

Effect of acute hypervolemic hemodilution of 6% hydroxyethyl starch 130/0.4 on the EC₅₀ of propofol at two clinical endpoints in patients

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Received September 18, 2014; Accepted June 22, 2015

DOI: 10.3892/etm.2015.2886

Abstract. Preoperative acute hypervolemic hemodilution (AHHD) is a technique used in anesthesia to reduce the number of blood cells lost during intraoperative bleeding. The aim of the present study was to evaluate the effect of the hypervolemic hemodilution of 6% hydroxyethyl starch 130/0.4 on the EC₅₀ of propofol at two clinical endpoints. A total of 20 patients undergoing AHHD following epidural anesthesia were studied, and 20 patients who did not receive hemodilution were used as a control group. All patients were American Society of Anesthesiologists grade I, aged 20-40 years and undergoing hip arthroplasty surgery. In the AHHD group, 10 ml/kg lactated Ringer's solution was infused over 20 min at the same time as the epidural test dose. The infusion was followed by the infusion of 6% hydroxyethyl starch 130/0.4 over 30 min. Patients in the control group received 10 ml/kg Ringer's solution over 50 min. Propofol was then delivered by a Diprifusor target-controlled infusion. The predicted blood and effect-site propofol concentrations were recorded at loss of consciousness (LOC) and return of consciousness (ROC). Probit analysis was used to estimate the values for predicted blood and effect-site concentrations at the two clinical endpoints. The results showed that the potency of propofol was decreased during AHHD. Compared with the controls, the predicted blood and effect-site concentrations of propofol at LOC were higher in patients of the hemodilution group, resulting in higher EC₅₀ values (P=0.001 and 0.025, respectively). At ROC, the effect-site EC₅₀ was 2.9 µg/ml [95% confidence interval (CI), 2.8-3.0] in hemodilution patients and 2.5 µg/ml (95% CI, 2.2-2.6) in control patients (P=0.001). With AHHD, the LOC time was significantly longer and the

propofol dose was higher, while ROC times were comparable. In conclusion, AHHD increases the requirement for propofol at LOC and prolongs LOC time. Patients with AHHD recovered consciousness at higher effect-site concentrations of propofol. Thus, the induction dose of propofol should be increased during AHHD.

Introduction

Preoperative acute hypervolemic hemodilution (AHHD) has been recommended as a cost-effective method of conserving blood, which aims to avoid or reduce homologous blood transfusion during surgical procedures (1). AHHD was administered through fast infusion of crystalloid or colloids, which is commonly 20-30% of blood volume after anesthesia. The degree of hemodilution depends on the extent of the capacity of the blood vessels' dilation (1). Fluid dynamics showed that the volume expansion rate of AHHD can be improved after anesthesia inducing vascular dilation; or according to the Starling Rule, most of the infused fluid is transferred into the extravascular space, decreasing the volume expansion rate and at the same time posing a risk for interstitial edema (2). Propofol is frequently used for general anesthesia due to its rapid onset and short-acting efficacy (2). Previous studies have found that changes in blood volume, regional organ blood flow, blood chemistry, body fluid distribution and hemodynamics (3-7) can alter the pharmacokinetic and pharmacodynamic profile of propofol (8,9). In addition, studies have indicated that hemodilution can increase the hypnotic potency of propofol in humans as a result of a significant increase in the unbound propofol plasma concentration and an increased cardiac output causing changes in compartment volumes and drug delivery to the effect-site (10,11). Other studies, however, have found the opposite (9,12). The aim of the present study was to determine the effect of AHHD on the EC₅₀ of propofol at loss of consciousness (LOC) and return of consciousness (ROC) in patients under combined propofol general and epidural anesthesia. The primary objective was to determine the EC₅₀ at the times of LOC and ROC, as well as the dose requirement of propofol, whereas the secondary objective was to determine the LOC and ROC times during the induction and recovery of anesthesia, with or without AHHD.

