and pulse oximetry (SpO₂). A radial artery cannula was inserted, and the pressure transducer was set to zero at the mid-axillary level to ambient pressure. The patients in three groups were given a predefined dosage of norepinephrine infusion before the initiation of general anesthesia. Then, general anesthesia was induced with fentanyl (20 to 30 μg.kg⁻¹ IV), lidocaine (1.5 mg.kg⁻¹ IV), and etomidate (up to 0.3 mg.kg⁻¹ IV) and maintained with propofol (1.5-3 mg.kg⁻¹.h⁻¹) and remifentanil (0.1-0.2 μg.kg⁻¹.min⁻¹). Neuro-muscular blockade was achieved with rocuronium (0.1mg.kg⁻¹ IV). Following endotracheal intubation, mechanical ventilation was performed without positive end-expiratory pressure using an inspired oxygen concentration of 50% and tidal volumes of 10 ml.kg⁻¹ to maintain an end-expiratory Pco₂ at 4-4.5 kPa. The patients’ lungs were ventilated with a tidal volume of 10 mg.kg⁻¹ of ideal body weight and an inspiration and expiration ratio of 1:2 with...
positive-end expiratory pressure (PEEP) of 5-8cmH₂O. After
the final measurement of the assessed variables, the tidal vol-
ume was reduced to 8 mL/kg of the ideal body weight. The
anesthesia was maintained with continuous infusion of
remifentanil (0.3-0.4 µg.kg⁻¹.min⁻¹) and propofol (4-6
kg⁻¹.h⁻¹) with bispectral index range between 50-60. The arte-
rial pressure waveforms were monitored with Phillips Intellivue
MP70 monitors (Intellivue MP70, Philips Medical Sys-
tems, Suresnes, France). The primary and secondary out-
comes were monitored at four intervals of T₁, T₂, T₃, and T₄
corresponding to before induction, 15 min following anesthe-
sia induction with the patient in a supine position, 60 min fol-
lowing surgery, and at the end of the surgery, respectively.

All patients were continuously prophylactically infused
norepinephrine of the respective dosage before the initiation
of general anesthesia. The RL 5 ml·kg⁻¹ was infused as a bolus
volume before general anesthesia induction. Then, the in-
fusion rate was reduced to keep the vein open following en-
dotracheal intubation. If PPV was less than 13%, the mainte-
nance volume of RL was infused at a rate of 2 ml·kg⁻¹.h⁻¹. If
PPV was more than 13%, the hydroxyethyl starch (HES,
130/0.4, Voluven) of 3 ml·kg⁻¹ (ideal body weight) was in-
fused during 3 min to test the fluid response to guide the in-
dividual fluid therapy. A PPV less than 13% was defined as
the negative fluid responsiveness. If PPV was within the tar-
get range and MAP was below the baseline, 12.5-25 mg urapidil was administered. If PPV was within the target range and blood pressure fluctuated within 20% of
the baseline, norepinephrine infusion was continued until 5 min after sewing.

The day before surgery, all patients were instructed on
the use of a 10-point numeric rating scale to assess their pain
intensity (0 = no pain, 10 = worst possible pain). Postoperative
patient-controlled intravenous analgesia was performed
with sufentanil (1.5µg·kg⁻¹) combined with ondansetron 8
mg. All patients received a basal dose of 0.015µg·kg⁻¹·h⁻¹
and PCA (0.030 µg·kg⁻¹·h⁻¹). The interval time was set at 10
min, and patient-controlled intravenous analgesia was main-
tained up to 72 h following surgery to make sure all patient
numeric rating scale scores were below 3.

2.4. Data Collection

Demographic data, including age, gender, body mass in-
dex, duration of surgery, ASA grade, and perioperative com-
lications were recorded. The mean blood pressure and heart
rate were monitored and recorded at T₁, T₂, T₃, and T₄
timepoints. The PPV was recorded at 15 min following anesthe-
sia induction with the patient in a supine position, 60 min fol-
lowing surgery, and at the end of the surgery. The surgical
indices, including blood loss, urine output, autologous blood
transfusion and fluid infusion volume (crystalloids and col-
loids) were recorded. The bradycardia, atropine require-
ments, intraoperative hypotension and hypertension, postop-
erative hospital stay were recorded. The incidence of nausea
and vomiting, first flatus, first ambulation, first intake tim-
ing were self-reported by patients and recorded by a fol-
low-up anesthesiologist who was blinded to group assign-
ments during follow-up.

