Int J Clin Exp Med 2017;10(6):9526-9535
www.ijcem.com /ISSN:1940-5901/IJCEM0052165

Original Article

Acute normovolemic hemodilution combined with controlled hypotension does not increase incidence of postoperative cognitive dysfunction in elderly spinal surgery patients

Huan Wang, Xinyue Gao, Na Lv, Qiang Tao, Dawei Yang, Jianrong Guo

Department of Anesthesiology, Gongli Hospital of Second Military Medical University, Shanghai 200135, China

Received March 4, 2017; Accepted March 31, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: Objectives: This study aimed to investigate influences of acute normovolemic hemodilution (ANH) combined with controlled hypotension (CH) on hemodynamics, inflammatory factors, cerebral oxygen metabolism, MMSE score in elderly spinal surgery patients. Meanwhile the incidence of postoperative cognitive dysfunction (POCD) was assessed. Methods: Eighty elderly patients undergoing spinal surgery were randomly divided into four groups (n = 20): Control group, ANH group, CH group and ANH + CH group (AC group). Hemodynamics was monitored at four time points, including after induction of anesthesia, immediately after ANH, 30 min after reaching target blood pressure by CH and after completion of surgery. Radial arterial and jugular bulb blood were collected for blood gas analysis and cerebral oxygenation calculations. One day preoperatively, after surgery completion, one day postoperatively and seven days postoperatively, serum levels of inflammatory factors, S-100β protein and NSE were detected. Meanwhile, MMSE was performed and incidence of POCD was calculated. Results: ANH combined with CH could markedly reduce blood loss and save blood, which did not interfere with changes in hemodynamics, levels of inflammatory factors, S-100β protein or NSE. ANH combined with CH had no significant effect on cerebral oxygen metabolism, and did not interfere with postoperative MMSE score or POCD incidence, which showed significant differences compared with alone using (P<0.05). Conclusion: ANH combined with CH does not increase the incidence of POCD, well maintains hemodynamic stability, and reduces intraoperative blood loss and allogeneic blood transfusion while having no significant effect on inflammatory cytokines or cerebral oxygen metabolism.

Keywords: Acute normovolemic hemodilution, controlled hypotension, blood protection, postoperative cognitive dysfunction, oxygen metabolism

Introduction

For patients with acute bleeding or coexisting anemia, surgery-induced massive bleeding may lead to increased complications and mortality [1-3]. Blood transfusion is a common treatment for acute bleeding. However, transfusion of various blood products not only increases costs, but more importantly, also has potential risks, such as hemolysis, infections, allergies, fever, renal injury and transfusion-related lung injury [1, 4, 5]. There is substantial evidence that transfusion of blood components is associated with increased complications and morbidity, and reduced survival [6, 7]. Therefore, it is highly necessary to reduce tissue blood loss by improving surgical techniques, or reduce allogeneic blood transfusion by various measures [8, 9].

Postoperative cognitive dysfunction (POCD) refers to postoperative changes in neurological function experienced by patients due to a variety of reasons, which is manifested in the sense of direction, memory, thinking, attention, observation and other central nervous system functions [10]. One-week postoperative incidence of POCD is about 25%, while 3-month postoperative incidence is around 10%. POCD mainly occurs in the elderly patients (≥60 years), which can lead to prolonged hospitalization, reduced quality of life, and increased postoperative complications and mortality [11, 12]. POCD was believed in the past to occur mainly

in patients underwent cardiovascular surgery, with a prevalence between 33-83%; besides, 7-69% of the patients could not recover in three months postoperatively. Now it is believed that various surgeries are all likely to cause POCD [13, 14].

Principle of acute normovolemic hemodilution (ANH) is to reduce blood viscosity, optimize hemorrheology, improve microcirculatory perfusion, and maintain stable circulation by removing blood and replacing it with an equal amount of fluid, thereby reducing the demand for allogeneic blood transfusion [15, 16]. Controlled hypotension (CH) refers to the lowering and maintenance of mean arterial pressure (MAP) at a certain level with antihypertensives or (and) by anesthesia and other techniques while ensuring perfusion of vital organs, in order to create appropriate conditions for surgical procedures. Moreover, after termination of CH, blood pressure can return to be normal. These measures have been clinically proven, but there are still reports indicating that CH can be complicated with cerebral ischemia and increase the risk of POCD in elderly patients [17]. ANH/CH can significantly reduce intraoperative blood loss and allogeneic blood transfusion, which is a relatively safe blood conservation measure [18, 19]. Specific association among ANH/CH, cerebral oxygen metabolism and POCD in elderly postoperative patients is still worthy of further exploration [20]. This study discussed the influences of ANH/CH on elderly patients underwent spinal surgery from the perspective of cerebral oxygen metabolism.

Methods

Patients

Eighty patients who scheduled for spinal surgery at our hospital from September 2013 to September 2014 were included. General information: age 65-75 years; weight 55-70 kg; ASA grade I-II; operative time >2 h; estimated intraoperative blood loss >600 mL; preoperative hemoglobin (Hb) ≥110 g/L; hematocrit (Hct) ≥35%; platelet (Plt) count ≥100 × 10^9/L.

