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Effect of NE Infusion on Postoperative Delirium in Elderly Patients Undergoing PFNA Internal Fixation

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Abstract: **Objective**: To observe the effect of blood pressure management by norepinephrine infusion on postoperative delirium (POD) in elderly patients undergoing PFNA internal fixation. **Methods**: 80 elderly patients undergoing elective PFNA internal fixation under spinal anesthesia, aged >65 years, ASA II or III, with body mass index(BMI) of 16.9 kg/m^2 to 27.8 kg/m^2, were included and divided into a test group(group T) and a control group (group C) using the random number table method, with 40 cases in each group. In group T, patients received an infusion of 8μg/mL norepinephrine (NE) that was begun at 15 mL/h immediately after spinal anesthesia, and then adjusted within the range 0-30mL/h according to systolic blood pressure(SBP) values measured noninvasively at 2-minute interval until the patients left the operating room, with the goal of maintaining values from baseline to 20% above the baseline; in group C, SBP values was allowed to fluctuate ±20% baseline by giving a bolus of 8μg NE(8 μg/mL). The incidence of POD within 7 days after surgery was recorded. SBP values, SpO2, and HR were recorded at the following endpoints: before the induction of anesthesia (T_1),4 minutes after anesthesia (T_2), before incision (T_3), 4 minutes, 10 minutes, 20 minutes after incision (T_{4-6}), at the end of surgery (T_7), 5 minutes before leaving the room (T_8).NE amount and occurrence of adverse events were recorded. **Results**: Compared with group C, the incidence of POD was reduced, SBP values at T2 to T8 and NE amount was increased (P<0.05). **Conclusion:** Infusion of 8μg/mL of NE maintaining SBP values from baseline to 20% above the baseline reduces the incidence of POD in elderly patients undergoing PFNA internal fixation.

Keywords: PFNA; Elderly; Delirium; Norepinephrine

1. Introduction

Elderly patients are prone to femoral trochanteric fractures or intertrochanteric fractures, and the preferred treatment option is surgery, which is PFNA (Proximal Femoral Nail Antirotation) internal fixation. This procedure is less invasive and has a shorter operating time, so the spinal anesthesia method is fitting. Elderly patients are more likely to have perioperative complications due to their physiopathological characteristics, such as co-morbidities and frailty. POD is one of the common complications in such patients, and its incidence can reach 5%-61%[1], while Xu Ming et al[2] reported a 31% incidence of POD in elderly patients undergoing PFNA internal fixation. POD occurs from 0 to 7 days postoperatively, with a high incidence within 3 days postoperatively[3], and it affects prognosis and increases morbidity and mortality.

POD belongs to the postoperative cognitive dysfunction, and its pathogenesis has not been fully clarified so far, and its occurrence may be related to many factors, such as age, anesthesia, drugs, surgery, and infection, hypotension is also one[4, 5]. However, some studies have concluded that intraoperative hypotension is not statistically significant for POD and that the risk factor is intraoperative blood pressure variability[6], namely, blood pressure fluctuations. In this study, we managed SBP by infusion of NE during operation to stabilize it from baseline to 20% above the baseline value to observe the effect on POD in elderly patients with PFNA internal fixation.

2. Material and methods

The study was approved by the ethics committee of our hospital and informed consent was signed by the patients. Eighty patients undergoing elective PFNA internal fixation were selected for the study. Inclusion criteria: accurate and

complete clinical data; age >65 years, ASA II-III; cardiac function II or above; no serious dysfunction of organs such as lung, liver, kidney, and brain; no shock or contraindications to spinal anesthesia; informed and voluntary participation in this study. Exclusion criteria: ASA IV or above; those with neuropsychiatric disorders; those taking benzodiazepines or opioids within 3 months; patients with severe anemia or blood transfusion. The 80 patients were divided into group C and group T at a 1:1 ratio according to the random number table method.

