ORIGINAL ARTICLE   **Open Access**

Acute hypervolemic hemodilution combined with controlled hypotension to minimize blood loss during operations of spine fusion: remifentanil versus magnesium sulfate

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Abstract

Background: Blood loss is one of the major problems during operations of spine fusion. Several blood-conservative measures were applied to reduce the incidence of blood loss—among them, acute hypervolemic hemodilution (AHH) and controlled hypotension (CH). This study was designed to detect the effect of combination of AHH with CH induced by remifentanil versus magnesium sulfate on the volume of blood loss, allogeneic blood transfusion, hemodynamics, coagulation, and electrolytes during operations for spine fusion which are risky operations with high incidence of blood loss and blood transfusion. Sixty patients scheduled for posterior fusion of the spine were randomly allocated into three groups of 20 patients each (group I (AHH), group II (AHH combined with remifentanil-based CH), and group III (AHH combined with magnesium sulfate-based CH)). Estimated blood loss and total volume of packed red blood cells (PRBCS) transfused were recorded. Arterial blood pressure (ABP) and heart rate (HR) measures were recorded. Blood samples were obtained for the detection of hemoglobin (Hb) and hematocrit (HCT).

Results: Estimated blood loss, percentage blood loss, and intraoperative RBC transfusion units were significantly high in group I in relation to group II and group III (Table 2). Cardiac output was significantly higher in group I in relation to group II and group III at 10, 15, 30, 45, and 60 min after start of AHH. MBP and HR results were significantly high in group I in comparison with group II and group III at 30, 45, 60, and 90 min and 2 and 3 h after start of study drugs. CVP results were significantly high in group I in relation to group II and group III at 15, 30, 45, 60, and 90 min after start of AHH. PTT was significantly increased in the three study groups in comparison with baseline inside each group after AHH.

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Conclusion: Combination of AHH with CH induced by remifentanil or magnesium sulfate was associated with reduction in estimated blood loss, and total volume of PRBCS transfused. There was no significant difference between hemodynamic parameters with the use of remifentanil or magnesium sulfate except that SBP, DBP, and MBP results were significantly high with magnesium sulfate at 15 min after drug infusion. There was significant increase in PT and PTT after AHH that was not reflected by significant blood oozing from the operative field, or by difficulty in hemostasis.

Keywords: Acute hypervolemic hemodilution, Controlled hypotension, Remifentanil, Magnesium sulfate, Spine fusion

Background

Blood loss in spine surgery is an important issue, and decreasing bleeding is essential for maintaining patient hemodynamic equilibrium, allowing better view of surgical field and reducing the incidence of blood transfusion (Laratta, 2016). Allogeneic transfusion has long been considered to be a relatively safe and extremely effective treatment especially in emergency (Guo et al., 2010). However, observational studies associate allogeneic transfusion with risk in the form of postoperative infection (Dafna et al., 2016), impaired pulmonary function (Acheson et al., 2012), and increased length of stay and mortality (Webster, 2017), (Meier et al., 2016). Researchers are trying to apply effective blood conservations to control blood loss and decrease or avoid allogeneic blood transfusion during surgery (Oriani et al., 2011). Among those are acute hypervolemic hemodilution (AHH) and acute normovolemic hemodilution (ANH). AHH is a procedure in which a certain amount of crystalloid or colloid fluid is rapidly infused in a short time, which ultimately leads to rapid dilution of blood volume and decrease of hematocrit level (Menghu et al., 2008), while ANH is an effective strategy to decrease blood loss which has been established but requires a certain amount of extra time and effort with increased danger of infection as patient's blood is withdrawn prior to operation simultaneously with infusion of crystalloid or colloid solutions (Brile et al., 2017). Controlled hypotension (CH) is another blood sparing technique that is widely applied to spine surgery, and good results have been published since 1970 (Menghu et al., 2008). Although the primary premise for the use of controlled hypotension is to limit intraoperative blood loss which is expected to be high in procedures of posterior fusion, an additional benefit may be improved visualization of surgical field which is an important issue especially in spinal cord surgery because important neuronal structures are located in the field (Mohammed et al., 2014). Multiple varieties of drugs have been applied for reduction of blood pressure including vasodilators (e.g. nitroprusside), alpha-2 receptor agonist (e.g. dexmedetomidine), and beta-adrenergic antagonist (e.g. labetalol). However, several disadvantages like reflex tachycardia and tachyphylaxis were encountered; therefore, use of drugs must be with dose response effect (Wael et al., 2015). In recent years, remifentanil, as a short-acting opioid receptor agonist, has been used for this purpose for mild-to-moderate reduction of blood pressure and as an effective agent for controlled hypotension (Kadriye et al., 2012). Intravenous (IV) magnesium sulfate is a good agent for controlled hypotension as it stabilizes the cell membrane and intracytoplasmic organelles by mediating the activation of membrane Ca ATPase and Na–K ATPase involved in membrane ion exchanges during depolarization and repolarization phases (Mohammed et al., 2014). In addition, it acts as a vasodilator by increasing prostacyclin as well as inhibiting angiotensin-converting enzyme activity (Mohammed et al., 2014). Combination of CH with AHH can modestly dilate vessel capacity and maintain a normal central venous pressure (CVP). More importantly, it can avoid dangerous clinical symptoms such as heart failure (Xuekang et al., 2015).

