의학과 석사학위논문

간이식 환자에서
혼합혈액의 급속 수혈

2014년 **7**월

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Abstract

Background

There is little information regarding the use of rapid infusion device and blood mixture prefilled in the reservoir. The current study aimed at describing acute biochemical changes following rapid transfusion of blood mixture during liver transplantation.

Methods

Ten adult liver recipients treated with massive transfusion during hepatic dissection were sequentially enrolled. Blood mixture composed of red blood cell, fresh frozen plasma and normal saline (4 units: 4 units: 800 ml) was prepared in the reservoir of the rapid infusion device. During massive hemorrhage, 300 ml bolus of blood mixture was repeatedly transfused at a rate of 500 ml/min. Blood samples were gathered during the 1st, 3rd, 5th and 7th bolus transfusions. For each transfusion, three sequential blood samples were taken from the arterial line, blood mixture and the arterial line, respectively, before, during and after transfusion. Changes of pH, base excess, hematocrit and concentrations of potassium, sodium, ionized calcium, glucose and lactate were measured and analyzed.

Results

Significant increase of potassium and decrease of hematocrit were observed during the former and latter half of transfusion, respectively. Hypocalcemia

and acidosis needed immediate corrections after each bolus transfusion. Significant changes were observed for sodium, glucose and lactate after transfusion of one reservoir volume, however of little clinical importance.

Discussion & Conclusions

Acute hypocalcemia and acidosis require prompt corrections during rapid transfusion. Acute hyperkalemia and anemia as well as delayed hyperglycemia may be potential risks associated with repeated infusions of blood mixture. We conclude that rapid transfusion of blood mixture is substantially safe only if aggressive intraoperative care be given during liver transplantation surgery.

Keywords : Liver transplantation, massive transfusion, rapid transfusion

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Introduction

Massive hemorrhage is not uncommon during dissection period of liver transplantation. Anesthetic guidelines for liver transplantation emphasize that large amount of blood products should be prepared to cope with acute and massive hemorrhage [1]. The use of rapid infusion device with a reservoir is also recommended for massive transfusion because standard methods of transfusion are unfit for rapidly infusing large amounts of warm blood. A 3 L-sized reservoir is filled with blood mixture composed of packed red blood cell (RBC), fresh frozen plasma (FFP), and normal saline at a ratio of 1 unit, 1 unit, and 200-250 ml, to constitute a hematocrit of 25-30%. Intravascular volume, hematocrit level, and adequate coagulation can be provided with less effort by the use of rapid infusion device and appropriate blood mixture [2].

Anesthetic concerns during massive transfusion include various acute complications like hypervolemia, hypothermia, metabolic acidosis, hypocalcemia and hyperkalemia. The occurrence of these complications is closely related with the speed of transfusion, patient characteristics and the typical biochemical properties of blood products. Liver transplantation recipients may be particularly susceptible to these adverse effects because transfusion is frequently massive; reduced hepatic function is less capable of metabolizing citrate in the blood products, leading to a more severe acidosis

and hypocalcemia [3, 4]; and increased level of potassium in irradiated RBC may exacerbate hyperkalemia [5]. Massive transfusion of saline-mixed blood can also cause rapid increase of plasma sodium resulting in central pontine myelinolysis in a chronic hyponatremia patient [6].

Previous reports addressing complications related with massive transfusion for the most part dealt with the use of unadulterated packed RBCs. Very limited information is currently available regarding the effects and adverse effects of rapid infusion of blood mixture, especially in liver transplant recipients [7]. In the current study, the risks associated with massive transfusion of preserved blood mixture were evaluated. We attempted to describe the biochemical changes in the blood mixture while it was stored in the reservoir, and to investigate the immediate and cumulative effects of rapid transfusion of the blood mixture on the body during liver transplant surgery.