All subjects routinely abstained from drinking and fasting for 8 hours. After entering the operating room, the upper limb venous access was opened, electrocardiogram (ECG), heart rate (HR), blood oxygen saturation (SpO2), non-invasive blood pressure (NIBP) (upper limb contralateral to the venous access), nasal catheter oxygenation with an oxygen flow rate of 2-4 L/min.Then the anesthesiologist received the envelope that contained the drug preparation instruction and the grouping. Spinal anesthesia was performed after liquid capacity expansion by infusion of compound sodium chloride (8 ml/kg). Patients were placed in the lateral position with the affected lower limb on top. The spinal needle was inserted at L_{3-4} vertebral interspace, and 0.75% ropivacaine (Batch No. 7B210201, Jiabao Pharmaceutical, Guangdong, China.) was administered 1.3 to 1.5 mL after seeing the cerebrospinal fluid. The maintenance fluids were compound sodium chloride and hydroxyethyl starch (HES) 130/0.4(Batch No.1C22011902, Qidu Pharmaceutical, Shandong, China.) in a 2:1 ratio in the operating room.

The baseline noninvasively SBP was measured in the ward. The SBP was measured at 10:00 a.m. on the day before surgery when the patient was quiet and stable without other discomforts, and it was taken as the baseline SBP (T_0) regarding the SBP in the same state on the previous day and the difference was less than 10%. In group T, patients received an infusion of 8μg/mL NE(Batch No. 2202121, Lijun Pharmaceutical, Xian, China.) that was begun at 15 mL/h immediately after spinal anesthesia, and then adjusted within the range of 0-30mL/h via an infusion pump (Model CP-1100, Slgo Technology, Beijing, China.)according to SBP values measured noninvasively at 2-minute interval until the patients left the operating room, to maintain values from baseline to 20% above the baseline; in group C, SBP values was allowed to fluctuate ±20% baseline by giving a bolus of 8μg NE(8 μg/mL). When the intraoperative SBP increased more than 120% of the baseline blood, nitroglycerin 50 μg/time was administered until the SBP was controlled in the target range. When the heart HR was <50 beats/min, IV atropine 0.5mg was done and repeated if necessary. At the end of the surgery, the patients were withdrawn from vasoactive drugs and sent back to the ward after observation of stable blood pressure.

The Confusion Assessment Method (CAM) was used to assess delirium[3] 7 days after operation in two groups, and among the evaluation tools for delirium, the CAM scale with its concise and clear items performed well in an emergency, postoperative, and mixed hospitalization settings and best in the psychiatric geriatric group[7]. Assessment criteria: <19 points means no delirium, 20-22 points with suspected delirium, and>22 points stands for delirium. The primary endpoint was the incidence of POD. In addition, SBP values, SpO2, and HR were recorded at the following endpoints: before the induction of anesthesia (T_1),4 minutes after anesthesia (T_2), before incision (T_3), 4 minutes, 10 minutes 20 minutes after incision (T_{4-6}), at the end of surgery (T_7), 5 minutes before leaving the room (T_8). Nausea and vomiting were recorded; the duration of anesthesia and operation, fluid balance, hemoglobin(HGB), and the amount of vasoactive agent used were recorded.

SPSS25(IBM SPSS, Inc, Chicago, IL) was used for statistical analysis. The mean±standard deviation ($\bar{x}\pm s$) was used to describe normally distributed continuous variables which were analyzed using Student's t-test; the count and categorical data were expressed as relative numbers and were compared using the χ^2 test. Statistical significance was determined at $p < 0.05$(two-sided).

3. Results

Baseline blood pressure was measured in 80 patients whose follow-up and assessment of POD were completed. There were no statistically significant differences between the two groups in terms of age, gender, BMI, ASA, hemoglobin (HGB), and comorbid diseases (P>0.05), as shown in Table 1.