The primary outcome was the incidence of complica-
tions, such as cerebral complications, renal complications,
pulmonary complications, cardiac complications and other
complications (the incidence of fever, wound infection and
delayed wound healing). The delayed wound healing was
defined as the duration of wound healing more than fourteen
days. The pulmonary infection, respiratory failure, pulmo-
ary infarction and pulmonary embolism were recorded as
pulmonary complications. Acute myocardial injury and
acute myocardial infarction were included as cardiac compli-
cations. Progressive neurological deficit and acute cerebral
infarction were a part of the cerebral complications, and olig-
uria and acute kidney injury (AKI) were included in the re-
nal complications. Secondary outcomes were the incidence
of intraoperative nausea and vomiting, the frequency of hy-
pertension, the frequency of hypotension, first intake, first
flatus, ambulation timing, postoperative hospital stay, the
volume of autologous transfusion, the intraoperative blood
loss volume, the urine output volume and postoperative hos-
pital stay (days from admission). The intraoperative hypoten-
sion and hypertension were defined as a decrease and in-
crease of >20% of the baseline level, respectively. The defi-
nition of bradycardia was set as a heart rate (HR) less than
55 beats per minute. If the HR was below 50 beats per
minute, 0.3-0.5 mg atropine depending on patient's HR was
injected intravenously. Further details of intraoperative fluid
management protocol are presented in Fig. (1).

2.5. Sample Size

The sample size was calculated with the Power Analysis
and Sample Size (PASS Version 2019) Software with the in-
cidence of postoperative complications as the primary out-
come. The preliminary experimental results showed the inci-
dence of postoperative complications about 40% of the elder-
ly patients undergoing spinal surgery without norepinephrine infusion, while only 10% incidence of postopera-
tive complications following prophylactic dose of 0.060
µg.kg⁻¹.min⁻¹ norepinephrine infusion. At the alpha error of
0.05, we calculated that eighty seven patients (n=29 each
group) would give 80% power to detect a 20% absolute re-
duction in the incidence of postoperative complications in
the treatment group. However, we defined a sample size of
108 (n=60 each group) to allow the comparisons between
the control and each treatment group.
2.6. Statistical Analysis

Statistical Package for Social Science (SPSS) package (SPSS Inc., Chicago, IL, USA) was used for data analysis. Categorical data were expressed as frequency (%). Continuous data were tested for normality and presented as mean (±SD) using the Shapiro–Wilk test. The primary outcome (frequency of complications) was analyzed with Fisher’s exact test. Continuous data were analyzed with one-way ANOVA. For repeated measures, a two-way repeated-measures ANOVA was used to evaluate the dose (between-groups factor) and time (repeated measures). Post hoc pairwise comparison was performed with an LSD test. A P-value ≤0.05 was considered statistically significant.

3. RESULTS

A total of 108 patients were screened for eligibility, of which 18 subjects were excluded, 12 patients did not meet inclusion criteria, four patients declined to participate, two patients were excluded for other reasons. Finally, 90 patients were selected to undergo the randomization process (Fig. 2). Overall, there are homogeneity in age (P=0.173), body mass index (BMI) (P=0.085), gender (P=0.843), ASA grade classification (P=0.425), duration of surgery (P=0.563) and preoperative complications (Table 1).

There was no significant difference in the incidence of total postoperative complications among the three groups (P>0.05). The incidence of delayed wound healing and wound infection were significantly reduced among three groups (P<0.05), especially in the 0.060 and 0.090 groups, compared to the 0.030 group (0.030 vs. 0.060 vs. 0.090: 33.3% vs. 10% vs. 10%, P=0.024; 26.7% vs. 6.7% vs. 6.7%, P=0.031) (Table 2).

The three groups showed different postoperative first intake and first flatus periods (P<0.01). The 0.060 group enhanced the postoperative first intake by 1.4 hours and first flatus by 1.1 hours, compared to the 0.030 dosage (P<0.01). Similarly, postoperative hospital stay was reduced by around 1 day in the 0.060 and 0.090 groups, compared to 0.030 group (0.030 vs. 0.060 vs. 0.090: 7.1 vs. 6.0 vs. 6.2, P=0.066). There was no significant difference in the incidence of nausea and vomiting among the three groups (Table 3).
Fig. (2). Patients' fluid management flowchart in three dosages of norepinephrine infusion groups (0.030 μg.kg⁻¹.min⁻¹ vs. 0.060 μg.kg⁻¹.min⁻¹ vs. 0.090 μg.kg⁻¹.min⁻¹). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 1. Demographic and clinical characteristics of the patients in the three dosages of norepinephrine infusion groups.