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Key words: acute hypervolemic hemodilution, propofol, anesthesia

Patients and methods

Patient recruitment. This study was approved by the Ethics Committee of the First Affiliated Hospital of the College of Medicine (Zhejiang, China) and written informed consent was obtained from each patient. The inclusion criteria were patients with American Society of Anesthesiologists classification I, aged 20–40 years and undergoing elective hip arthroplasty surgery. The exclusion criteria were a body mass index of <18 or >26 kg/m², medical conditions that could affect consciousness levels, such as stroke, stupor or dementia, patients with cardiac or respiratory diseases, abnormalities of hepatic or renal function or hypertension. None of the patients suffered any disease or had received sedative or opioid drugs recently. Those with anemia (hemoglobin concentration <12 g/dl), bleeding diathesis, hypersensitivity to amide local anesthetics, previous lumbar surgery and chronic back pain were also excluded. The patient characteristics are shown in Table I. The subjects were randomly assigned to either the control group (n=20) or the AHHD group (n=20). Randomization was performed by the statistician according to a random number generated by the computer. Following randomization, an opaque, sealed, sequentially numbered envelope containing the regimen of anesthesia and fluid was prepared for each participant according to the study protocol.

Procedures. The patients were not premedicated prior to anesthesia. On arrival in the operating theater, a catheter was inserted in the radial artery to enable the continuous monitoring of arterial blood pressure and for sample collection. One intravenous cannula was inserted into a large forearm vein for the infusion of anesthetics and fluid.

Once all the monitoring devices had been connected, the patients were arranged in the left lateral decubitus position, and an epidural catheter was inserted through a 17-gauge Tuohy needle (Zhejiang Haisheng Medical Device Co. Ltd., Shaoxing, China) at L₂–L₃ and advanced 3–4 cm. Once the catheter had been aspirated to confirm that the placement was not intrathecal or intravenous (IV), the catheter was secured and the patients were returned to a supine position. A total of 3 ml lidocaine solution (2%; Shanxi Jinxin Shuanghe Pharmaceutical Co. Ltd., Jinxin, China) was injected through an epidural catheter as a test dose. Five minutes later, 15 ml ropivacaine (Naropin®; AstraZeneca, Sodertalje, Sweden) without epinephrine was administered slowly through the catheter at a rate of 1 ml/sec. The AHHD patients were given a loading dose of 10 ml/kg Ringer's solution (Pharmacia, Shanghai, China) over 20 min, at the same time as the epidural test dose. This infusion was followed by 6% hydroxyethyl starch 130/0.4 (Fresenius SE & Co. KGaA, Bad Homburg, Germany) over a period of 30 min. To simulate the conditions of the AHHD group prior to the induction of anesthesia to the greatest extent possible, patients in the control group were placed in identical ambient conditions and evenly infused with ~5 ml/kg lactated Ringer's solution via a cubital vein cannula.

During the study, electrocardiograms, invasive arterial blood pressure, pulse oxygen saturation and partial pressure of end-tidal carbon dioxide were continuously monitored. The patients received oxygen through facemasks at a flow rate of 3 l/min. When a patient suffered dyspnea, appropriate

respiratory support was supplied. Hypotension was defined as a reduction in systolic blood pressure by >30% of the pre-anesthetic value or a systolic blood pressure of <90 mmHg. Patients with hypotension received treatment of 6 mg IV ephedrine. Bradycardia was defined as a heart rate (HR) of <55 bpm and was treated by administering 0.5 mg IV atropine. Hematocrit (Hct) and hemoglobin concentration values were determined with a blood i-STAT analyzer (i-STAT Corp., East Windsor, NJ, USA) prior to and during the study. Total plasma protein and albumin were also measured with an automatic biochemical analyzer (Hitachi 7600; Hitachi Co. Ltd., Tokyo, Japan) in the First Affiliated Hospital College of Medicine (Zhejiang, China) central laboratory.