Materials and Methods

Patient selection

This prospective observational study was approved by our institutional review board (H-1012-063-344) and registered at a publicly accessible clinical trial registration site, clinicaltrials.gov (NCT01448343). Written informed consent was obtained from all patients or next of kin during the preoperative visit.

Liver transplantation recipients aged between 20 and 65 were screened for eligibility. Preoperative selection excluded patients with cardiac dysfunction (right heart failure, pulmonary hypertension, coronary artery disease, and severe dysrhythmia), renal failure and electrolyte imbalances. Patients with a hematocrit greater than 30% preoperatively or whose transfusion requirement during surgery was less than one reservoir volume were excluded during the study.

Anesthesia and preparation for massive transfusion

Patient arrived at the operating room without any premedication. Anesthesia was induced with 30 mg of lidocaine, 1.5-2 mg/kg of propofol, and 1 mg/kg of rocuronium. After tracheal intubation, mechanical ventilation was adjusted to maintain 35 mmHg of end-tidal carbon dioxide tension.

Arterial lines were inserted at the radial and femoral arteries for frequent blood samplings and continuous monitoring of arterial pressure. Large bore Swan-Ganz introducer with 3 lumens (Advanced venous access, AVA®, Edwards Lifesciences LLC, Irvine, CA) and Swan-Ganz catheter were inserted into the right internal jugular vein. Anesthesia was maintained with sevoflurane, oxygen, and air. Atracurium was continuously infused to provide adequate muscle relaxation. Normal saline and 20% albumin were used to maintain intravascular volume.

Medical risk factors of bleeding such as prolonged prothrombin time (international normalized ratio > 3), decreased fibrinogen level (< 100 mg/dl) and platelet count (< 20,000/mm^3) were corrected before surgery. During laparotomy, the attending surgeon evaluated surgical risk factors, which included fragile intraperitoneal vessels, redundant collateral veins, deeply located hepatic vein, and adhesions due to previous liver resection, cancer invasion or spontaneous bacterial peritonitis. If surgical risk was considered high, or the initial hemoglobin level was lower than 10 g/dl, the reservoir was filled with blood mixture before hepatectomy.

The fluid management system (FMS; FMS 2000, Belmont Instrument Corporation, Billerica, MA), which is the only rapid infusion device with a volume reservoir, was prepared. Blood mixture in the reservoir of FMS was composed of 4 units of RBC, 4 units of FFP, and 800 ml of normal saline. According to the quality control report of our national blood bank, the volume

of a unit of leukocyte depleted RBC is 303 ± 11 ml with a hematocrit of 57 ± 3%; one unit of FFP has a volume of 170 ± 16 ml. Therefore, the estimated volume and hematocrit of the mixture were 2584-2800 ml and 22.5-29.2%.

Conduction of transfusion and data collection

The criteria for rapid transfusion were a low hematocrit level (< 30%) and an acute loss of intravascular volume (> 300 ml). Transfusion was done by administering a 300 ml bolus that was infused at a rate of 500 ml/min. The total volume of the reservoir was 2584-2800 ml enabling 7 to 8 consecutive boluses. Measurements of blood samples were performed during the 1st, 3rd, 5th and 7th bolus transfusion. Time intervals between the time of reservoir filling and each bolus transfusion were measured (time intervals 1, 3, 5, and 7). For each transfusion, three sequential blood samples were taken from the arterial line, blood mixture and the arterial line, respectively, before, during and after transfusion (pretransfusion, posttransfusion, and blood mixture values). Blood mixture sample was taken from the side port of infusion line of FMS while each bolus transfusion was being done. Blood pH, base excess, and levels of potassium, sodium, ionized calcium, glucose, and lactate were immediately evaluated with a point-of-care analyzer (GEM Premier 4000, Instrumentation Laboratory Company, Bedford, MA) at the operating room.