|                | 0.030 Group (n=30) | 0.060 Group (n=30) | 0.090 Group (n=30) | P-value |
|----------------|--------------------|--------------------|--------------------|---------|
| Age (years)    | 67.1 ± 2.7         | 68.0 ± 2.4         | 66.7 ± 2.8         | 0.173   |
| BMI (kg/m²)    | 22.1 ± 2.1         | 21.1 ± 2.4         | 22.7 ± 2.1         | 0.085   |
| Male/Female    | 8/22               | 7/23               | 9/21               | 0.843   |
| ASA II/III     | 19/11              | 14/16              | 17/13              | 0.425   |
| Time of surgery (min) | 97.0 ± 17.1       | 99.8 ± 14.2        | 97.3 ± 11.0        | 0.563   |

Preoperative complications

|                | -                  | 0.060 Group (n=30) | 0.090 Group (n=30) | -       |
|----------------|--------------------|--------------------|--------------------|---------|
| Hypertension (%) | 11 (36.7)         | 10 (33.3)          | 13 (43.3)          | 0.718   |
| Diabetes (%)    | 7 (23.3)           | 6 (20)             | 7 (23.3)           | 0.938   |
| Heart disease (%) | 6 (20)            | 7 (23.3)           | 7 (23.3)           | 0.938   |
| Cerebrovascular disease (%) | 10 (33.3)   | 13 (43.3)          | 11 (36.7)          | 0.718   |

Data are expressed as mean (SD), n (%). BMI, body mass index; ASA, American Society of Anesthesiologist.
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Table 2. The primary and secondary outcomes and incidence of complications in three dosages of norepinephrine infusion groups (0.030 vs. 0.060 vs. 0.090).

| Parameter                        | 0.030 Group (n=30) | 0.060 Group (n=30) | 0.090 Group (n=30) | 0.030 vs. 0.060 | 0.060 vs. 0.090 | 0.030 vs. 0.090 | Overall |
|----------------------------------|--------------------|--------------------|--------------------|-----------------|----------------|----------------|---------|
| Total complications (%)          | 6 (20)             | 4 (13.3)           | 5 (16.7)           | 0.488           | 0.718          | 0.739          | 0.787   |
| Cerebral complications (%)       | 1 (3.3)            | 0 (0)              | 1 (3.3)            | -               | -              | 1              | 0.600   |
| Renal complications (%)          | 0 (0)              | 0 (0)              | 0 (0)              | -               | -              | -              | -       |
| Pulmonary complications (%)      | 3 (10)             | 2 (6.7)            | 3 (10)             | 0.640           | 0.640          | 1              | 0.872   |
| Cardiac complications (%)        | 2 (6.7)            | 2 (6.7)            | 1 (3.3)            | 1               | 0.554          | 0.554          | 0.809   |
| Wound infection (%)              | 8 (26.7)           | 2 (6.7)            | 2 (6.7)            | 0.038           | 1              | 0.038          | 0.031   |
| Fever (%)                        | 5 (16.7)           | 3 (10)             | 2 (6.7)            | 0.448           | 0.640          | 0.228          | 0.690   |
| Delayed wound healing (%)        | 10 (33.3)          | 3 (10)             | 3 (10)             | 0.028           | 1              | 0.028          | 0.024   |

Data are expressed as mean ± SD. n (%).

Table 3. Postoperative outcome in three dosages of norepinephrine infusion groups (0.030 vs. 0.060 vs. 0.090).

| Parameter                       | 0.030 Group (n=30) | 0.060 Group (n=30) | 0.090 Group (n=30) | 0.030 vs. 0.060 | 0.060 vs. 0.090 | 0.030 vs. 0.090 | Overall |
|---------------------------------|--------------------|--------------------|--------------------|-----------------|----------------|----------------|---------|
| Nausea and vomiting (%)         | 8 (26.7)           | 6 (20)             | 7 (23.2)           | 0.761           | 1.000          | 0.761          | 0.830   |
| Time of first flatus (h)        | 5.9 ± 0.8          | 4.8 ± 1.4          | 5.1 ± 1.5          | 0.003           | 0.562          | 0.053          | 0.004   |
| Time of first ambulation (h)    | 50.5 ± 12.7        | 48.9 ± 8.9         | 48.6 ± 8.7         | 0.818           | 0.994          | 0.762          | 0.749   |
| Time of first intake            | 6.8 ± 1.3          | 5.4 ± 1.9          | 5.8 ± 1.9          | 0.007           | 0.647          | 0.072          | 0.008   |
| Postoperative hospital stays (d)| 7.1 ± 2.3          | 6.0 ± 2.0          | 6.2 ± 1.3          | 0.073           | 0.914          | 0.17           | 0.066   |

Data are expressed as mean ± SD. n (%).