This study was designed to detect the effect of the combination of remifentanil versus magnesium sulfate by acute hypervolemic hemodilution and controlled hypotension on volume of blood loss, allogeneic blood transfusion, hemodynamics, coagulation, and electrolytes during operations for spine fusion which are risky operations with high incidence of blood loss and blood transfusion.

Methods

Approval of our human ethical committee (IRB: institutional review board) and informed written consent obtained from patients included this study was done in Dr. Sulaiman Al Habib Hospital (Riyadh, Saudi Arabia) over a period of 12 months (from January 2019 to December 2019) on 60 patients. The inclusion criteria were patients with American Society of Anesthesiologists I and II, aged 40–60 years, undergoing posterior fusion of the spine for one or two levels due to degenerative disk diseases including herniated disc, spondylolisthesis, or spinal stenosis with expected intraoperative blood loss of around 700 to 1500 cc with preoperative hematocrit (HCT) 35–45%, hemoglobin (HB) > 10 g/dl, and

albumin 35–45 g/l. We excluded patients with history of cardiac disease (hypertension, arrhythmias, ischemic heart disease, and valve lesions). Preoperative echocardiogram was done for all patients included in the study to exclude patients with low ejection fraction, high pulmonary artery pressure, valve lesions, or arrythmias. Patients with preexisting coagulation defects, hepatic or renal dysfunctions, diabetes mellitus, neuromuscular disorders, and known allergy to any of the drugs used in the study were also excluded.

Patients were randomly allocated to one of three groups on the morning of the operation by using the sealed envelope technique—group I (20 patients): (AHH); group II (20 patients): AHH combined with remifentanil-based controlled hypotension (CH); and group III (20 patients): AHH combined with magnesium sulfate-based CH.

All the patients were admitted at least 1 day before the surgery. Twelve hours of fasting were required before operation. Upon arrival of the patients to the operation rooms (OR) holding area a 20-G cannula was inserted to each patient, and infusion of Ringer's Lactate solution has been started at a rate of 7 ml/kg/h to compensate for the loss of body fluids caused by fasting. Midazolam in a dose of 0.05 mg/kg was given. Intravenous premedication consisted of 10 mg of metoclopramide, 40 mg of Pantozole, 8 mg of dexamethasone, and 50 mg of ranitidine were given.

Inside the operation room, standard anesthesia monitoring was applied including electrocardiogram (ECG), pulse oximeter for oxygen saturation (O_2 sat), end-tidal CO_2 monitoring (ET CO_2), and radial artery catheterization was conducted for continuous invasive monitoring of arterial blood pressure (ABP), and to collect blood samples for laboratory Hb monitoring, peripheral nerve stimulator for monitoring of the muscle relaxant effect, and temperature probe for temperature monitoring. For monitoring of the depth of anesthesia, entropy (State entropy, and Response entropy) analysis was used (Datex-Ohmeda S/5 module, Aisys workstation TM GE Healthcare, Helsinki, Finland). Pre-oxygenation for 3 min was done before anesthesia start. Anesthesia was induced with fentanyl 2 μg/kg IV, propofol 1.5 mg/kg IV, lidocaine 1 mg/kg IV. After loss of eyelid reflex, cisatracurium 0. 15 mg/kg IV was given to facilitate tracheal intubation. Anesthesia was maintained with 1 to 1.5 MAC of sevoflurane targeting BIS (bispectral index score) between 40 and 60 with a mixture of oxygen and nitrous oxide (fraction of inspired oxygen was 50%). Cisatracurium in a dose of 0.04 mg/kg every 45 min on need was given IV. All patients were mechanically ventilated with a tidal volume of 8 ml/kg of the ideal body weight with a respiratory rate of 10 to 15 to maintain end-tidal concentration of carbon dioxide (ET CO_2) between 30 and 35 mmHg.