Table 1. Baseline characteristics of the patients($\bar{x}$±s) or n

	group C n=40	group T n=40	P value
Age (year)	80.17±7.42	81.20±7.78	0.548
Gender(M/F)	12/28	17/23	0.352
BMI(kg/m^2)	22.65±2.96	21.84±2.87	0.217
ASA(Ⅱ/Ⅲ)	31/9	24/6	0.567
HGB(g/L Pre）	102.42±12.71	101.60±19.28	0.822
HGB(g/L Post)	84.13±12.46	83.45±16.77	0.839
hypertension(n)	23	26	0.646
DM(n)	18	10	0.101

Note: DM =diabetes mellitus, Pre= preoperative, Post= postoperative

There was no statistical significance in fluid intake, urine volume, blood loss, duration of anesthesia and operation, ropivacaine dosage, and anesthesia plane(P>0.05); the anesthesia plane was divided into two categories above (>T_{10}) and below the thoracic vertebra 10 plane (<T_{10}). No nausea or vomiting was observed during and after the operation. Nitroglycerin and atropine were not used, and the oxygen saturation was 99-100%. Compared with group C, the dosage of NE was increased(P<0.05). The incidence of POD was 37.5% in group C and 17.5% in group T, which was statistically significant (P<0.05). See Table 2.

Table 2.Intraoperative and postoperative characteristics($\bar{x}$±s) or n

	group C n=40	group T n=40	P value
Fluid intake (ml)	752.50±304.23	687.50±238.52	0.291
Urine loss (ml)	198.75±144.40	167.75±79.50	0.238
Blood loss(ml)	43.75±46.50	38.75±19.51	0.532
Duration of anesthesia (min)	68.20±16.82	62.73±13.82	0.116
Duration of operation (min)	51.12±14.13	46.35±14.54	0.14
Block height (<T10/>T10)	28/12	27/13	1
Ropivacaine(ml)	1.44±0.14	1.40±0.13	0.218
NE(μg)	42.23±41.61	87.83±61.14	0.001
POD(n)	15	7	0.045

Baseline blood pressure and heart rate measured at all time points were not statistically different between group C and group T (P>0.05). SBP from T_1 to T_8 was higher in group T than in group C but was statistically significant from T_2 to T_8. There was no statistical difference in heart rate at each point. See Table 3.

Table 3.HR(times/minute) and SBP(mmHg) characteristics($\bar{x}$±s)

	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8
group C	/	85±12	79±11	79±10	78±9	76±9	75±10	76±9	75±10
group T	/	86±12	82±12	80±10	79±11	79±11	77±10	77±10	77±10
group C	128±7	141±18	122±21	118±18	116±10	118±10	126±14	122±12	118±11
group T	126±7	148±17	139±13^a	137±11^a	135±11^a	136±11^a	138±12^a	135±11^a	130±8^a

Note: T0 represents baseline SBP, P^a<0.05

4. Discussion

Elderly patients are prone to hypotension after spinal anesthesia because of their frailty and their physiological characteristics. Clinically, blood pressure often drops 20% or even 30% of the baseline before vasoactive drugs are administered, which in turn leads to excessive blood pressure elevation, and this leads to drastic blood pressure fluctuations. Studies have shown that frequent blood pressure fluctuations affect cerebral perfusion, which in turn has a detrimental effect on cognitive function[8]. In contrast, intraoperative hypotension with excessive fluctuations may lead to cerebral infarction with cerebral ischemia-reperfusion injury[9], thus increasing the incidence of POD. Clinically, elderly patients' perioperative blood pressure fluctuations are permitted within ±20% of the baseline, but it is unclear whether there is an ideal blood pressure target for the prevention of POD in PFNA patients. Therefore, this trial was designed to maintain SBP from baseline to 20% above the baseline to observe the effect on POD.