During the study period, hypotension (more than 20% decrease of mean arterial pressure compared to the baseline value) was treated with 5-10 mg of

ephedrine or 10 mcg of epinephrine. Abnormal parameters were immediately corrected after evaluation of posttransfusion values. Arterial pH lower than 7.25 accompanied by base deficit greater than 10 mmol/L was treated with sodium bicarbonate. When ionized calcium was lower than 1.0 mmol/L, 300 or 600 mg of calcium chloride was administered. Potassium level higher than 6.5 mmol/L was treated with immediate infusion of insulin and glucose.

Patient characteristics were recorded from the anesthesia chart after surgery.

Sample size estimation and statistical analyses

The initial assumption based on our experience was that hematocrit of the blood mixture would decrease along with time in the reservoir. Detection of time-related changes of 4 repeated measures within group required 9 patients with a type I error of 0.05 and 80% power. Sample size was increased to 10 subjects, expecting dropout rate of 10%.

Descriptive statistics was performed on 8 parameters measured during 4 bolus transfusions.

Spearman partial correlation tests were performed between duration of blood bank storage of packed RBCs and parameters of the first blood mixture sample using the time interval 1 as controlled variable. Sequential changes of blood mixture values among 4 bolus transfusions were evaluated with

repeated measures analysis of variance and *post hoc* multiple comparison with Bonferroni correction.

Immediate posttransfusion changes in the body were evaluated with Wilcoxon signed rank test between pretransfusion and posttransfusion values. The cumulative changes of body compositions were evaluated with Wilcoxon signed rank tests between the 1st and 7th pretransfusion values.

The occurrence of significant acidosis (pH < 7.20), hypocalcemia (ionized calcium < 0.42 mmol/L), hyperkalemia (potassium concentration > 6.5 mmol/L) and anemia (hematocrit < 20%) during study period was also recorded.

Values are expressed as mean (SD), median (range) or absolute numbers. Significance was achieved at $P < 0.05$. All statistical analyses were performed using IBM SPSS Statistics software (version 19, SPSS Inc., IL)

Results

A total number of 24 patients were assessed for eligibility, however, 14 of those were excluded from analysis: 10 patients refused to participate in the study; 2 patients failed to finish the study because blood loss was smaller than 1 reservoir volume; bleeding was too massive to proceed with the study in 2 patients. Finally 10 patients finished the study and were included into analysis. Characteristics of enrolled patients are described in table 1.

Median duration of blood bank storage of packed RBCs was 6 (1-18) days. Time intervals 1, 3, 5 and 7 were measured 29 (5-95), 51 (40-120), 67 (60-135) and 88 (70-157) min, respectively.

Biochemical changes of blood mixture are plotted in figure 1. Strong relationship with increasing duration of blood bank storage of packed RBC was shown in initial values of pH (r = -0.919, $P = 0.000$), base excess (r = -0.975, $P = 0.000$), potassium concentration (r = 0.764, $P = 0.017$) and lactate concentration (r = 0.901, $P = 0.001$). Significant sequential changes were observed for hematocrit ($P = 0.000$), potassium ($P = 0.004$), sodium ($P = 0.005$) and glucose ($P = 0.031$) concentrations.

Posttransfusion changes in the body are illustrated in figure 2. Immediate posttransfusion changes were significant in base excess, pH, and ionized calcium level ($P < 0.05$). Marginal and significant decrease of hematocrit was

observed during latter half of the study period ($P = 0.054$ and $P = 0.016$ after the 5th and 7th transfusions, respectively), and increase of potassium concentration during the former half ($P = 0.058$ and $P = 0.012$ after the 1st and 3rd transfusions, respectively). Lactate level was constant. Cumulative effects of transfusion were observed in three parameters. Sodium, glucose and lactate concentrations showed significant increases at the 7th pretransfusion values compared to the 1st pretransfusion values ($P < 0.05$); the increments were 2 (-2-5) mmol/L, 18 (7-108) mg/dL and 1.0 (-0.2-1.7) mmol/L, respectively.