After anesthesia induction and intubation, central venous pressure (CVP) line was inserted in the right internal jugular vein for monitoring the CVP. Transesophageal Doppler was used for monitoring the cardiac output for follow-up of the volume status after AHH (Hemosonic 100, Arrow International; Reading PA, USA). Probe was inserted orally and advanced through the esophagus around 35–40 cm from the teeth (corresponds mostly to level of the 5th–6th thoracic vertebrae) to measure blood flow in the descending aorta depending on the Doppler shift in frequency that occurs when ultrasound wave is reflected back from moving RBCs which is proportional to the velocity of blood flow combined with the measurement of cross-sectional area of the descending thoracic aorta based on age weight and height of patients. Probe was fixed and secured to maintain adjusted accurate depth with best imaging during changing patients to prone position. Refocusing was done prior to each reading. A urinary catheter was inserted for the follow-up of urine output.

After stabilizing the patients of all study groups in prone position on the Jackson table that was used to minimize the increase in intraabdominal pressure with minimal effects on cardiac output, and after ensuring hemodynamic stability, baseline readings were taken for invasive arterial blood pressure (IABP), heart rate, CVP, and cardiac output of all patients included in the study (around 10 min after prone position). AHH was started by transfusion of 6% hydroxyethyl starch 130/0.4 (HAES steril 6%^{TM}; Fresenius, Germany) at a rate of 15 ml/kg to a maximum of 1000 cc over 30 min via a separate venous line in the contralateral arm for all patients of all study groups. The target was to reduce the hematocrit (HCT) to 25–30% which was confirmed by a blood sample analyzed by the central laboratory for checking of HCT and Hb after finishing HAES infusion. The intraoperative fluid loss was replaced with Ringer's solution in a volume of 1–1. Allogeneic blood transfusion was implemented when the Hb < 8 g/dl, HCT < 25%, or intraoperative blood loss > 20% of the total blood volume which was calculated by multiplying the patients' weight by 75 ml/kg.

Medications used to induce CH in group II and group III were started after stabilization of the patients in prone position at the time starting AHH. CH was achieved for all patients of group II by using remifentanil in a loading dose of 1 μg/kg followed by 0.25 μg/kg/min throughout the surgery. In order to avoid hyperalgesia response caused by remifentanil withdrawal, 100 μg of fentanyl was given IV for all patients in group II half an hour before the end of the operation (after fixation of the rods and starting the closure of the wound). CH was

Elnaghy *et al. Ain-Shams Journal of Anesthesiology*   (2021) 13:51

Page 4 of 10

achieved for all patients of group III by using magnesium sulfate in a loading dose of 50 mg/kg diluted in 100 cc of normal saline infused over 10 min followed by magnesium sulfate infusion in a dose of 15 mg/kg/h throughout the operation. Magnesium sulfate was stopped about half an hour before the end of surgery to reduce the chance of prolonged muscle relaxation.

In CH groups (group II and group III), MAP between 60 and 70 mmHg was our target to be maintained during the operation. If hypertension or tachycardia over 20% of the preoperative value occurred during anesthesia with a BIS maintained between 40 and 60, it was assumed to be due to insufficient analgesia, and IV bolus of fentanyl 1μg/kg was given IV. If hypotension occurred with a MAP under 60 mmHg or bradycardia with HR < 40 beats/min and a BIS maintained between 40 and 60 min, sevoflurane concentration was reduced to half, and if there was no response within 5 min, ephedrine 10 mg IV for hypotension and atropine 0.5 mg IV for bradycardia were given.

Measurements

Patients' demographics (age, gender, and ASA physical status) and surgical variables (surgery type, procedure duration, estimated blood loss calculated from the number of saturated sponges or surgical gauze, and the amount of suctioned blood in waste canister), total volume of IV fluids given, and total volume of packed red blood cells (PRBC) transfused were recorded. MAP, HR, and CVP measures were recorded in all patients of all the study groups before anesthesia induction (baseline), while cardiac output (COP) was recorded after stabilization of patients in prone position (baseline), then all the parameters were followed 15, 30, 45, 60, and 90 min after AHH and CH, every 30 min for the second hour, then after 3 h. Venous blood samples were obtained before surgery for detection of baseline Hb and HCT values then every hour during operation (or more often if clinically indicated: blood loss > 20 % of the total blood volume at any time) by withdrawing 3 ml of blood from the arterial line for analysis by the central laboratory. The changes of prothrombin time (PT), activated partial thromboplastin time (PTT), and electrolytes were measured before operation (baseline) then 30 min after AHH by withdrawing of 3 ml of venous blood for central lab analysis. The drains and urine output were monitored in the postoperative period every hour for 24 h.

Statistical analysis

A power analysis of $\alpha = 0.05$ and $\beta = 0.90$ showed that 20 patients were required as sample size per each study group to detect 20% reduction in volume of allogeneic blood transfusions. For statistical analysis, a statistical software package for windows (Graph Pad In Stat, version 3.00; Graph Pad Software Inc., San Diego, CA, USA) was used. Data were presented as mean ± SD, number and percentage of patients, or median (interquartile range) as appropriate. Nominal data were compared using Fisher's exact test. Groups were compared using the parametric or nonparametric versions of analysis of variance followed by appropriate post hoc analysis if significance was detected. P value of < 0.05 was considered significant.