Following infusion, a target-controlled infusion (TCI) of propofol was administered to all patients using a Diprifusor TCI pump (Graseby 3500 pump; Graseby Medical Ltd., Watford, UK), incorporating a three-compartment pharmacokinetic algorithm of the Marsh pharmacokinetic model (13). This system shows the predicted blood and effect-site (an estimate of the drug concentration at its site of action) propofol concentrations. Subsequent to entering the age, weight and gender of the patient, the TCI was started to achieve a target plasma concentration of propofol of 1.5 µg/ml. The plasma concentration was selected rather than the effect-site concentration TCI, as the propofol plasma concentration equilibration with the hypothetical effect-site compartment predicted by the Diprifusor was likely to have required 10 min. The target concentration was increased in increments of 0.5 µg/ml every 30 sec until LOC occurred, and the target concentration was then set to zero to discontinue the infusion; however the Diprifusor remained switched on. The time to ROC following the discontinuation of the infusion was determined by the response to the name of the patient being loudly called at 30-sec intervals. The time to LOC, predicted plasma and effect-site propofol concentrations and propofol dose requirements for LOC were recorded. Following the discontinuation of the infusion, the ROC time and predicted plasma and effect-site concentrations of propofol at ROC were recorded. On completion of the ROC evaluation, analgesia was assessed bilaterally in the anterior axillary line by pinpricking using a short beveled 25-gauge needle. Analgesia was defined as the inability to detect a sharp pinprick. The maximum cephalad level of analgesia (peak analgesia level) was then recorded for all patients.

Study design. When a patient was recruited according to the inclusion criteria, the statistician distributed an opaque, sealed, sequentially numbered envelope to the anesthesiologist in the trials the day before the study, which contained the regimen of anesthesia and the fluid. Both the anesthesiologist and investigator were blinded to the regimen of the experiment for the specific patients. All of the patients and the personnel involved, including the study designer, investigator and statistician, were unaware of the subject assignments until the data analysis was complete.

Statistical analysis. Quantitative variables are presented as the mean ± standard deviation or median with interquartile range. Categorical variables were analyzed using χ^2 or Fisher exact tests. Continuous variables were assessed with the Mann-Whitney U

Table I. Baseline patient characteristics.

Characteristic	AHHD group, n=20	Control group, n=20	P-value
Male/female, n/n	9/11	10/10	1.000
Age ^a , years	33±5	32±7	0.500
Weight ^a , kg	59±10	61±11	0.600
Height ^a , cm	164±7	166±8	0.433
BMI ^a , kg/m ²	21.9±3.0	22.1±3.0	0.874
Maximum cephalad level of analgesia	T ₁₀ (T ₉ -T ₁₁)	T ₁₀ (T ₉ -T ₁₁)	0.717

^aData are presented as the mean ± standard deviation. Maximum cephalad level of analgesia is presented as the median (interquartile range). BMI, body mass index; AHHD, acute hypervolemic hemodilution.

Table II. Laboratory parameters of patients in the AHHD and control groups before and after AHHD.

Parameter	Before AHHD	After AHHD
Hemodilution group		
Hb (g/l)	133.2±17.8	104.1±15.7 ^{a,b}
Hct (%)	39±5	31±1 ^{a,b}
TPP (g/l)	70.7±5.2	53.0±6.4 ^{a,b}
Alb (g/l)	45.4±3.4	34.7±3.5 ^{a,b}
Control group		
Hb (g/l)	126.7±14.6	122.9±16.1
Hct (%)	37±4	36±5
TPP (g/l)	69.8±7.9	67.4±8.1
Alb (g/l)	43.9±4.9	42.1±4.3

Data are presented as the mean ± standard deviation. ^aP<0.001 compared with before AHHD; ^bP<0.001 compared with the control group. Hb, hemoglobin; Hct, hemotocrit; TPP, total plasma protein; Alb, albumin; AHHD, acute hypervolemic hemodilution.

or Student *t*-tests depending on the distribution of the data. Repeated measures analysis of variance was used to compare the difference between the times in the two groups. A P-value of <0.05 was considered to indicate a statistically significant difference and was adjusted for multiple comparisons when appropriate. A quantal response model (probit analysis) was used to calculate the EC_{0.5}, EC₅₀ and EC₉₅ at each endpoint based on the predicted plasma and effect-site propofol concentrations. The following software packages were used to perform the analysis: Excel 2000 (Microsoft Corp., Redmond, MA, USA) and SPSS software version 10.0 (SPSS, Inc., Chicago, IL, USA). Since the EC₅₀ changes of propofol at the time of LOC during AHHD had not been previously examined, a convenient sample size of 20 patients was selected. The statistically significant decline in the value of the EC₅₀ of propofol at LOC indicated that the present study was adequately powered.