Acidosis was observed in 3 out of 40 measurements (8%; in the 1st patient) and hypocalcemia in 2 out of 40 measurements (5%; in the 9th patient), which were rapidly corrected. Neither hyperkalemia nor anemia was observed during the study period. Mean arterial pressure and central venous pressure were maintained adequately (62-95 mmHg and 2-10 mmHg, respectively) without hypoxemia ($SpO_2 \geq 98\%$).

Discussion & Conclusion

We demonstrated the biochemical change of blood mixture prefilled in a reservoir and the effect of rapid transfusion in adult liver transplantation recipients. The main findings of this study were that 1) sequential decrease of hematocrit, potassium and glucose, and increase of sodium were observed in the prefilled blood mixture, 2) statistically significant biochemical changes in the body occurred immediately after rapid transfusion except lactate level, and 3) statistically significant effects of transfusion were observed in sodium, glucose and lactate levels after transfusion of one reservoir volume of blood mixture.

The main purpose of transfusion is increasing hemoglobin level to assure adequate oxygen transport. However, the current study showed that the transfusion of latter half volume of blood mixture rather lowered the hematocrit level immediately as opposed to the first half. Discordance in transfusion effect might be resulted from the sedimentation of erythrocytes in a blood filled column like a reservoir. Considering that the usual sedimentation rate of erythrocytes, which is dependent on the age and gender, is 12-23 mm/hr, a larger difference in hematocrit might have been resulted in according to the latency between the first and last boluses [8, 9]. This problem

was not solved by the use of the integrated function like “recirculation” of FMS in our pilot study because the internal circulation was just made between the bottom of reservoir and internal circuit. The easiest way to avoid separation of layers was shaking the reservoir externally to stir up upper and lower blood layers just before transfusion, although stability of the device might have been damaged. The level of hematocrit was above a presumed threshold level in liver transplant (20-25%) during this study, however the risk of continuing anemia even after transfusion still resides.

Metabolic acidosis is a possible adverse effect during the immediate phase of massive transfusion because of the citrate in packed RBC and FFP, and lactate and pyruvate originated from metabolism of erythrocytes. The blood mixture in the reservoir consistently showed low pH (< 7.0) with large base deficit (> 20 mmol/L) causing statistically significant acidosis on every bolus transfusion and required 30 (range 0-240) mEq of sodium bicarbonate to treat acidosis. Liver transplantation recipients, especially cirrhotic patients, have limited capacity of handling citrates owing to the diminished hepatic function [3]. Nevertheless, clinically significant acidosis was observed in only 3 measurements in 1 patient in the current study. Frequent administration of bicarbonate, control of ventilation, and partially functioning liver during pre-anhepatic phase may have contributed.

Potassium concentration in substrate gradually increases during cold preservation of packed RBC due to the suppression of sodium-potassium pump activity. The extracellular potassium concentration of stored units increases at a rate of 2 mmol/L per day [10]. Moreover, irradiation of packed RBC increases potassium concentration [5]. Transfusion of packed RBC generally does not result in hyperkalemia due to relatively small volume of substrate, however rapid transfusion may cause fatal arrhythmia or cardiac arrest [11]. In the current study, the infusion of the former half resulted in a statistically significant increase of arterial potassium concentration without any clinical manifestation. Based on our result, the estimated change in the arterial potassium immediately after transfusion of initial blood mixture is only 0.5 mmol/L in a 60 kg patient. Use of a relatively fresh packed RBCs (median storage = 6 days), diluting effect of FFP and normal saline, and gradual restoration of potassium pump activity during preservation in the reservoir may be some of the factors that limit the increase of potassium. However, cautions should be taken in patients with increased risk of hyperkalemia during initial infusion of the reservoir volume [12].