Results

Sixty patients were enrolled in the study. Two patients in group I and one patient in group III were withdrawn from the study as they developed severe hypertension that was not controlled according to study protocol, and labetalol was given to control blood pressure. The remaining 57 patients (35 males, 22 females) composed the study and underwent thoracolumbar (10 cases), or lumbosacral fusion (47 cases) due to degenerative disc diseases including spondylisthesis (Xuekang et al., 2015), spinal stenosis (Christian et al., 2001), or herniated disc (27). As regard patients' demographic data, there was no significant difference between the three study groups (Table 1).

Surgery duration ranged from 220 to 300 min with a median duration of 260 min in group I in comparison with 225 to 320 min with a median duration of 245 min in group II (Table 2) and range of 235 to 310 min with a median duration of 255 min in group III. In group I, estimated blood loss ranged from 1100 to 1800 ml with a median amount of 1200 ml in relation to 550 to 1200 ml with a median of 620 ml in group II, and 600 to 1250 ml with a median of 650 ml in group III (Table 2). Intraoperative RBC transfusion units were significantly high in group I in relation to group II and group III. It was 3.2 ± 1.2 units in group I in relation to 2.1 ± 1.1 units in group II and 2.3 ± 1.3 units in group III (Table 2).

Table 1 Patients' demographics and surgery type in the three study groups

	Group I (N = 18)	Group II (N = 20)	Group III (N = 19)	p value
	11/7	12/8	12/7	0.831
Age (years)	36 ± 13	38 ± 12	35 ± 15	0.493
Weight (kg)	73 ± 16	76 ± 14	74 ± 1	0.541
ASA Status I/II (%)	60/40	63/37	65/35	0.723
Procedures (n):	18	20	19	> 0.05
Herniated disc	8	9	10	
Spondylisthesis	4	5	4	
Spinal stenosis	6	6	5	

-p > 0.05 (non-significant)
- Data are presented as mean ± SD or number of patients.

Table 2 Surgery and transfusion variables of patients in the three study groups

	Group I (N = 18)	Group II (N = 20)	Group III (N = 19)	p value
Duration of surgery (min)	260 (220–300)	245 (225–320)	255 (235–310)	0.346
Estimated blood loss (ml)	1200 (1100–1800)	620 (550–1200)*	650 (600–1250)*	< 0.001
Percentage of blood loss (%)	23.8 ± 6.3	12.6 ± 7.3*	13.2 ± 7.2*	< 0.001
Number and percentage of patients who received blood, N (%)	13 (72.2%)	6 (30.0%)	7 (36.8%)	0.021
Intraoperative RBC transfusion units	3.2 ± 1.2	2.1 ± 1.1*	2.3 ± 1.3*	0.005
Baseline Hb (before operation)	11.2 ± 1.3	10.9 ± 1.3	11.1 ± 1.4	0.482
Post AHH Hb (after AHH)	9.1 ± 1.3	9.2 ± 1.2	8.9 ± 1.2	0.440
Post-transfusion Hb	10.3 ± 1.4	10.2 ± 1.3	10.1±1.3	0.655
Postoperative Hb	10.5 ± 1.2	10.4 ± 1.4	10.2±1.4	0.165

-Percentage of blood loss (volume of total blood loss/ estimated total blood volume)
-Data are presented as mean ± SD, median (interquartile range), number, and percentage of patients. p < 0.05 is considered significant.
-*Significant in group II or group III in relation to group I.

Percentage blood loss was 23.8± 6.3 % in group I which is significantly high in comparison with 12.6 ± 7.3% in group II and 13.2 ± 7.2% in group III (Table 2). There was no significant difference between the three study groups as regard baseline Hb (before operation), post AHH Hb (after AHH), post transfusion Hb, postoperative Hb, and number and percentage of patients who received blood (Table 2).

There was no significant difference between the three study groups as regard cardiac output at baseline (after stabilization of patients in prone position). Cardiac output was significantly higher in group I in relation to group II and group III at 10, 15, 30, 45, and 60 min after start of AHH with results of 5.56 ± 1.32, 5.87 ± 1.31, 5.81 ± 1.21, 5.52 ± 1.15, and 5.32 ± 1.12 in group I in relation to 4.67 ± 1.35, 4.71 ± 1.46, 4.78 ± 1.15, 4.63 ± 1.31, and 4.51 ± 1.21 in group II and 4.63 ± 1.31, 4.67 ± 1.47 ,4.72 ± 1.16, 4.67 ± 1.08, and 4.56 ± 1.11 in group III at the previous times, respectively (Table 3).

CVP results were significantly high in group I in relation to group II and group III at 15, 30, 45, 60, and 90 min after start of AHH (Table 4).