Exclusion criteria: Patients with central nervous system diseases, cancer, preoperative coagulation abnormalities, severe hypotension, mental diseases, cerebrovascular diseases, preoperative presence of lower extremity venous thrombosis, or dysfunction of heart, liver, kidney, lungs or other vital organs; or patients with a MMSE score ≤25. This research was approved by the Ethics Committee of our hospital. All patients agreed and signed the informed consent.

Eighty patients were randomly divided into four groups (n = 20). (1) Control group (Con group): Routine anesthesia and surgery without using blood conservation measures. (2) ANH group: After smooth induction of general anesthesia, autologous blood (400-800 mL) was collected via radial artery, which was transfused back before completion of surgery. Volume of collected blood was calculated according to formula. Where EBV was the estimated internal blood volume, which was body weight × 70 ml for men, and body weight × 60 mL·kg^{-1} for women. Hct_{actual} denoted hematocrit before dilution, while Hct_{target} represented the target hematocrit after dilution. In this research, target Hct was set as 30%, and volume of blood collected was calculated at a 1.06 g·ml^{-1} density after weighing. (3) CH group: After surgical bone procedure began, sodium nitroprusside ((0.5-6.0) μg·kg^{-1}·min^{-1}) was infused to maintain MAP not less than 55 mmHg. Meanwhile, pump speed was adjusted according to the hemodynamic monitoring. After completion of major steps, sodium nitroprusside was discontinued to allow MAP to return to the level before CH; time ≤90 min. (4) ANH + CH group (AC group): After smooth induction of general anesthesia, ANH was performed by removing blood via radial artery. After surgical bone procedure began, CH was performed by continuously infusing sodium nitroprusside with micro-pump.

Methods

All patients were fasted for solids and liquids preoperatively, and received no premedication. After entering the operating room, patients received non-invasive ECG and blood pressure monitoring. After smooth induction of general anesthesia, left radial artery catheterization was performed, as well as simultaneous invasive arterial pressure waveform monitoring (FloTrac). Right internal jugular vein was retrogradely punctured, and catheterized (12-14 cm) towards the cephalic end, so that the catheter tip reached the level of internal jugular bulb for monitoring cerebral oxygen metabo-

Table 1. The hemodynamic parameters, Hb, HCT, ACT at the T_2, T_3, T_1, T_4 time point in four groups

	Group (n = 20)	T_1	T_2	T_3	T_4
MAP (mmHg)	CON	87.9 ± 10.2			86.8 ± 8.9
	ANH	87.9 ± 10.4	81.0 ± 10.2*		87.2 ± 10.0
	CH	87.2 ± 14.3		61.4 ± 4.1*,Δ	86.9 ± 14.3
	AC	87.9 ± 13.1	81.4 ± 14.5*	61.0 ± 4.6*,Δ	87.3 ± 13.5
HR (min^{-1})	CON	66.2 ± 7.7			66.8 ± 7.3
	ANH	65.3 ± 8.3	76.9 ± 7.9*		63.0 ± 9.3
	CH	65.4 ± 9.0		81.9 ± 7.3*,Δ	68.1 ± 10.4
	AC	65.6 ± 9.3	78.0 ± 8.7*	78.1 ± 11.0*,Δ	64.1 ± 9.1
CVP (cmH_2O)	CON	7.0 ± 1.4			7.3 ± 1.5
	ANH	7.0 ± 1.5	7.7 ± 1.1*		7.3 ± 2.2
	CH	6.9 ± 1.6		5.4 ± 1.2*,Δ	7.2 ± 1.7
	AC	7.0 ± 1.8	7.6 ± 1.9*	6.7 ± 1.9Δ	7.3 ± 1.8
CO (L/min)	CON	5.8 ± 1.4			5.7 ± 1.2
	ANH	5.5 ± 1.2	6.7 ± 0.9*		5.6 ± 1.1
	CH	5.5 ± 1.2		5.7 ± 0.9Δ	5.6 ± 1.1
	AC	5.6 ± 1.2	6.7 ± 1.2*	6.4 ± 1.1*,Δ	5.6 ± 1.1
SVV (%)	CON	9.8 ± 2.2			9.9 ± 1.9
	ANH	9.5 ± 2.9	8.5 ± 3.1*		9.3 ± 3.0
	CH	9.8 ± 2.5		13.9 ± 2.9*,Δ	9.7 ± 2.4
	AC	9.6 ± 3.5	8.3 ± 2.9*	9.6 ± 2.8	9.8 ± 2.2
SVR ($Dyn/s.cm^2$)	CON	1094.9 ± 137.2			1091.7 ± 134.3
	ANH	1087.8 ± 168.7	837.9 ± 91.8*		1072.3 ± 149.9
	CH	1067.9 ± 183.4		788.3 ± 205.1*,Δ	1073.9 ± 165.9
	AC	1067.8 ± 163.2	879.2 ± 89.5*	646.4 ± 112.0*,Δ	1058.7 ± 160.9
HB (g/mL)	CON	123.2 ± 11.0			96.4 ± 7.1*,Δ,#
	ANH	121.7 ± 8.4	97.2 ± 6.0*		103.2 ± 7.2*,Δ,#
	CH	122.3 ± 8.8		109.3 ± 8.1*,Δ	101.0 ± 8.1*,Δ,#
	AC	122.7 ± 8.1	98.2 ± 5.7*	97.8 ± 5.7*,Δ	111.7 ± 3.6*,Δ,#,$
HCT (%)	CON	37.6 ± 2.9			28.5 ± 2.0*
	ANH	37.3 ± 2.6	29.8 ± 1.8*		31.5 ± 2.1*,Δ
	CH	37.2 ± 2.8		36.5 ± 2.9Δ	30.8 ± 2.4*,Δ,#
	AC	37.5 ± 2.4	30.1 ± 1.7*	30.0 ± 1.7*	34.0 ± 1.2*,Δ,#,$
PLT (× 10^9/L)	CON	195.6 ± 45.2			144.0 ± 39.2*
	ANH	194.9 ± 40.3	155.1 ± 40.0*		180.3 ± 38.9*,Δ
	CH	197.5 ± 43.0		189.4 ± 44.7*	177.2 ± 42.1*,Δ
	AC	196.1 ± 55.9	156.7 ± 41.3*	151.7 ± 39.5*	175.7 ± 50.5*,Δ