Three components of blood mixture are external sources of sodium; the amount of sodium from the components are about 170 mmol/L from packed RBC and FFP, and 154 mmol/L from normal saline, although the sodium in packed RBC gradually decreases to 111 mmol/L on the 35th day of storage

[10]. In the current study, sodium concentration of blood mixture continuously increased from 141 mmol/L to 147 mmol/L during 1.5 hours in the reservoir. This may be due to enhanced sodium-potassium pump activity of erythrocytes. Sodium concentration increased with every bolus transfusion, however the concentration increased by only 2 (-2-5) mmol/L after one whole reservoir volume transfusion. The total increase was trivial and within physiological range, thus complication related with rapid increase of sodium such as central pontine myelinolysis is less likely to occur using blood mixture [6].

Rapid metabolism of citrate via Krebs cycle in the liver, and mobilization of calcium from internal reservoir of the body prevent critical citrate intoxication in healthy populations. However, hypovolemic shock, hypothermia, hyperventilation, neonate, end-stage liver disease and liver transplantation surgery are conditions prone to acute hypocalcemia. Depressed cardiac contractility and vasodilation are the major manifestations associated with acute hypocalcemia [13]. In the current study, clinically significant decrease of ionized calcium level developed with every bolus. Spontaneous recovery may be delayed or absent during massive transfusion in liver cirrhosis patient without supplementation of calcium [4]. Our result shows that repeated injections of calcium chloride of up to 1800 mg were required to maintain an ionized calcium level of 1.0 mmol/L and stable

arterial pressure with minimum use of vasopressor. Hypocalcemia should be carefully examined and managed during rapid infusion of blood mixture.

Previous studies have failed to demonstrate the relationship between the amount of transfusion and serum glucose level that typically increased during hepatectomy [14, 15]. Nevertheless, massive transfusion still remains a potential cause of hyperglycemia during liver transplantation because all current blood preservatives include dextrose. Dextrose in CPDA-1 preserved packed RBC is up to 440 mg/dL on the 1st day, and gradually decreases to 84 mg/dL after 35 days. FFP also contains 535 mg/dL of glucose [16]. In the present study, median increase of serum glucose was 18 mg/dL, however, the ninth patient showed doubling of glucose level after one reservoir volume transfusion (from 89 to 197 mg/dL). Unpredictable glucose homeostasis of liver cirrhosis patients in response to external glucose mandates careful management of serum glucose level to prevent hyperglycemia and related morbidities [17].

Lactate is a byproduct of anaerobic metabolism of erythrocytes, and its concentration in the packed RBC is proportionate to the duration of blood bank storage. The initial lactate concentration was as high as 5.2 mg/dL. Externally administered lactate should be considered when we assess patient's state during ischemic period like clamping of large vessels or during recovery