Results of the MBP before induction of anesthesia in the three study groups were 96.2 ± 12.2, 94.2 ± 11.2, and 97.8 ± 10.5 respectively with no significant difference ($p > 0.05$). At 30, 45, 60, and 90 min and 2 and 3 h after start of CH, MAP significantly decreased in group II and group III in comparison with group I ($p < 0.05$) with no significant difference between group II and group III ($p > 0.05$) (Table 5). At 15 min after start of CH, MAP was significantly different in group II in comparison with group III (Table 5). Before induction of anesthesia, HR results were 81.6 ± 10.1, 82.4 ± 12.1, and 84.2 ± 7.9 in the three study groups, respectively ($p > 0.05$) (Table 6), with significant decrease in group II and group III in comparison with group I at 5, 10, 15, 30, 45, 60, and 90 min and 2 and 3 h after start of the CH ($p < 0.05$) and no significant difference between group II and group III at all the previous times ($p > 0.05$) (Table 6).

Table 3 Cardiac output expressed in l/min in the three study groups

	Group I (N = 18)	Group II (N = 20)	Group III (N = 19)	p value
Baseline	4.43 ± 1.14	4,52 ± 1.32	4.48 ± 1.21	0.820
5 min after start of AHH	5.21 ± 1.17	4.61 ± 1.18	4.58 ± 1.32	0.124
10 min after start of AHH	5.56 ± 1.32	4.67 ± 1.35*	4.63 ± 1.31*	0.038
15 min after start AHH	5.87 ± 1.31	4.71 ± 1.46*	4.67 ± 1.47*	0.013
30 min after start AHH	5.81 ± 1.21	4.78 ± 1.15*	4.72 ± 1.16*	0.008
45 min after start of AHH	5.52 ± 1.15	4.63 ± 1.31*	4.67 ± 1.08*	0.026
60 min after start of AHH	5.32 ± 1.12	4.51 ± 1.21*	4.56 ± 1.11*	0.042
90 min after start of AHH	5.31 ± 1.22	4.83 ± 1.21	4.72 ± 1.12	0.134
2 h after start of AHH	5.24 ± 1.13	4.42 ± 1.05	4.69 ± 1.36	0.026
3 h after start of AHH	5.11 ± 1.18	4.52 ± 1.17	4.58 ± 1.21	0.130

-Data are presented as mean ± SD. p < 0.05 is considered significant.
*Significant in group II or group III in relation to group I.

Table 4 Central venous pressure expressed in mmHg in the three study groups

	Group I (N = 18)	Group II (N = 20)	Group III (N = 19)	p value
Baseline	7.21 ± 1.12	7.32 ± 1.23	6.96.1 ± 1.42	0.402
5 min after AHH start	7.32 ± 1.23	7.21±1.12	7.30 ± 1.27	0.961
10 min after AHH start	7.87 ± 1.92	7.32 ± 1.30	6.99 ± 1.13	0.096
15 min after AHH start	8.31±1.52*	6.98 ± 1.43	6.77 ± 1.33	0.002
30 min after AHH start	8.68 ± 1.41*	7.01 ± 1.52	6.68 ± 1.48	0.0002
45 min after AHH start	8.94 ± 1.37*	6.92 ± 1.31	7.15 ± 1.19	0.0009
60 min after AHH start	8.21 ± 1.83*	6.56 ± 1.87	6.62 ± 1.25	0.0103
90 min after AHH start	7.78 ± 1.32*	7.31 ± 1.28	6.87 ± 1.19	0.0317
2 h after AHH start	7.53 ± 1.21	6.98 ± 1.29	7.08 ± 1.51	0.1902
3 h after AHH start	7.61 ± 1.18	7.15 ± 1.34	7.41 ± 1.19	0.6111

-Data are presented as mean ± SD. p < 0.05 is considered significant.
-*Significant in group I, in relation to group II and group III

Before operation, PT results in the three study groups were 12.9 ± 1.2, 13.4 ± 1.3 and 13.2 ± 1.3, respectively ($p > 0.05$). Thirty minutes after finishing AHH, PT results were 13.9 ± 1.2 in group I, 14.3 ± 1.2 in group II, and 14.1 ± 1.2 in group III ($p < 0.05$). PTT in group I was 29.1 ± 3.3 before operation in comparison with 28.7 ± 2.9 in group II and 30.1 ± 2.5 in group III ($p > 0.05$). Thirty minutes after finishing AHH, there was a significant increase in PTT in the three study groups (34.2 ± 4.2 in group I, 33.5 ± 5.4 in group II, and 35.2 ± 3.1 in group III) in comparison with the baseline in each group ($p < 0.05$), with no significant difference between the three study groups ($p > 0.05$) (Table 7). There was no significant difference between the three study groups as regard urine output at the end of the operation. It was 912 ± 211 in group I, 887 ± 227 in group II, and 895 ± 241 in group III ($p > 0.05$) (Table 7). There was no significant difference between the three study

groups as regard Na^+, K^+, and Cl^- concentrations ($p > 0.05$) (Table 7).