Notes: *represent P<0.05 compared with T_1; Δrepresent P<0.05 compared with T_2; #represent P<0.05 compared with T_3; $represent P<0.05 compared with T_4.

lism. At the same time, right subclavian vein was punctured for central venous pressure (CVP) monitoring. Anesthesia was maintained by combined intravenous and inhalation. Intraoperative BIS fluctuated from 40 to 60. Blood transfusion and fluid infusion were performed according to hemodynamic changes. Radial arterial and jugular bulb blood were collected at four time points, including after induction of anesthesia (T_1), immediately after ANH (T_2), 30 min after reaching target blood pressure by CH (T_3) and after completion of surgery (T_4), respectively, for blood gas analysis. Radial arterial blood oxygen content and blood oxygen content in jugular bulb were given by C_aO_2 and $C_{jv}O_2$ respectively: $C_aO_2 = (Hb \times 1.34 \times S_aO_2) + (P_aO_2 \times 0.003)$; $C_{jv}O_2 = (Hb \times 1.34 \times S_{jv}O_2) + (P_{jv}O_2 \times 0.003)$.

Table 2. Urine volume, blood loss and blood transfusion volume during operation in four groups ($\bar{x} \pm s$, n = 20)

Group (n = 20)	Blood loss (mL)	Allogeneic blood transfusion volume (mL)	Urine (mL)	Allogeneic blood transfusion	
				N	(%)
CON	1174.7 ± 400.0	413.3 ± 324.8	629.5 ± 163.4	16	80
ANH	1022.9 ± 341.9	200.0 ± 320.7*	630.4 ± 135.7	8*	40*
CH	794.0 ± 224.3*	207.1 ± 292.1*	620.9 ± 161.6	9*	45*
AC	736.9 ± 174.2*	20 ± 20*,Δ	623.3 ± 137.1	2*,Δ	10*,Δ

Notes: *represent *P*<0.05 compared with group CON; Δrepresent *P<0.05* compared with group ANH or CH.

According to Fick's equation, radial arterial-jugular bulb venous blood oxygen content difference ($D_{a\text{-}jv}O_2$), cerebral metabolic rate of oxygen ($CERO_2$) and jugular bulb venous-radial arterial difference of lactate (VADL) were calculated. $D_{a\text{-}jv}O_2 = C_aO_2\text{-}C_{jv}O_2$; $CERO_2 = D_{a\text{-}jv}O_2/C_aO_2 \times 100\%$.

Radial arterial-jugular bulb venous difference of lactate content ($D_{a\text{-}jv}L$) = $D_aL\text{-}D_{jv}L$. After surgery, pain was managed with intravenous patient-controlled pump using the same analgesics in the same way in all patients. Cognitive function test was performed by the same mental health-trained anesthesiologist. One-day preoperatively, 1 d postoperatively and 7 d postoperatively, MMSE test were performed, which comprised the following categories: (a) orientation test, (b) memorization test, (c) attention and calculation, (d) delay memory, (e) language test, and (f) visuospatial test. The entire test was a 30-point questionnaire consisting of 30 questions, where 1 point was scored for each correct answer and 0 point for wrong answer. A patient was considered to have POCD if his/her postoperative score was 2 points lower than the preoperative one. One day preoperatively, at completion of surgery, 1 d postoperatively and 7 d postoperatively, respectively, 2 ml of venous blood was collected and coagulated naturally for 30 min, which was then centrifuged to collect serum and stored in a -80°C refrigerator. Serum levels of TNF-α, IL-1β, IL-6, IL-8, S-100β protein and NSE were determined by ELISA. Intraoperative allogeneic transfusion volume, blood loss, urine volume and operative time were calculated.

Statistical analysis

Data were analyzed using SPSS 19.0 software. Measurement data were expressed as $\bar{x} \pm s$ and compared by *t* test or one-way ANOVA. Enumeration data were compared by *chi-square* test or *Fisher's* exact test. Comparison of non-normal data was done by rank sum test. *P*< 0.05 was considered statistically significant.

Results

No significant difference was found in sex ratio, age, weight, height, MMSE score or operative time among patients in the four groups.