Results

Patient characteristics and laboratory parameters. No statistically significant differences were found between the

two groups in terms of age, body weight, height or maximum cephalad level of analgesia. In the AHHD group the Hct levels and hemoglobin concentration decreased from 39 to 31% and from 133.2 to 104.1 g/l, respectively. Compared with the preoperative values, the postoperative levels of hemoglobin, Hct, total protein and albumin were found to have decreased significantly in the AHHD patients but were observed to have remained stable in the control group. Significant differences in the hemoglobin, Hct, total protein and albumin levels were found between the two groups following the AHHD (Table II).

Primary objectives. Compared with the controls, the predicted plasma and effect-site concentrations of propofol in the AHHD patients at LOC were higher, resulting in higher EC₅₀ values (P=0.001 and 0.025, respectively; Table III). At ROC, the effect-site EC₅₀ was 2.9 µg/ml [95% confidence interval (CI), 2.8-3.0] in the AHHD patients and 2.5 µg/ml (95% CI, 2.2-2.6) in the control patients (P=0.001; Table IV); however, no significant difference was observed between the AHHD and control patients in predicted blood EC₅₀ (P=0.066; Table IV).

Secondary objectives. The LOC time was significantly longer (4.2 min for the AHHD patients and 3.6 min for the controls, P=0.04) and the propofol requirement was significantly higher (2.1 mg/kg for the AHHD patients and 1.8 mg/kg for the controls, P=0.008) in the AHHD group compared with the control group (Table III); however, no significant difference was found between the two groups with regard to the ROC time (4.0 min for AHHD patients and 3.4 min for the controls, P=0.08).

HR and blood pressure. A significant difference in HR was found between the AHHD and control groups at the post-AHHD, LOC and ROC time-points, with significantly higher values in the AHHD group. By contrast, the blood pressure values were comparable between the two groups (Fig. 1).

Propofol potency. As shown in Figs. 2 and 3, the curves for the probability of LOC and ROC versus the predicted blood and effect-site propofol concentrations were shifted to the right in a parallel fashion for the AHHD group, which indicated that the potency of propofol was decreased in patients undergoing AHHD.

Table III. Propofol concentration at the time of LOC and LOC time.

Parameter	Hemodilution group, n=20	Control group, n=20
Predicted blood concentration, $\mu\text{g/ml}$		
EC _{0.5}	4.4 (3.9-4.7)	4.0 (3.3-4.3)
EC ₅₀	5.4 (5.1-5.6) ^a	4.8 (4.5-5.0)
EC ₉₅	6.6 (6.3-7.1) ^b	5.8 (5.5-6.6)
Effect-site concentration, $\mu\text{g/ml}$		
EC _{0.5}	1.8 (1.4-2.0)	1.5 (1.1-1.7)
EC ₅₀	2.5 (2.2-2.6) ^b	2.1 (1.9-2.3)
EC ₉₅	3.5 (3.3-3.9) ^b	3.0 (2.8-3.5)
Propofol requirements at LOC, mg/kg	2.1 \pm 0.4 ^b	1.8 \pm 0.4
LOC time, min	4.2 \pm 0.8 ^b	3.6 \pm 1.0

Values in parentheses are 95% confidence intervals. Propofol requirements and LOC times are presented as the mean \pm standard deviation. ^aP<0.01 and ^bP<0.05 compared with the control group. LOC, loss of consciousness.

Table IV. Propofol concentration at the time of ROC and ROC time.

Parameter	Hemodilution group, n=20	Control group, n=20
Predicted blood concentration, $\mu\text{g/ml}$		
EC _{0.5}	1.5 (1.2-1.7)	1.4 (1.0-1.6)
EC ₅₀	2.2 (2.0-2.3)	2.0 (1.8-2.1)
EC ₉₅	3.2 (2.9-3.6)	2.9 (2.6-3.3)
Effect-site concentration, $\mu\text{g/ml}$		
EC _{0.5}	2.2 (1.9-2.4)	1.9 (1.4-2.1)
EC ₅₀	2.9 (2.8-3.0) ^a	2.5 (2.2-2.6)
EC ₉₅	3.8 (3.6-4.2) ^b	3.3 (3.1-3.7)
ROC time, min	4.0 \pm 1.3	3.4 \pm 1.0

Values in parentheses are 95% confidence intervals. ROC times are presented as the mean \pm standard deviation. ^aP<0.01 and ^bP<0.05 compared with the control group. ROC, recovery of consciousness.