Discussion
CH has been used to reduce intraoperative bleeding and subsequently the need of homologous blood transfusion with all its dangers (Xuekang et al., 2015). However, a dry surgical field might require other approaches than just reduction of blood pressure as dry surgical field is also determined by the regional perfusion (Mohammad et al., 2014). Results of the present study determined that combination of AHH with CH by either remifentanil or magnesium sulfate was associated with reduction in estimated blood loss, intraoperative RBC transfusion units, and percentage of blood loss. Another point was raised in the work of Krengel et al. about the possibility of neurological damage at the level of the already compressed and compromised nerve roots with the prolonged application of CH (Krengel et al., 1993) which

Table 5 Mean arterial blood pressure expressed in mmHg in the three study groups

	Group I (N = 18)	Group II (N = 20)	Group III (N = 19)	p value
Baseline (before induction)	96.1 ± 12.2	94.2 ± 11.2	97.8 ± 10.5	0.619
5 min after AHH start	93.1 ± 11.3	88.7 ± 10.8	88.6 ± 11.7	0.242
10 min after AHH start	89.6 ± 10.9	87.0 ± 9.5	84.9 ± 10.1	0.439
15 min after AHH start	90.3 ± 11.1	68.6 ± 10.6*⁺	75.4 ± 9.8*	< 0.001
30 min after AHH start	89.8 ± 12.1	69.2 ± 11.4*	69.4 ± 10.6*	< 0.001
45 min after AHH start	86.7 ± 9.9	68.8 ± 10.3*	67.2 ± 11.1*	< 0.001
60 min after AHH start	87.9 ± 10.4	68.9 ± 9.1*	67.8 ± 9.9*	< 0.001
90 min after AHH start	85.6 ± 9.8	66.7 ± 11.1*	66.4 ± 10.2*	< 0.001
2 h after AHH start	86.7 ± 11.6	66.3 ± 10.7*	66.7 ± 12.5*	< 0.001
3 h after AHH start	84.4 ± 12.3	67.7 ± 12.2*	69.6 ± 11.6*	< 0.001

-Data are presented as mean ± SD. p < 0.05 is considered significant.
-*Significant in group II or group III in relation to group I
-⁺Significant in group II in relation to group III

Table 6 Heart rate in the three study groups

	Group I (N = 18)	Group I (N = 20)	Group III (N = 19)	p value
Baseline (before induction)	81.6 ± 10.1	82.4 ± 12.1	84.2 ± 7.9	0.587
5 min after AHH start	79.3 ± 12.2	63.3 ± 13.2*	68.2 ± 10.2*	0.0004
10 min after AHH start	76.2 ± 9.6	65.1 ± 10.4*	68.4 ± 11.2*	0.0016
15 min after AHH start	78.7 ± 8.9	65.9 ± 11.5*	67.1 ± 10.7*	0.0010
30 min after AHH start	75.4 ± 11.2	62.8 ± 9.4*	65.4 ± 9.5*	0.0059
45 min after AHH start	78.9 ± 10.5	61.4 ± 10.7*	63.2 ± 12.4*	< 0.0001
60 min after AHH start	76.3 ± 12.6	61.1 ± 8.3*	64.8 ± 13.3*	< 0.0001
90 min after AHH start	79.9 ± 9.3	62.7 ± 11.3*	66.4 ± 11.8*	< 0.0001
2 h after AHH start	80.2 ± 10.9	58.5 ± 12.5*	59.7 ± 10.6*	< 0.000
3 h after AHH start	81.3 ± 10.7	61.4 ± 9.9*	62.6 ± 9.3*	< 0.0001

-Data are presented as mean ± SD. p < 0.05 is considered significant.
-*Significant in group II or group III in relation to group I

was abolished with the use of AHH that improved the dehydrated situation resulting from fasting and improved reduction of tissue perfusion induced by CH (Mohammed et al., 2014).

Several works were done before to study the effect of combination of AHH and CH on blood loss and allogeneic blood transfusion. Among them, work done by Xuekang et al. (Xuekang et al., 2015) that compared between nitroglycerin and remifentanil in AHH combined with CH during intracranial aneurysm surgery detected reduced blood loss and allogeneic blood transfusion which runs with the results of the present study. But tachycardia that may associate the use of nitroglycerin may carry risk of increasing the cardiac oxygen consumption that may lead to serious damage of the myocardial system during hypotension. Another work done by Zhou et al. (Zhou et al., 2008) where nicardipine was used for induction of CH and gave the same results of the present

study as regard blood loss. Another study used nitroprusside versus remifentanil for conduction of CH in combination with AHH and gave the same results as the present study, but also, nitroprusside use carries the risk of serious side effects like severe hypotension and cyanide poisoning (Christian et al., 2001).