Compared with T_1, MAP, SVR and SVV markedly decreased while HR, CVP and CO elevated markedly at T_2 in the ANH and AC groups. At T_3, CVP and CO markedly elevated while SVV and SVR decreased markedly in the ANH group. In the CH and AC groups, markedly decreased MAP, SVR and markedly increased HR were noted at T_3; meanwhile, CVP and CO markedly decreased in the CH group and CO markedly elevated in the AC group. HB, HCT and PLT markedly decreased at T_2, T_3 and T_4 compared with at T_1 in the ANH and AC groups. For CH group, HB, HCT and PLT decreased markedly at T_3 and T_4. Compared with the Con group, HB, HCT and PLT elevated markedly at T_4 in the ANH, CH and AC groups. Compared with the ANH and CH groups at T_4, HB and HCT were significantly higher in the AC group (*P*<0.05) (**Table 1**).

No significant difference was found in intraoperative urine volume among the four groups of patients. Compared with the CON group, intraoperative blood loss was significantly reduced in the CH and AC groups. Significantly reduced intraoperative transfusion volume was noted in the ANH, CH and AC groups. Compared with the ANH and CH groups, transfusion volume was significantly reduced for the AC group (*P*<0.05) (**Table 2**).

Serum levels of IL-1β, IL-6, IL-8, TNF-α, S-100β protein and NSE elevated significantly in all four groups at completion of surgery and 1 d after surgery as compared with 1 d before surgery. 1 d postoperative S-100β protein, NSE and TNF-α levels were significantly lower than those at completion of surgery (*P*<0.05). Compared with 1 d before surgery, the 7 d postoperative IL-1β, IL-6, IL-8, TNF-α, S-100β and NSE returned to the preoperative levels (**Table 3**).

Table 3. Change of serum inflammatory factors over time ($\bar{x} \pm s$, n = 20)

	Group	1 d preoperative	Completion of surgery	1 d postoperative	7 d postoperative
IL-1β (pg/mL)	CON	11.32 ± 4.17	20.41 ± 6.19*	19.19 ± 3.73*	12.60 ± 4.75
	ANH	11.56 ± 4.38	20.98 ± 4.61*	19.87 ± 3.12*	11.73 ± 3.89
	CH	11.48 ± 4.42	22.04 ± 7.07*	20.77 ± 5.65*	11.77 ± 4.04
	AC	11.75 ± 5.58	21.98 ± 4.33*	20.18 ± 4.15*	11.60 ± 4.51
IL-6 (pg/mL)	CON	10.39 ± 4.22	18.00 ± 8.24*	18.70 ± 8.98*	12.19 ± 6.86
	ANH	10.37 ± 4.19	18.74 ± 9.53*	19.35 ± 10.44*	12.14 ± 6.23
	CH	10.45 ± 5.04	19.05 ± 9.40*	19.35 ± 10.19*	11.57 ± 5.40
	AC	10.54 ± 4.97	19.70 ± 6.10*	20.88 ± 6.14*	12.00 ± 4.75
IL-8 (pg/mL)	CON	31.57 ± 13.89	45.89 ± 19.81*	45.53 ± 19.08*	32.27 ± 13.66
	ANH	32.15 ± 13.72	46.81 ± 18.88*	47.67 ± 19.89*	32.97 ± 13.04
	CH	31.77 ± 12.95	47.64 ± 19.09*	47.83 ± 17.43*	31.94 ± 13.07
	AC	31.62 ± 12.59	47.06 ± 18.02*	47.74 ± 17.31*	32.08 ± 12.99
TNF-α (pg/mL)	CON	28.04 ± 4.64	37.58 ± 8.01*	31.53 ± 4.41*,Δ	29.04 ± 4.19
	ANH	28.17 ± 5.32	38.19 ± 9.55*	31.87 ± 3.77*,Δ	29.20 ± 5.62
	CH	28.13 ± 5.74	38.61 ± 9.30*	32.12 ± 3.47*,Δ	29.65 ± 5.45
	AC	27.91 ± 5.12	38.45 ± 7.21*	32.56 ± 5.57*,Δ	28.49 ± 4.60
S-100β (μg/L)	CON	0.21 ± 0.14	0.52 ± 0.26*	0.31 ± 0.18*,Δ	0.21 ± 0.16
	ANH	0.19 ± 0.10	0.56 ± 0.21*	0.34 ± 0.18*,Δ	0.21 ± 0.10
	CH	0.22 ± 0.12	0.55 ± 0.25*	0.35 ± 0.24*,Δ	0.22 ± 0.13
	AC	0.21 ± 0.07	0.69 ± 0.20*	0.46 ± 0.29*,Δ	0.23 ± 0.07
NSE (μg/L)	CON	9.48 ± 2.37	12.23 ± 2.51*	10.67 ± 2.58*,Δ	9.97 ± 2.16
	ANH	8.86 ± 2.10	13.02 ± 4.30*	11.04 ± 3.21*,Δ	9.45 ± 1.99
	CH	8.57 ± 2.27	13.33 ± 3.19*	10.48 ± 3.28*,Δ	8.75 ± 2.07
	AC	8.57 ± 2.30	14.54 ± 2.75*	12.54 ± 3.56*,Δ	8.89 ± 2.71

Notes: *represent $P<0.05$ compared with 1 d preoperative; Δrepresent $P<0.05$ compared with completion of surgery.