The patients in the 0.060 and 0.090 dosage groups had higher MAP compared to the 0.030 dosage group at the T1, (P<0.05) and T3, time points (P<0.01) (Table 4). The incidence of intraoperative hypotension in the 0.060 and 0.090 dosages of norepinephrine infusion groups were effectively decreased compared to the 0.030 dosage (P<0.01) at T1, T2, T3, time points. Intraoperative infusion of crystalloids, colloids and total fluid volume in the 0.030 dosage group were higher than the 0.060 and 0.090 groups (P<0.01). The elderly patients in the 0.090 dosage group exhibited significantly lower HR than the 0.060 and 0.030 groups (P<0.05). The frequency of bradycardia in the patients of the 0.090 group was significantly greater than the 0.030 and 0.060 groups (P<0.05). The number of required atroventricular injection to the patients in the 0.090 dosage group was significantly higher than the 0.030 and 0.060 groups (P<0.01) (Tables 4 and 5).

4. DISCUSSION

With advances in public health and continued medical progress, the elderly has been a fast-growing segment of the population [25]. This will lead to a proportional increase in age-related diseases such as lumbar disc herniation, stenosis and spondylolisthesis. However, the elderly population, especially those older than 80 years, are more likely to have a higher comorbidity and osteoporosis burden, often with multiple systems involved [26]. The complexity of the health status may increase the risks of complications, poor functional outcomes and mortality after surgery in patients aged 80 years and older [27]. It has been demonstrated that perioperative fluid management influences postoperative complication rates. However, the optimal intraoperative fluid regimen is still controversial. Especially in the use of vasoressors, or a goal-directed hemodynamic therapy [16]. To improve the quality of postoperative recovery and shorten hospital stays, significant efforts have been made to facilitate the early return to normal organ function.

Norepinephrine is a vasopressor with potent α-adrenergic agonistic activity in addition to some β-adrenergic agonistic activity; thus, it has been suggested as an alternative to phenylephrine that would not compromise the cardiac function. This makes norepinephrine a possible choice for elderly patients with relative contraindications of phenylephrine, such as low baseline HR or poor cardiac function. We did not include such patients because of the monitoring indicators, PPV, which was not suitable for patients with arrhythmias [28]. Currently, studies are exploring the optimum single dose for use as a continuous infusion rate during other surgeries in elderly patients.
Table 4. Intraoperative hemodynamic parameters’ trend in three dosage of norepinephrine infusion groups (0.030 vs. 0.060 vs. 0.090).

| Parameter | T | Intervention | P-value |
|-----------|---|--------------|---------|
|           |   | 0.030 Group (n=30) | 0.060 Group (n=30) | 0.090 Group (n=30) | 0.030 vs. 0.060 | 0.060 vs. 0.090 | 0.030 vs. 0.090 | overall |
| MAP       |   | 98.3 ± 6.5         | 98.1 ± 8.1         | 100.6 ± 7.2         | 0.888          | 0.183           | 0.233           | 0.342 |
|           | T1| 71.8 ± 7.7         | 73.6 ± 7.8         | 72.4 ± 7.8         | 0.390          | 0.563           | 0.778           | 0.680 |
|           | T2| 56.9 ± 7.4         | 62.2 ± 7.9         | 63.3 ± 6.9         | 0.014          | 0.615           | 0.003           | 0.007 |
|           | T3| 75.2 ± 7.6         | 81.2 ± 8.1         | 81.5 ± 7.7         | 0.005          | 0.830           | 0.003           | 0.004 |
| HR        |   | 72.0 ± 8.0         | 74.3 ± 6.7         | 71.7 ± 6.9         | 0.228          | 0.178           | 0.887           | 0.334 |
|           | T1| 63.3 ± 4.8         | 62.7 ± 6.1         | 57.1 ± 3.1         | 0.629          | 0.001           | 0.001           | 0.001 |
|           | T2| 72.0 ± 8.6         | 68.8 ± 7.6         | 62.3 ± 7.3         | 0.114          | 0.002           | 0.001           | 0.001 |
|           | T3| 74.5 ± 8.6         | 69.3 ± 7.0         | 62.3 ± 7.3         | 0.740          | 0.048           | 0.022           | 0.045 |
| PPV       |   | 12.7 ± 1.7         | 12.5 ± 1.9         | 12.2 ± 1.1         | 0.740          | 0.508           | 0.322           | 0.599 |
|           | T1| 12.3 ± 1.7         | 11.5 ± 1.2         | 11.4 ± 1.3         | 0.233          | 0.927           | 0.199           | 0.357 |
|           | T2| 8.3 ± 0.8          | 8.0 ± 1.6          | 8.2 ± 0.9          | 0.296          | 0.513           | 0.695           | 0.571 |