The use of magnesium sulfate in this study was associated with mild CH as the target of keeping the MAP between 60 and 70 mmHg was reached after 30 min of magnesium sulfate infusion which is against the results of Mohammad et al. who compared CH induced by remifentanil versus magnesium which may be due to the difference between the two study protocols as they used additional nitroglycerine infusion after 5 min of failure of getting the target of MAP; also, they did not use AHH in their study, which was used in the protocol of our study (Mohammad et al., 2014). The present study showed that magnesium sulfate is as effective as

Table 7 Coagulation profile, electrolytes, and urine output in the three study groups

	Group I (N = 18)	Group II (N = 20)	Group III (N = 19)	p value
PT before operation	12.9 ± 1.2	13.4 ± 1.3	13.2 ± 1.3	0.227
PT 30 min after AHH	13.9 ± 1.2[+]	14.3 ± 1.2[+]	14.1 ± 1.2[+]	0.0174
PTT before operation	29.1 ± 3.3	28.7 ± 2.9	30.1 ± 2.5	0.115
PTT30 min after AHH	34.2 ± 4.2[+]	33.5 ± 5.4[+]	35.2 ± 3.1[+]	< 0.001
Na$^+$ before operation	138.2 ± 7.9	140.2 ± 6.1	142.2 ± 5.4	0.079
Na$^+$ 30 min after AHH	137.3 ± 8.4	139.6 ± 5.4	141.3 ± 4.4	0.289
K$^+$ before operation	3.9 ± 1.2	3.7 ± 1.1	3.8 ± 1.3	0.595
K$^+$ 30 min after AHH	3.7 ± 1.2	3.5 ± 1.2	3.6 ± 1.2	0.611
Cl$^-$ before operation	103.2 ± 3.7	101.2 ± 5.3	104.2 ± 3.9	0.0524
Cl$^-$ 30 min after AHH	102.4 ± 5.9	103.4 ± 5.1	105.4 ± 5.6	0.121
Urine output at the end of operation	912 ± 211	887 ± 227	895 ± 241	0.728

-PT prothrombin time, PTT partial thromboplastin time, Na$^+$ sodium, K$^+$ potassium, Cl chloride, CVP central venous pressure. Data are presented as mean ± SD.
-p < 0.05 is considered significant.
-[+]Significant for comparison with the baseline inside each group

remifentanil regarding inducing CH except that the MAP target (between 60 and 70 mmHg) was reached with the use of magnesium sulfate after 30 min of infusion with only significant difference between both drugs at 15 min, but after that, the same range of CH was achieved. Magnesium sulfate is a non-competitive NMDA receptor agonist used as a vasodilator to control hypertension and thus reducing the blood loss during surgery. This vasodilatation occurs through direct action, as well as indirectly by sympathetic blockade and inhibition of catecholamine release (Ahmed et al., 2019), while remifentanil, as a potent ultra-short-acting μ-opioid receptor agonist, has moderate advantage as antihypertensive through the suppression of the autonomic or central nervous system, inhibition of catecholamine release during operation specially on adrenaline, dilatation on blood vessels through endothelial-dependent release of prostacyclin, and endothelial-independent dilatation on blood vessels through voltage-dependent calcium channel (Schuttler et al., 1997). Induced vasodilation with the use of either remifentanil or magnesium sulfate with different mechanisms was responsible of the significant difference of CVP between group II and group III in comparison with group I at some intervals through reduction of the venous return.

For monitoring of the COP, the use of transesophageal Doppler (TED), which is a minimally invasive technique, gave the chance of monitoring hemodynamic state and follow-up of the cardiac condition during and after AHH away from the use of the invasive methods like pulmonary artery catheters with their side effects. Several previous works used TED as the sole COP monitor; among them, work of Hussein et al. that detected a role of TED to maintain fluid management during liver transplantation (Saudi Journal of Anesthesia, 2011). A significant increase in COP that occurred in group I at several study intervals after AHH in the present study was due to the volume loading compensated with CH induced in group II and group III. CH was associated with the reduction of HR in group II and group III through different mechanisms with either remifentanil or magnesium sulfate.