Table 4. The comparison of MMSE score and POCD in each group after operation ($\bar{x} \pm s$, n = 20)

Group (n = 20)	MMSE score			POCD (%)	
	1 d preoperative	1 d postoperative	7 d postoperative	1 d postoperative	7 d postoperative
CON	27.1 ± 1.2	26.4 ± 1.9*	26.9 ± 1.6	25	5*
ANH	27.3 ± 1.2	26.5 ± 1.9*	27.1 ± 1.2	20	5*
CH	27.2 ± 1.0	26.3 ± 2.0*	27.0 ± 1.3	20	0*
AC	27.1 ± 1.2	26.1 ± 2.2*	26.9 ± 1.5	25	5*

Notes: *represent $P<0.05$ compared with 1 d preoperative.

Compared with the 1 d preoperative MMSE score, 1 d postoperative score was significantly lower ($P<0.05$), while 7 d postoperative score showed no statistical significance. There was no significant difference in the 1 d and 7 d postoperative incidences of POCD among the four groups of patients (**Table 4**).

Compared with C_aO_2 and $C_{jv}O_2$ at T_1, all groups showed varying degrees of significant decrease at T_2, T_3 and T_4. The values were markedly higher for the CH group at T_3, and for the AC group at T_4. Compared with $S_{jv}O_2$ at T_1, AC group showed significant decrease at T_3. Compared with $D_{a-jv}O_2$ at T_1, CON, ANH and CH groups exhibited significant decrease at T_4. Besides, the value was significantly higher ($P<0.05$) for the AC group at T_4. No significant difference was found in P_aO_2, $P_{jv}O_2$, $CERO_2$ or VADL among the four groups at any time point (**Table 5**).

Discussion

At present, safe, reliable, simple and rational blood conservation techniques are used as far as possible in the clinical settings to reduce

Table 5. Changes of cerebral oxygen metabolism during operation in each group ($\bar{x} \pm s$, n = 20)

	Group	T_1	T_2	T_3	T_4
P_aO_2 (mmHg)	CON	417.8 ± 66.2			415.1 ± 61.8
	ANH	389.4 ± 72.6	389.4 ± 72.6		392.3 ± 69.8
	CH	384.8 ± 86.1		385.9 ± 82.5	385.9 ± 82.5
	AC	411.8 ± 67.4	412.1 ± 67.4	416.0 ± 59.7	416.0 ± 59.7
C_aO_2 (ml/L)	CON	163.6 ± 13.7			135.4 ± 10.0*
	ANH	163.9 ± 11.8	131.5 ± 7.6*		138.9 ± 9.7*
	CH	164.0 ± 11.2		150.6 ± 10.1*	136.4 ± 11.4*
	AC	163.3 ± 10.4	132.6 ± 7.3*	131.9 ± 7.3*,Δ	151.5 ± 5.4*,#
$P_{jv}O_2$ (mmHg)	CON	35.6 ± 7.1			38.0 ± 1.4
	ANH	35.0 ± 6.7	32.9 ± 4.0		38.0 ± 1.8
	CH	34.9 ± 7.0		34.2 ± 6.2	38.4 ± 1.5
	AC	35.7 ± 8.2	32.7 ± 5.8	27.4 ± 5.0*,Δ	37.9 ± 1.1
$S_{jv}O_2$ (%)	CON	67.7 ± 9.8			68.0 ± 3.3
	ANH	67.6 ± 7.9	63.9 ± 6.1		68.0 ± 4.8
	CH	67.6 ± 8.6		64.3 ± 8.4	68.1 ± 4.8
	AC	67.6 ± 7.4	64.4 ± 6.5	58.6 ± 4.7*,Δ	67.4 ± 3.8
$C_{jv}O_2$ (ml/L)	CON	109.8 ± 17.5			89.9 ± 9.6*
	ANH	110.3 ± 14.3	83.3 ± 9.7*		92.7 ± 9.6*
	CH	110.5 ± 17.4		102.5 ± 16.5*	91.8 ± 8.3*
	AC	109.5 ± 14.0	84.6 ± 10.7*	76.7 ± 8.7*,Δ	101.1 ± 6.2*,Δ
$D_{a\text{-}jv}O_2$ (ml/L)	CON	53.8 ± 17.4			42.5 ± 4.0*
	ANH	53.6 ± 14.0	50.1 ± 8.5		45.2 ± 7.3*
	CH	53.6 ± 13.3		54.9 ± 12.8	44.6 ± 8.2*
	AC	53.7 ± 12.8	51.0 ± 8.1	55.3 ± 15.9	51.3 ± 6.2#
$CERO_2$ (%)	CON	32.8 ± 9.8			32.7 ± 3.2
	ANH	32.7 ± 7.9	36.6 ± 6.1		32.5 ± 4.8
	CH	32.8 ± 8.7		36.3 ± 8.3	32.6 ± 4.7
	AC	32.9 ± 7.5	36.3 ± 6.4	42.0 ± 4.6*,Δ	33.2 ± 3.7
VADL (mmol/L)	CON	0.17 ± 0.05			0.15 ± 0.05
	ANH	0.15 ± 0.05	0.15 ± 0.05		0.16 ± 0.08
	CH	0.15 ± 0.05		0.14 ± 0.05	0.15 ± 0.05
	AC	0.17 ± 0.05	0.17 ± 0.06	0.16 ± 0.04	0.15 ± 0.05