Hypotension occurs in elderly patients after spinal anesthesia because of increased basal sympathetic tone and reduced baroreceptor sensitivity[10]. Decreased blood pressure can be manifested as irritability, nausea, and vomiting, which interferes with surgery and is not only associated with POD but is also a risk factor for postoperative mortality[11]. Therefore, the prevention of intraoperative hypotension in elderly patients is particularly necessary. NE is a strong α and weak β agonist that increases arterial pressure, improves mean systemic filling pressure, enhances cardiac contractility and cardiac output through vasoconstriction and positive inotropic effects, making it an ideal drug for the prevention of hypotension； and it can be administered through peripheral veins, as Mostafa et al[12] did in elderly patients by infusion of 8 μg/mL NE, and the NE dose of 8 μg was equal to a PE dose of 100 μg; Hasanin et al[13] used NE 0.05 μg/kg/min infusion during cesarean section; Ngan et al[14] managed the SBP at the rate of 0-60 mL/h during cesarean section. In practice, the infusion rate of vasoactive drugs is often adjusted by the target blood pressure, and considering the feasibility and convenience, furthermore referring to the study of Brassard et al[15] in which the rate of NE infusion greater than 0.1 μg/kg/min was detrimental to brain tissue oxygenation, NE at 8 μg/mL was selected in this study to be administered immediately after spinal anesthesia at 15 mL/ h via peripheral intravenous administration infusion, and then adjust within the range 0-30mL/h(0-4μg/min, less than 0.1μg/kg/min) according to SBP, with a bolus of 8 μg if necessary.

The incidence of POD in group C in this study was 37.5%, which was similar to the results obtained by Xu Ming et al[2]; and the incidence of POD was reduced to 17.5% by increasing SBP by 20% above baseline with NE, which was similar to the results of XingMei et al[3], who compared the effects of different blood pressure management strategies under general anesthesia on the incidence of delirium after hip replacement, MAP maintained at 10% above baseline helped to reduce the incidence of POD. The reasons for the result could be increased regional oxygen saturation in brain tissue with increasing blood pressure[16]; moreover, one study indicated that NE improved the oxygen supply to brain tissue, and that continuous infusion of NE avoided sharp fluctuations of hemodynamic and regional oxygen saturation[17], avoiding cerebral ischemia-reperfusion injury and the damage to various organs due to ischemia and hypoxia. Conversely, when administered intermittently, it is not conducive to the prevention of POD.

In this study, SBP at all points after anesthesia was higher in the group T, indicating that continuous infusion of NE was more effective in managing blood pressure and could better maintain blood pressure stability; the high blood pressure of T_1 was due to pain stimulation caused by moving of the patient during room admission, while Blood pressure often dropped to some extent after anesthesia, so it was not treated. However, the statistically significant difference in blood pressure from T_2 to T_8 indicates the difference between intermittent and continuous dosing, with continuous infusion of NE being more advantageous than single dosing for maintaining blood pressure. Although the amount of NE used and the heart rate at each moment was higher in group T, there was no statistical difference, probably because NE is a weak β agonist and this dose difference was not enough to produce significant changes in heart rate; in addition, the anesthetic level required for this operation was not high, and when the anesthetic level was below T_{10}, the sympathetic nerve was not inhibited, so the heart rate did not produce large fluctuations. In this trial, the maximum level of anesthesia was T_6, and although the decrease in blood pressure was dramatic compared with the level above T_{10}, the blood pressure could be better managed by the strategy. There were no statistical differences in other aspects such as duration of anesthesia and operation, ropivacaine dosage,

anesthesia plane, blood loss, and urine volume. No nitroglycerin and atropine were used, and there were no adverse effects such as severe hypertension or nausea, or vomiting, indicating that the dose of NE used in the study was relatively safe.

The study also had limitations in that local cerebral tissue oxygen monitoring and blood markers such as IGF-I, IL-6, and S100β could not be measured due to the limited conditions; and invasive arterial blood pressure monitoring was not performed in this study considering the short duration of surgery and the small amount of blood loss; and finally, only NE was used to manage blood pressure without the use of other vasoactive drugs, which needs to be further investigated.

In conclusion, maintaining the SBP from baseline to 20% above the baseline by infusion of NE can reduce the incidence of POD in elderly patients after PFNA internal fixation, and the mechanism may be related to improving the cerebral blood and oxygen supply and avoiding cerebral ischemia-reperfusion injury due to less blood pressure fluctuation.