Discussion

To the best of our knowledge, the present study is the first to investigate the effect of AHHD of 6% hydroxyethyl starch 130/0.4 on the EC₅₀ of propofol in patients during the induction of anesthesia using a TCI technique at the two clinical endpoints of LOC and ROC. In this study, the effect-site EC₅₀ of propofol at LOC and ROC in patients undergoing hemodilution was increased by 19 and 16%, respectively, compared with the controls. The data also showed that, compared with the control group, the LOC time was significantly longer and the propofol requirement was significantly higher in the hemodilution group, indicating a significant reduction in propofol potency with AHHD. It is possible that the greater propofol requirement with AHHD was due to the markedly increased blood volumes associated with acute colloidal solutions of 6% hydroxyethyl starch 130/0.4. In the present study, the Hct in the AHHD group decreased to a level of 25-40% following the infusion of 6% hydroxyethyl starch 130/0.4 at a rate of 20 ml/kg over a period of 30 min. Kumar *et al* (14)

demonstrated that hypervolemic haemodilution caused a reduction in the level of Hct to ~30% following the infusion of 20 ml/kg gelofusine (4%), which was consistent with the finding in the present study. The half-life of 6% hydroxyethyl starch 130/0.4 is 4-6 h, and the starch can maintain the state of hemodilution for a long duration. During hemodilution, the blood viscosity is decreased and the cardiac output and velocity of blood flow are increased; thus, the distribution of drugs from the blood (the central compartment) to the peripheral tissues, including the tissues with a rich blood supply (shallow peripheral compartment) and the tissues with an inadequate blood supply (deep peripheral compartment) is greater than that from the peripheral compartment to the central compartment. Consequently, the amount of drug delivered to the brain (effect-site) is relatively small, leading to a reduction in the propofol sedation/hypnotic effect (12). As a result, the increase in the distribution of propofol during hemodilution causes the reduction in the propofol concentration in the plasma. The propofol dose should therefore be increased to achieve the same depth of sedation/anesthesia.

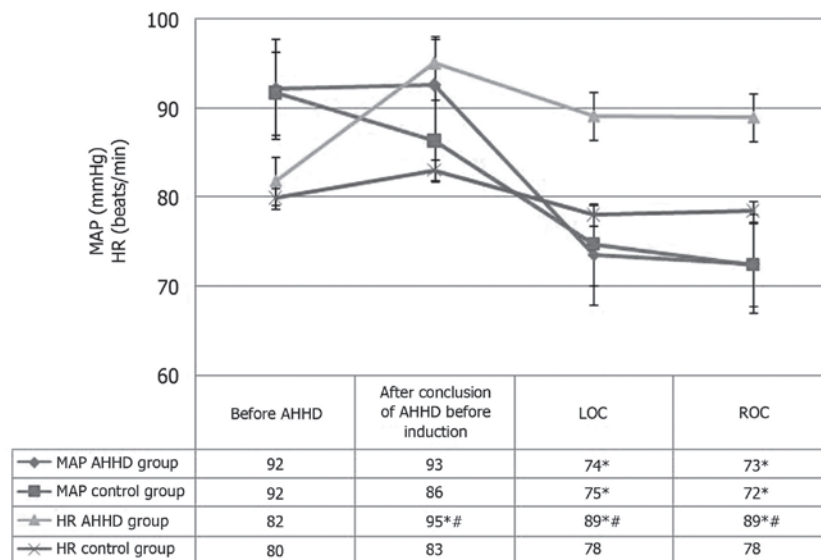


Figure 1. MAP and HR before and after AHHD, at the time of LOC and at the time of ROC in the AHHD and control groups. *P<0.001 compared with before AHHD, #P<0.01 compared with the control group. MAP, mean arterial pressure; HR, heart rate; AHHD, acute hypervolemic hemodilution; LOC, loss of consciousness; ROC, recovery of consciousness.