Notes: *represent *P<0.05* compared with T_1; Δrepresent *P<0.05* compared with T_2; #represent *P<0.05* compared with T_3.

unnecessary allogeneic transfusions and to avoid potential transfusion-related risk [21-23]. Elderly patients undergoing spinal surgery studied in this trial had large blood loss, so blood conservation was of great clinical significance. MMES is currently one of the most influential POCD screening tools, which is also the preferred method of screening for dementia [24, 25]. In this trial, one day postoperative MMSE scores were all lower than 1 d preoperative scores. Seven days postoperatively, the MMSE score basically returned to normal, without showing any statistical significance among each group at any time point. This indicates that ANH and CH, whether used alone or in combination, do not significantly increase the incidence of POCD.

Several studies have confirmed that the perioperative alterations of inflammatory cytokines caused by anesthesia and surgical trauma, as well as postoperative systemic inflammatory response are important causes of POCD [26, 27]. IL-6 and S-100β are inflammatory markers which correlated with POCD strongly, while IL-1 and TNF-α could weak such correlation [24]. IL-1β promotes neuroinflammation in patients with neurological disorders and promotes the progression of neuroinflammation together with TNF-α, IL-6 and so on [28, 29]. Inhibition of TNF-α release may reduce IL-1 synthesis, limit the development of neuroinflammation, and reduce the incidence of cognitive impairment [30]. Therefore, some researchers consider TNF-α as an important inflammatory cytokine causing neurological disorders and cognitive dysfunction. Some cognitive disorders are treatable by blocking TNF-α synthesis [31]. As a glial marker protein and also a brain-specific protein, S-100β has a significant role in promoting the occurrence of cognition, which is the best indicator of brain injury at present. Serum S-100β level can be used as an important indicator for assessing

the incidence, duration and outcome of POCD [24, 25, 32]. NSE is specifically present in neurons and neuroendocrine cells, whose concentration in serum may indicate the severity of brain injury [33]. Detection of changes in levels of inflammatory cytokines like IL-1, IL-6, IL-8 and TNF-α in this trial showed that ANH and CH, whether used alone or in combination, did not interfere with the trend of changes in postoperative inflammatory factors. In this study, all four groups of patients had significantly elevated S-100β and NSE levels at completion of surgery and 1 d after surgery, which returned to the preoperative levels 7 d after surgery. This suggests that ANH combined with CH does not aggravate cerebral tissue damage in patients.

There is the risk of cerebral ischemia-hypoxia caused by decreased tissue perfusion pressure after CH. However, currently accepted safety limit for CH is MAP at 50-55 mmHg. In this experiment, MAP is not less than 55 mmHg and not longer than 90 min, in order to avoid the cerebral hypoperfusion caused by long-term hypotension. In this experiment, SVV and SVR decreased while CVP and CO increased after ANH in the ANH and AC groups. In the CH group, hypotension caused vasodilation of middle and small arteries, systemic hypovolemia and decreased CVP and SVR. Hypotension also caused compensatory heart rate increase. The accelerated heart rate was insufficient to compensate for the lack of systemic blood volume, so CO decreased. As for the AC group, hemodilution was performed first to lower blood viscosity and accelerate blood flow, followed by controlled hypotension, where HR, CO, CVP were relatively stable. This suggests that combined ANH and CH has smaller impact on hemodynamics than using alone and can achieve more stable hemodynamic indices.

It has been reported that during ANH, neuronal apoptosis at the porcine hippocampus or cerebral cortex does not increase significantly in the acute phase even if Hct decreases to between 10-15%, while acute hypoxia causes evident neuronal stress response [34]. Some studies have shown that stable oxygen supply in tissues and organs can be maintained when Hct is not less than 20%. Oxygen supply can reach the maximum at the level between 20-30%. This indicates that ANH has preventive and protective effects on cerebral ischemia reperfusion injury, which can guarantee normal oxygen metabolism [35]. In clinical settings, cerebral venous blood is often replaced by jugular bulb venous blood in the determination of $S_{jv}O_2$. VADL within the blood of this site can reflect the net production of lactate in brain tissues, that is, anaerobic metabolism of brain tissues, which thus can accurately reflect the relationship of cerebral oxygen supply-consumption balance [36]. Increased VADL reflects reduced cerebral oxygen supply. Continuous increase in lactate level may endanger the brain function, resulting in cognitive impairment and other damage [37, 38]. $D_{a\text{-}jv}O_2$ and $CERO_2$ are blood metabolic indices reflecting the degree of matching between blood flow and oxygen consumption in brain tissues. Decreased $D_{a\text{-}jv}O_2$ and $CERO_2$ indicate reduced cerebral oxygen consumption and sufficient oxygen supply, while increased $D_{a\text{-}jv}O_2$ and $CERO_2$ indicate increase in cerebral oxygen consumption and shortage of oxygen supply. Results of this study showed no significant change in $CERO_2$ in the ANH group, suggesting that the increased cerebral blood flow is sufficient to compensate for the inadequate blood oxygen supply. In the CH group, lack of blood volume and accelerated heart rate partially compensated for decreased CO caused by reduction in stroke volume, while showing no significant influence on $CERO_2$. Increase in $CERO_2$ was noted in the AC group, suggesting lack of oxygen supply and increased cerebral oxygen consumption. However, no significant change in VADL was noted, indicating absence of anaerobic metabolism within brain tissue. Organisms maintain cerebral oxygen consumption at a stable level by increasing $CERO_2$.