Data are expressed as mean ± SD. n (%).

Table 5. Intraoperative basic materials and morbidity in three dosages of norepinephrine infusion groups (0.030 vs. 0.060 vs. 0.090).

| Parameter                          | Intervention | P-value |
|------------------------------------|--------------|---------|
|                                    | 0.030 Group (n=30) | 0.060 Group (n=30) | 0.090 Group (n=30) | 0.030 vs. 0.060 | 0.060 vs. 0.090 | 0.030 vs. 0.090 | Overall |
| Total fluid volume                 | 1522.9 ± 138.2 | 1340.2 ± 240.2 | 1352.1 ± 298.1 | 0.001 | 0.076 | 0.001 | 0.005 |
| Crystalloid                        | 1035.1 ± 236.4 | 883.2 ± 208.1 | 838.3 ± 231.1 | 0.029 | 0.721 | 0.003 | 0.003 |
| Colloid                            | 610.2 ± 180.2 | 475.2 ± 206.7 | 467.8 ± 205.2 | 0.026 | 0.989 | 0.018 | 0.01 |
| Autologous blood transfusion       | 104.2 ± 45.8 | 101.8 ± 44.4 | 83.6 ± 26.8 | 0.971 | 0.185 | 0.117 | 0.096 |
| Blood loss                         | 278.6 ± 128.7 | 241.3 ± 119.3 | 226.6 ± 71.6 | 0.387 | 0.862 | 0.163 | 0.171 |
| Urine output                       | 680.5 ± 253.1 | 651.1 ± 246.4 | 603.2 ± 262.9 | 0.895 | 0.797 | 0.980 | 0.805 |
| Intraoperative hypotension (%)     | 10 (33.3) | 2 (6.7) | 1 (3.3) | 0.01 | 0.554 | 0.003 | 0.001 |
| Bradycardia (%)                    | 1 (3.3) | 2 (6.7) | 8 (26.7) | 0.554 | 0.038 | 0.026 | 0.012 |
| Intraoperative hypertension (%)    | 0 | 0 | 1 (3.3) | - | 1 | 1 | 0.364 |
| Atropine requirements (mg)         | 0.1 ± 0.2 | 0.1 ± 0.1 | 0.3 ± 0.3 | 0.369 | 0.001 | 0.005 | 0.001 |

Data are expressed as mean ± SD. n (%).

Norepinephrine is currently a novel option for the prevention and treatment of hypotension, and to the best of our knowledge, this is the first study to determine the optimal infusion rate of norepinephrine, which in any format manages hypotension and avoids fluid overload complications during general anesthesia for spinal surgery. However, there may be some concern regarding the administration of norepinephrine via peripheral veins. Significant morbidity was not demonstrated in a recent study wherein norepinephrine infusions were administered in hypertensive patients for an average of 32 h at a maximal rate of 30 μg.min⁻¹ via 18-gauge and 20-gauge cannulate in the antecubital fossa, dorsum of the hand, and forearm flexor veins. Minor complications (extravasation) occurred at a rate of 5.45% [29]. Previous studies demonstrated that extravasation was observed in the veins distal to the antecubital fossa or in the feet, and recent reports suggested that placement within a large proximal vein might be preferred [30, 31]. Moreover, the drug manufacturer does not specify that norepinephrine needs to be administered centrally, rather via a large vein, preferably antecubital and avoiding the lower extremities [32]. Furthermore, in this study, the small infusion rate of norepinephrine (8 μg/mL) was used. Therefore, the risk of local tissue injury was minimal, and we did not observe any adverse effects.