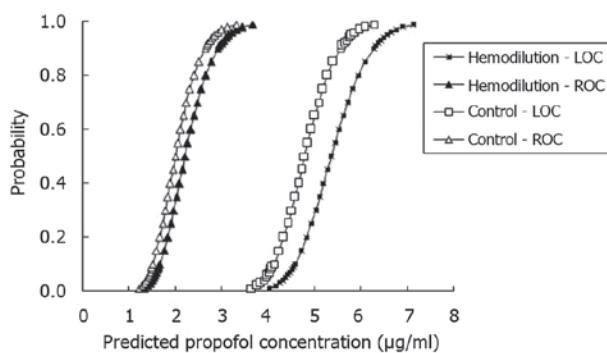


Figure 2. Predicted plasma concentration of propofol vs. probability of LOC and ROC in the two groups. LOC, loss of consciousness; ROC, recovery of consciousness.

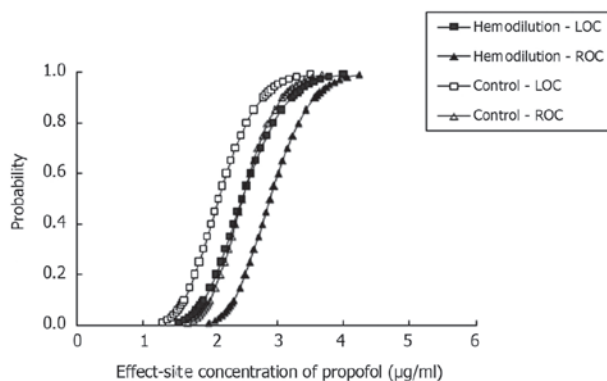


Figure 3. Predicted effect-site concentration of propofol vs. probability of LOC and ROC in the two groups. LOC, loss of consciousness; ROC, recovery of consciousness.

Another relevant factor is that hemodilution is considered to cause a higher plasma clearance of propofol, which is associated with a lower plasma concentration of propofol (15). Propofol

is mainly metabolized through the liver, and most propofol metabolites are cleared through the kidneys. As is well known, such factors as the hepatic blood supply, drug uptake rate and the activity of liver metabolic enzymes determine the propofol hepatic metabolism. Hypervolemic hemodilution resulted in an augmentation of the blood volume, thereby increasing the flow of blood to the liver, and then consequently increasing the hepatic metabolism of propofol. By contrast, propofol reduces cardiac output and liver perfusion (16,17). Previous studies have indicated that, during the induction of anesthesia with propofol, liver blood flow is increased or remains unaltered (18,19). In 2001, Nollert *et al* (20) showed in a pig study that both liver blood flow and Hct were independent of influential factors of hepatic metabolism function. Furthermore, Tang *et al* (12) reported that the whole-body clearance and elimination-rate constant of propofol were decreased significantly in the hemodilution group. The present study showed that the LOC time was significantly prolonged in the AHHD group, which may have been associated with the aforementioned factors. Propofol is a highly fat-soluble intravenous anesthetic that is generally found in combination with plasma proteins, with a combination rate as high as 96-98% and only a small amount of propofol existing in the free form (21). The activity of drugs depends on the degree of integration with the plasma protein, as only free drugs are active; therefore, AHHD will have a far greater impact on the effect of drugs exhibiting a high degree of plasma protein binding. For intravenous and liver enzyme unrestricted drugs, an increased non-associative fraction will not affect the whole-body clearance, due to the high removal efficiency of the drug; this means that the protein-binding rate does not restrict their clearance. On the contrary, for the liver enzyme restricted drugs, an increase in the unconjugated drug therefore gives rise to a short, even, persistent rise in the concentration of unconjugated drug in the plasma, which has important clinical significance for drugs such as propofol with a narrow therapeutic window (22). In the present study, the total plasma protein and albumin levels

were both lower in the AHHD group than those in the control group following AHHD, with decreases of 25 and 22%, respectively. Therefore, the unbound fraction and concentration of propofol increased in the plasma during hemodilution, which could have resulted in an enhanced effect of propofol. Previous studies have demonstrated that the potency of muscle relaxants is increased during AHHD, which is likely due to the reduction in plasma protein conjugation and an increase in the free-drug concentration (23,24). In the current study, during the period of hemodilution, the impact of the increase in plasma distribution and clearance overcame the impact of the increase in free drug concentration on the hypnotic effects of propofol.