Currently, pathogenesis of POCD is not very clear yet. Previous studies suggested that POCD might be associated with preoperative diabetes, low level of education, perioperative inflammatory response, postoperative complications, perioperative ischemia and hypoxia [36, 39]. Our study showed that factors such as central nervous system degeneration and calcium dyshomeostasis are involved in damage and apoptosis of brain cells in elderly patients. Besides, poor cerebrovascular autoregulation easily leads to intraoperative imbalance of cerebral oxygen supply-consumption, thereby causing POCD [12]. There are also some limitations in our research. Firstly, the need for

strict indications and clinical experience may not be conducive to the technological practice at primary hospitals; secondly, the small number of patients is insufficient to explain the test results of this study. In addition, animal experiments are needed for investigating the changes in hippocampus and cortical brain function on a molecular level.

In summary, ANH combined with CH does not increase the incidence of POCD compared with using alone. ANH combined with CH also has the following advantages: It does not significantly impact hemodynamic stability; it significantly reduces blood loss and allogeneic blood transfusion; it does not exacerbate inflammation; and it has no significant influence on S-100β and NSE level.

Acknowledgements

The study was supported by Innovation of Pudong New Area Science and Technology Development Fund (Grant No. PKJ2012-Y54) and Shanghai Health and Family Planning Commission (201440456) and Funded by Outstanding Leaders Training Program of Pudong Health Bureau of Shanghai (Grant No. PWR12013-03) and Young Medical Talents Training Program of Pudong Health Bureau of Shanghai (Grant No. PWRq12016-28).

Disclosure of conflict of interest

None.

Address correspondence to: Jianrong Guo, Department of Anesthesiology, Gongli Hospital of Second Military Medical University, Shanghai 200135, China. E-mail: guojianrong_sh@163.com

References

[1] Irisson E, Hemon Y, Pauly V, Parratte S, Argenson JN and Kerbaul F. Tranexamic acid reduces blood loss and financial cost in primary total hip and knee replacement surgery. Orthop Traumatol Surg Res 2012; 98: 477-483.

[2] Beattie WS, Karkouti K, Wijeysundera DN and Tait G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology 2009; 110: 574-581.

[3] Hausenloy DJ and Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest 2013; 123: 92-100.

[4] Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL and Rossaint R. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 2013; 17: R76.

[5] Shander A, Knight K, Thurer R, Adamson J and Spence R. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. Am J Med 2004; 116 Suppl 7A: 58S-69S.

[6] Sukeik M, Alshryda S, Haddad FS and Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br 2011; 93: 39-46.

[7] Mariette C, Alves A, Benoist S, Bretagnol F, Mabrut JY and Slim K. [Perioperative care in digestive surgery. Guidelines for the French society of digestive surgery (SFCD)]. Ann Chir 2005; 130: 108-124.

[8] Perazzo P, Vigano M, De Girolamo L, Verde F, Vinci A, Banfi G and Romagnoli S. Blood management and transfusion strategies in 600 patients undergoing total joint arthroplasty: an analysis of pre-operative autologous blood donation. Blood Transfus 2013; 11: 370-376.

[9] Noticewala MS, Nyce JD, Wang W, Geller JA and Macaulay W. Predicting need for allogeneic transfusion after total knee arthroplasty. J Arthroplasty 2012; 27: 961-967.

[10] Li X, Wen DX, Zhao YH, Hang YN and Mandell MS. Increase of beta-amyloid and C-reactive protein in liver transplant recipients with postoperative cognitive dysfunction. Hepatobiliary Pancreat Dis Int 2013; 12: 370-376.

[11] Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE and Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International study of post-operative cognitive dysfunction. Lancet 1998; 351: 857-861.

[12] Maekawa K, Baba T, Otomo S, Morishita S and Tamura N. Low pre-existing gray matter volume in the medial temporal lobe and white matter lesions are associated with postoperative cognitive dysfunction after cardiac surgery. PLoS One 2014; 9: e87375.

[13] Mu DL, Li LH, Wang DX, Li N, Shan GJ, Li J, Yu QJ and Shi CX. High postoperative serum cortisol level is associated with increased risk of cognitive dysfunction early after coronary artery bypass graft surgery: a prospective cohort study. PLoS One 2013; 8: e77637.