Hasanin et al. reported both the 0.050 μg·kg⁻¹·min⁻¹ and 0.075 μg·kg⁻¹·min⁻¹ norepinephrine infusion rates effectively
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reduced the post-spinal hypotension during cesarean delivery as compared to the 0.025 μg·kg⁻¹·min⁻¹ infusion rate [33]. Kee et al. investigated the efficacy of manually titrated prophylactic norepinephrine infusion for maintaining the blood pressure during spinal anesthesia for elective cesarean delivery. The study reported that for these patients, a manually titrated infusion of 5 μg·ml⁻¹ of norepinephrine is effective for maintaining blood pressure and decreasing the incidence of hypotension without significant adverse events on the neonatal outcome [34]. The middle dose reported by the previously conducted studies (0.060 μg·kg⁻¹·min⁻¹) was used in the current study. Significant reductions in the heart rate were observed in all groups, compared to the baseline reading. However, in the higher doses, a few cases experienced marked bradycardia requiring atropine: 1 (3%) case in the 0.030 group, 2 (6.7%) in the 0.060 group, and 8 (26%) in the 0.090 group. Thus, we speculated that norepinephrine could be the appropriate vasopressor in elderly patients with low baseline HR. We did not measure the patients’ cardiac output; however, it has been recently suggested that monitoring the HR could be used as a potential surrogate for cardiac output [35]. Furthermore, only a few cases of intraoperative hypotension were observed in the three study groups. These events were transient and resolved by stopping the fluid infusion. However, this side effect could not be evaluated in this study. Our primary outcomes were the incidence of complications (cerebral complications, renal complications, pulmonary complications, and cardiac complications). The two higher dose groups had fewer complications, but the differences were not statistically significant, which might be attributed to the anesthesiologists’ concern about the elderly patients with more complications, poor organ reserve function, and reduced tolerance to cyclic fluctuation; during anesthesia management, attention is paid to maintaining perfusion pressure to ensure the perfusion of critical organs.

We used a continuous infusion rate of norepinephrine before starting the anesthesia. Our hypothesis was based on a previous study, which reported that the use of a prophylactic bolus of phenylephrine before starting infusion was beneficial [36]. Herein, we hypothesized that the prophylactic administration of norepinephrine could increase the peripheral vascular resistance, reduce the amount of fluid required to achieve goal-directed fluid therapy, and facilitate the rehabilitation process of elderly patients.

The prone position increases abdominal pressure, which results in reduced venous return and lung compliance. Yu et al. reported that high predictability of PPV, remained as useful indices for guiding fluid therapy in prone patients with minimal alterations in the optimal cutoff values to predict fluid responsiveness [37]. The PPV, contrary to the SVV, does not require additional kits and can reduce the patients’ financial burden and the accuracy is similar [38]. However, some researchers questioned the accuracy of the predicted volume of PPV in the prone position. Biais et al. reported that prone position induces a significant increase in PPV and SVV but does not alter their abilities to predict the responsiveness of the fluid [38]. The 13% PPV threshold value was also based on previous studies.

Nevertheless, there were several possible limitations to the present study. We did not use advanced hemodynamic monitors for cardiac output and peripheral vascular resistance. Moreover, the volume status of elderly patients suffering from lumbar disk herniation or lumbar spondylolisthesis was different. In future studies, more attention should be paid on perioperative endothelial function, especially the relationship between perioperative complications and syndecan-1.

CONCLUSION

In conclusion, the dosage 0.060 μg·kg⁻¹·min⁻¹ of norepinephrine infusion combined with goal-directed fluid therapy (PPV) is more suitable for elderly patients’ intraoperative management who had undergone lumbar spinal fusion during general anesthesia. It can improve the elderly patients’ postoperative outcome and facilitate their rehabilitation process by decreasing the incidence of intraoperative hypotension, bradycardia and fluid overloading risk.

AUTHORS’ CONTRIBUTIONS

Conceptualization: TW and FW; methodology: TW; software: TL; validation: TW, FW; formal analysis: TL; investigation: FW; resources: YM and JW; data curation: TL; writing-original draft preparation: LF and HF; writing-review and editing: FW; visualization: WX; supervision: FW; project administration: WX; funding acquisition: TW. The manuscript has been approved for publication by all listed authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethical Committee of Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, P.R. China (Ethic code: NO. KY (2018022)).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study on humans was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

All patients filled and signed written consent form for participation in the study.

STANDARDS OF REPORTING

CONSORT guidelines were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

All the data used in this study are available from the corresponding author [TW] on reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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