References

[1]Jones CA, Jhangri GS, Feeny DH, et al. Cognitive Status at Hospital Admission: Postoperative Trajectory of Functional Recovery for Hip Fracture[J]. J Gerontol A Biol Sci Med Sci, 2017,72(1): 61-67.

[2]Xu M, Lu Y, Li YN, et al. Surgical Apgar score in predicting postoperative delirium in patients undergoing PFNAinternal fixation for femoral intertrochanteric fractures[J]. Chin J Bone Joint Injury, 2019, 34(02): 121-125.

[3]Xu X, Hu X, Wu Y, et al. Effects of different BP management strategies on postoperative delirium in elderly patients undergoing hip replacement: A single center randomized controlled trial[J]. J Clin Anesth, 2020,62: 109730.

[4]Bi J, Shan W, Luo A, et al. Critical role of matrix metallopeptidase 9 in postoperative cognitive dysfunction and age-dependent cognitive decline[J]. Oncotarget, 2017,8(31): 51817-51829.

[5]Valentin LS, Pereira VF, Pietrobon RS, et al. Effects of Single Low Dose of Dexamethasone before Noncardiac and Nonneurologic Surgery and General Anesthesia on Postoperative Cognitive Dysfunction-A Phase III Double Blind, Randomized Clinical Trial[J]. PLoS One, 2016,11(5): e152308.

[6]Hirsch J, Depalma G, Tsai TT, et al. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery[J]. Br J Anaesth, 2015,115(3): 418-426.

[7]De J, Wand AP. Delirium Screening: A Systematic Review of Delirium Screening Tools in Hospitalized Patients[J]. Gerontologist, 2015,55(6): 1079-1099.

[8]Zou JH, Xu Y. Hypertension and cognitive impairment[J]. International Journal of Cerebrovascular Diseases, 2018,26(07): 546-551.

[9]Bijker JB, Gelb AW. Review article: the role of hypotension in perioperative stroke[J]. Can J Anaesth, 2013, 60(2): 159-167.

[10]Priebe HJ. The aged cardiovascular risk patient[J]. Br J Anaesth, 2000,85(5): 763-778.

[11]White SM, Moppett IK, Griffiths R, et al. Secondary analysis of outcomes after 11,085 hip fracture operations from the prospective UK Anaesthesia Sprint Audit of Practice (ASAP-2)[J]. Anaesthesia, 2016,71(5): 506-514.

[12]Mostafa M, Hasanin A, Mostafa M, et al. Hemodynamic effects of norepinephrine versus phenylephrine infusion for prophylaxis against spinal anesthesia-induced hypotension in the elderly population undergoing hip fracture surgery: a randomized controlled trial[J]. Korean J Anesthesiol, 2021,74(4): 308-316.

[13]Hasanin AM, Amin SM, Agiza NA, et al. Norepinephrine Infusion for Preventing Postspinal Anesthesia Hypotension during Cesarean Delivery: A Randomized Dose-finding Trial[J]. Anesthesiology, 2019,130(1): 55-62.

[14]Ngan KW, Lee S, Ng FF, et al. Prophylactic Norepinephrine Infusion for Preventing Hypotension During Spinal Anesthesia for Cesarean Delivery[J]. Anesth Analg, 2018,126(6): 1989-1994.

[15]Brassard P, Seifert T, Secher NH. Is cerebral oxygenation negatively affected by infusion of norepinephrine in healthy subjects?[J]. Br J Anaesth, 2009,102(6): 800-805.

[16]Hayashi K, Tanabe K, Minami K, et al. Effect of blood pressure elevation on cerebral oxygen desaturation in the beach chair position[J]. Asian J Anesthesiol, 2017,55(1): 13-16.

[17]Zhou RL, Zhang ZQ, Bian QH, et al. Effect of Low-Dose Norepinephrine Combined With Goal-Directed Fluid Therapy on Cerebral Oxygen Metabolism in Patients Undergoing Intracranial Tumor Resection[J]. Chinese Journal of Anesthesiology, 2018,38(11): 1358-1361.