[14] Newman MF, Mathew JP, Grocott HP, Mackensen GB, Monk T, Welsh-Bohmer KA, Blumen-

thal JA, Laskowitz DT and Mark DB. Central nervous system injury associated with cardiac surgery. Lancet 2006; 368: 694-703.
[15] Oppitz PP and Stefani MA. Acute normovolemic hemodilution is safe in neurosurgery. World Neurosurg 2013; 79: 719-724.
[16] Rehm M, Orth V, Kreimeier U, Thiel M, Haller M, Brechtelsbauer H and Finsterer U. Changes in intravascular volume during acute normovolemic hemodilution and intraoperative retransfusion in patients with radical hysterectomy. Anesthesiology 2000; 92: 657-664.
[17] Choi WS and Samman N. Risks and benefits of deliberate hypotension in anaesthesia: a systematic review. Int J Oral Maxillofac Surg 2008; 37: 687-703.
[18] Guo JR, Jin XJ, Yu J, Xu F, Zhang YW, Shen HC and Shao Y. Acute normovolemic hemodilution effects on perioperative coagulation in elderly patients undergoing hepatic carcinectomy. Asian Pac J Cancer Prev 2013; 14: 4529-4532.
[19] Yao XH, Wang B, Xiao ZK, Zhou P, Chen CY and Qing ZH. [Acute normovolemic hemodilution combined with controlled hypotension in patients undergoing liver tumorectomy]. Nan Fang Yi Ke Da Xue Xue Bao 2006; 26: 828-830.
[20] Ge YL, Lv R, Zhou W, Ma XX, Zhong TD and Duan ML. Brain damage following severe acute normovolemic hemodilution in combination with controlled hypotension in rats. Acta Anaesthesiol Scand 2007; 51: 1331-1337.
[21] Seid M, Azazh A, Enquselassie F and Yisma E. Injury characteristics and outcome of road traffic accident among victims at adult emergency department of tikur anbessa specialized hospital, Addis Ababa, Ethiopia: a prospective hospital based study. BMC Emerg Med 2015; 15: 10.
[22] Jo KI and Shin JW. Can maximum surgical blood order schedule be used as a predictor of successful completion of bloodless surgery? Ann Lab Med 2013; 33: 116-120.
[23] Sant'Ana AJ, Otsuki DA, Noel-Morgan J, Leite VF, Fantoni DT, Abrahao Hajjar L, Barbosa Gomes Galas FR, Pinheiro De Almeida J, Fukushima J and Costa Auler JO Jr. Use of pulse pressure variation to estimate changes in preload during experimental acute normovolemic hemodilution. Minerva Anestesiol 2012; 78: 426-433.
[24] Peng L, Xu L and Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis. PLoS One 2013; 8: e79624.
[25] Xu JH, Zhang TZ, Peng XF, Jin CJ, Zhou J and Zhang YN. Effects of sevoflurane before cardiopulmonary bypass on cerebral oxygen balance and early postoperative cognitive dysfunction. Neurol Sci 2013; 34: 2123-2129.
[26] Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, Takata M, Lever IJ, Nanchahal J, Fanselow MS and Maze M. Role of interleukin-1beta in postoperative cognitive dysfunction. Ann Neurol 2010; 68: 360-368.
[27] Fidalgo AR, Cibelli M, White JP, Nagy I, Maze M and Ma D. Systemic inflammation enhances surgery-induced cognitive dysfunction in mice. Neurosci Lett 2011; 498: 63-66.
[28] Wu MD, Montgomery SL, Rivera-Escalera F, Olschowka JA and O'Banion MK. Sustained IL-1beta expression impairs adult hippocampal neurogenesis independent of IL-1 signaling in nestin+ neural precursor cells. Brain Behav Immun 2013; 32: 9-18.
[29] Barrientos RM, Frank MG, Hein AM, Higgins EA, Watkins LR, Rudy JW and Maier SF. Time course of hippocampal IL-1 beta and memory consolidation impairments in aging rats following peripheral infection. Brain Behav Immun 2009; 23: 46-54.
[30] Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M and Maze M. Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci U S A 2010; 107: 20518-20522.
[31] Belarbi K, Jopson T, Tweedie D, Arellano C, Luo W, Greig NH and Rosi S. TNF-αlpha protein synthesis inhibitor restores neuronal function and reverses cognitive deficits induced by chronic neuroinflammation. J Neuroinflammation 2012; 9: 23.
[32] Rothermundt M, Peters M, Prehn JH and Arolt V. S100B in brain damage and neurodegeneration. Microsc Res Tech 2003; 60: 614-632.
[33] Johnsson P. Markers of cerebral ischemia after cardiac surgery. J Cardiothorac Vasc Anesth 1996; 10: 120-126.
[34] Frazilio FO, Otsuki DA, Noel-Morgan J, Maximino JR, Oliveira GP, Chadi G, Auler JO Jr and Fantoni DT. Evaluation of neuronal apoptosis precursors in an experimental model of acute normovolemic hemodilution. PLoS One 2014; 9: e108366.
[35] Bennett J, Haynes S, Torella F, Grainger H and McCollum C. Acute normovolemic hemodilution in moderate blood loss surgery: a randomized controlled trial. Transfusion 2006; 46: 1097-1103.
[36] Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM and Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108: 18-30.
[37] Alves OL, Daugherty WP and Rios M. Arterial hyperoxia in severe head injury: a useful or harmful option? Curr Pharm Des 2004; 10: 2163-2176.

[38] Chieregato A, Marchi M, Fainardi E and Targa L. Cerebral arterio-venous pCO2 difference, estimated respiratory quotient, and early post-traumatic outcome: comparison with arterio-venous lactate and oxygen differences. J Neurosurg Anesthesiol 2007; 19: 222-228.

[39] Wan Y, Xu J, Ma D, Zeng Y, Cibelli M and Maze M. Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology 2007; 106: 436-443.