In contrast to the findings in the present study, Dahaba *et al* (25) showed that the hypnotic potency of propofol was increased and the LOC time was short in hemodilution patients. The removal of blood during the hemodilution may be one of the reasons for the two inconsistent results. In the study by Dahaba *et al* (25), hypovolemia was achieved by bloodletting 20 ml/kg and then inputting the same volume of 6% hydroxyethyl starch 130/0.4 in 0.9% NaCl. In the present study there was no bloodletting prior to hemodilution; however, patients were administered an equal quantity of 6% hydroxyethyl starch 130/0.4 in 0.9% NaCl. As a result, the concentration of plasma protein decreased due to dilution without plasma protein loss. Thus, the total plasma protein remained unchanged, and the total combined propofol in the plasma was also unchanged. It is considered likely that the concentration of the unbound drug did not change the hypnotic potency of propofol.

Previous studies that have investigated the effect of cardiac output on the plasma drug concentration of propofol have shown that cardiac output is inversely proportional to the plasma concentration of propofol (26-28). The present study found that the HR increased by 16% compared with that prior to hemodilution, and the mean arterial pressure (MAP) remained unchanged. Following the induction of anesthesia in the AHHD group, the HR increased by 14%, with no change in the MAP, compared with the control group. Therefore, it can be inferred that the propofol plasma concentrations were decreased during AHHD.

It must be emphasized that the aforementioned EC₅₀ values of this study were based on the calculated plasma and effect-site concentrations of propofol by the pharmacokinetic models installed in the TCI machine. Although a previous study showed that the pharmacokinetics of propofol could be changed by hemodilution (8), the determination of the blood drug concentration of propofol was not performed in the present study, as the TCI device was available for the clinical practice of anesthesia with a relatively reliable performance (29). The predicted concentrations in the blood and effect-site that were shown in real time provided the clinical anesthetologist with a useful reference during anesthesia (30,31).

The concept of a minimum alveolar concentration (MAC) for inhalational anesthetics is well known and widely applied in the clinic to guarantee adequate anesthesia for patients from intraoperative awareness (32). A similar concept applying to IV anesthetics is known as the median effective concentration (EC₅₀) (33). This is a practical clinical concept, as it tends to predict the concentrations of the anesthetic agent both in the

plasma and in the effect-site simulated by different pharmacokinetic models (32-34). The present results are reported as the predicted effect-site concentrations, since this is the physiologically relevant variable. The MAC and effect-site concentrations of inhaled and IV anesthetics, respectively, can be expressed for various endpoints, including movement, consciousness, recall or hemodynamic responses. In this case, the endpoints were loss and recovery of consciousness.

A limitation of the present study was that it would have been possible to obtain the actual EC₅₀ at LOC and ROC if the blood concentrations of propofol had been measured. Administering the normal saline-based 130/0.4 hydroxyethyl starch with more chloride than balanced hetastarch is likely to have affected the acid-base and electrolyte balance in the patients (35). Furthermore, in the present study, the effect of the two types of 6% hydroxyethyl starch on the propofol requirement at LOC and the LOC time was not compared.

In conclusion, the predicted effect-site EC₅₀ of propofol at LOC and ROC was increased in patients during AHHD of hydroxyethyl starch 130/0.4, which indicated that the potency of propofol decreased and the target concentration of propofol required to produce a comparable hypnotic effect was increased when using the TCI system for propofol during AHHD.

Acknowledgements

The study was supported by the Qianjiang Talents Project of the Technology Office in Zhejiang (no. 2012R10033) and the Clinical Scientific Research Funds of Zhejiang Provincial Medical Association (no. 2012ZYC-A72), China.

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