HR significantly decreased in both groups after 15 min. Reduction of the HR associated with the use of remifentanil may be possibly due to the associated excitation of the vagus nerve and the inhibition of sinus node regulated by the opioid receptor agonist (Xuekang et al., 2015), while the reduction of the HR associated with the use of magnesium sulfate was due to slowing of the atrial rate. Results of the present study run with the results of the work of Xuekang et al. as regard bradycardia associated with the use of remifentanil (Xuekang et al., 2015). There was non-significant bradycardia with the use of remifentanil after 10 min in comparison with the control group and magnesium sulfate group. This was different from the results of the work of Puri G et al. (Puri et al., 1998) that detected initial tachycardia due to the difference in the protocols of the study as magnesium sulfate was given during the work of Puri G et al. before tracheal intubation, and they returned this initial non-significant tachycardia to the sympathetic stress response that was attenuated by the endotracheal intubation, while in the present study, magnesium sulfate was given after tracheal intubation. Results of the work by Mohammad et al. (Mohammad et al., 2014) were different from the results of this study as nitroglycerin was used to reach the target of MAP with its known tachycardic effect, and also, AHH was not used that can modestly dilate vessel capacity and maintain a normal CVP during the period of CH. Those reasons might compensate the bradycardic effect of remifentanil and magnesium sulfate in Mohammad et al.'s work (Mohammad et al., 2014).

The use of AHH in the present study gave the advantages of improving microcirculation and prevented capillary leakage, but AHH alone inevitably could lead to increased cardiac preload with increased myocardial oxygen consumption and pulmonary capillary leakage (Jiao et al., 2009), so protocol of the present study used the combination of AHH with CH that could efficiently expand the plasma volume and possessed the characteristics of hematology that could improve the microcirculation and prevent the pulmonary capillary leakage. Subsequent reduction of hematocrit to 25% could offer the maximum amount of oxygen transport, decreasing blood viscosity that improved tissue blood perfusion and subsequently improved tissue oxygenation. In the present study, the AHH was induced with hydroxyethyl starch based on older studies that gave efficient results as volume expander more than sodium lactate as two thirds of the volume of sodium lactate would move out of the blood vessels with expansion capacity only contributing to 20% of the expanding volume (Guanglei et al., 2011).

There was significant increase of PT inside each group after finishing AHH in comparison with the level before operation. Although PT difference was significant, it was within the normal range so did not lead to difficulty in hemostasis. PT is specific for evaluation of the extrinsic coagulation pathway that is sensitive to reduction of factors II, V, and X (Guanglei et al., 2011). PTT was significantly increased in all study groups after AHH with hydroxyethyl starch infusion. It was a reflection of decreased plasma concentrations of coagulation factor VIII/ von Willebrand factor (vWF) which are determinants of the intrinsic pathway of coagulation that is reflected by PTT measurement (Sibylle & Kozek, 2005). Hydroxyethyl starch solutions have been consistently

shown to decrease the circulating plasma concentrations of coagulation factor III and vWF by up to 80% in healthy volunteers and in patients even when used below the recommended daily amount of 25 to 50 ml/kg (Sibylle & Kozek, 2005). But this increase of the PTT in the present study was not reflected by significant blood oozing from the operative field, or by difficulty in hemostasis.

Conclusion

The present study detected that the combination of AHH with controlled hypotension induced by remifentanil or magnesium sulfate during operations of spine fusion was associated with reduction in estimated blood loss, total volume of packed red blood cells (PRBC) transfused. There was no significant difference between hemodynamic parameters with the use of remifentanil or magnesium sulfate except that MBP results were significantly high with magnesium sulfate at 15 min after drug infusion. There was significant increase in PT and PTT after AHH that was not reflected by significant blood oozing from the operative field or by difficulty in hemostasis.

Abbreviations
AHH: Acute hypervolemic hemodilution; ANH: Acute normovolemic hemodilution; CH: Controlled hypotension; TED: Transesophageal Doppler; COP: Cardiac output; IV: Intravenous; CVP: Central venous pressure; HCT: Hematocrit; HB: Hemoglobin; NABP: Noninvasive arterial blood pressure; ECG: Electrocardiogram; OR: Operation room; O_2 SAT: Oxygen saturation; ET CO_2: End-tidal concentration of carbon dioxide; PRBCS: Packed red blood cells; MAP: Mean arterial pressure; HR: Heart rate; PT: Prothrombin time; PTT: Partial thromboplastin time; vWf: von Willebrand factor

Authors' contributions
KME: OR design of the work, the acquisition analysis, interpretation of data, creation of new software used in the work, and drafting and revision of the work. IAN: the acquisition analysis, interpretation of data, creation of new software used in the work interpretation of data, and drafting and revision of the work. EMK: the acquisition analysis drafted and revised the work. The authors have read and approved the manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was done after obtaining approval of Dr Sulaiman Alhabib hospital (Riyadh, Saudi Arabia) institutional review board (IRB) (Rn: ECAOO4/18) on 13/11/2018. Informed written consent was taken from all patients included.

Consent for publication
Informed written consent was taken from all patients included.

Competing interests
The authors declare that they have no competing interests.

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