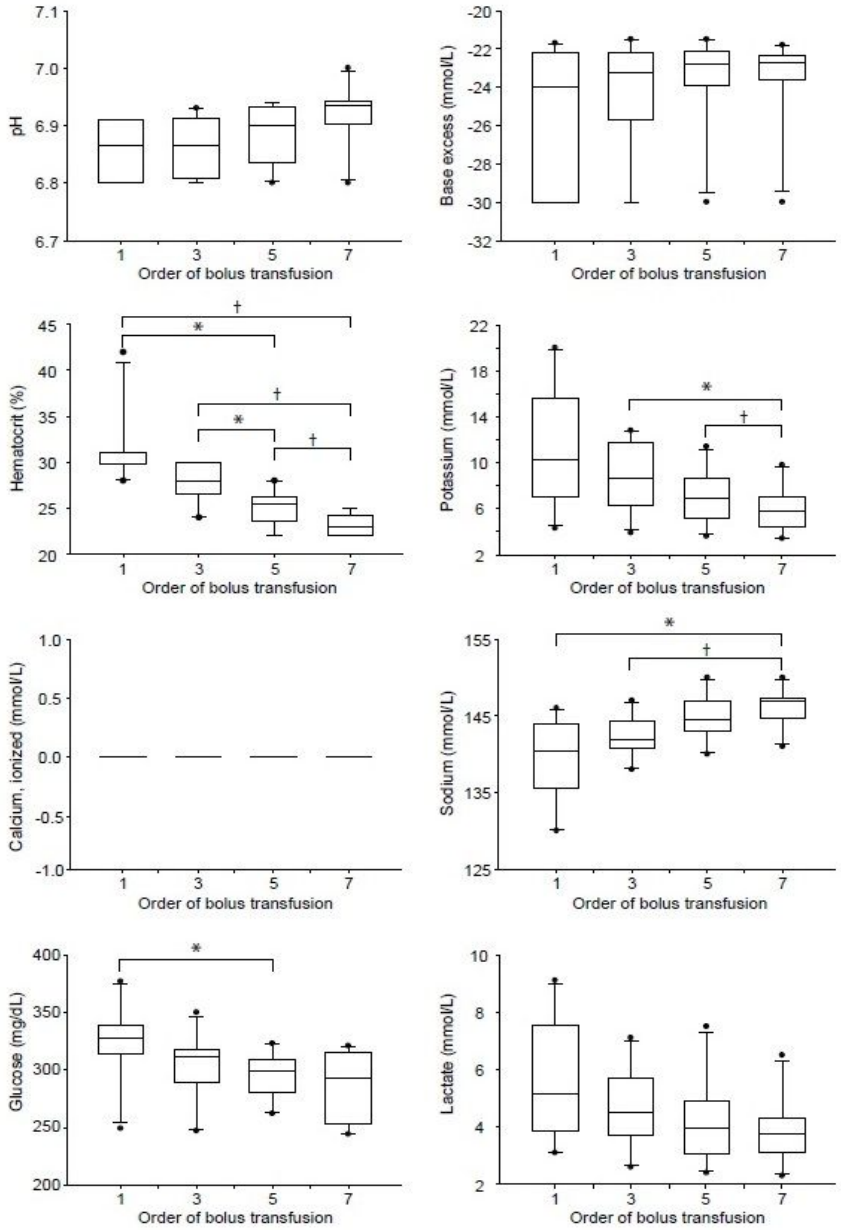
of graft function [18]. In the current study, we observed statistically significant but clinically trivial increase of lactate level (1 mg/dL). Well maintained systemic arterial pressure might have contributed to adequate perfusion and oxidation of tissues and clearance of lactate during study period.

There are two limitations of study that need to be considered. First, our institution uses CPDA-1 blood unexceptionally, however, other blood preservatives such as AS-1, AS-3 or AS-5 are currently used worldwide. For example, 85% of blood products are preserved in AS-1 in the US [19]. AS-1 blood contains more dextrose than CPDA-1 blood with less citrate. AS-1 stored blood showed different profile from CPDA-1 blood regarding glucose homeostasis, hypocalemia, arterial hypotension and mortality in a swine model simulating massive transfusion [20]. Thus we claim that our result would have more implications in massive transfusion cases using CPDA-1 preserved blood. Second, we performed this study in carefully selected liver transplantation recipients. If a patient has very poor hepatic and renal functions, the consequences of massive transfusion may go beyond the results of our study.

In conclusion, blood mixture preserved in a reservoir underwent preferable changes, possibly due to dilution effect and increased erythrocyte activity. Acute hypocalcemia and acidosis needed immediate corrections, contrary to

hyperkalemia which was just a potential risk. Hyperglycemia seems another potential risk after repeated infusions of blood mixture. Considering that immediate and cumulative biochemical changes in the body were trivial in the current study, rapid transfusion of blood mixture seems relatively safe if aggressive intraoperative care such as frequent administration of calcium and bicarbonate be given to the patients.

Figure 1. Biochemical changes of blood mixture preserved in a reservoir during rapid transfusion.



Values were consistently low (pH, base excess and ionized calcium) or high (lactate). However, significant sequential decrease (hematocrit,

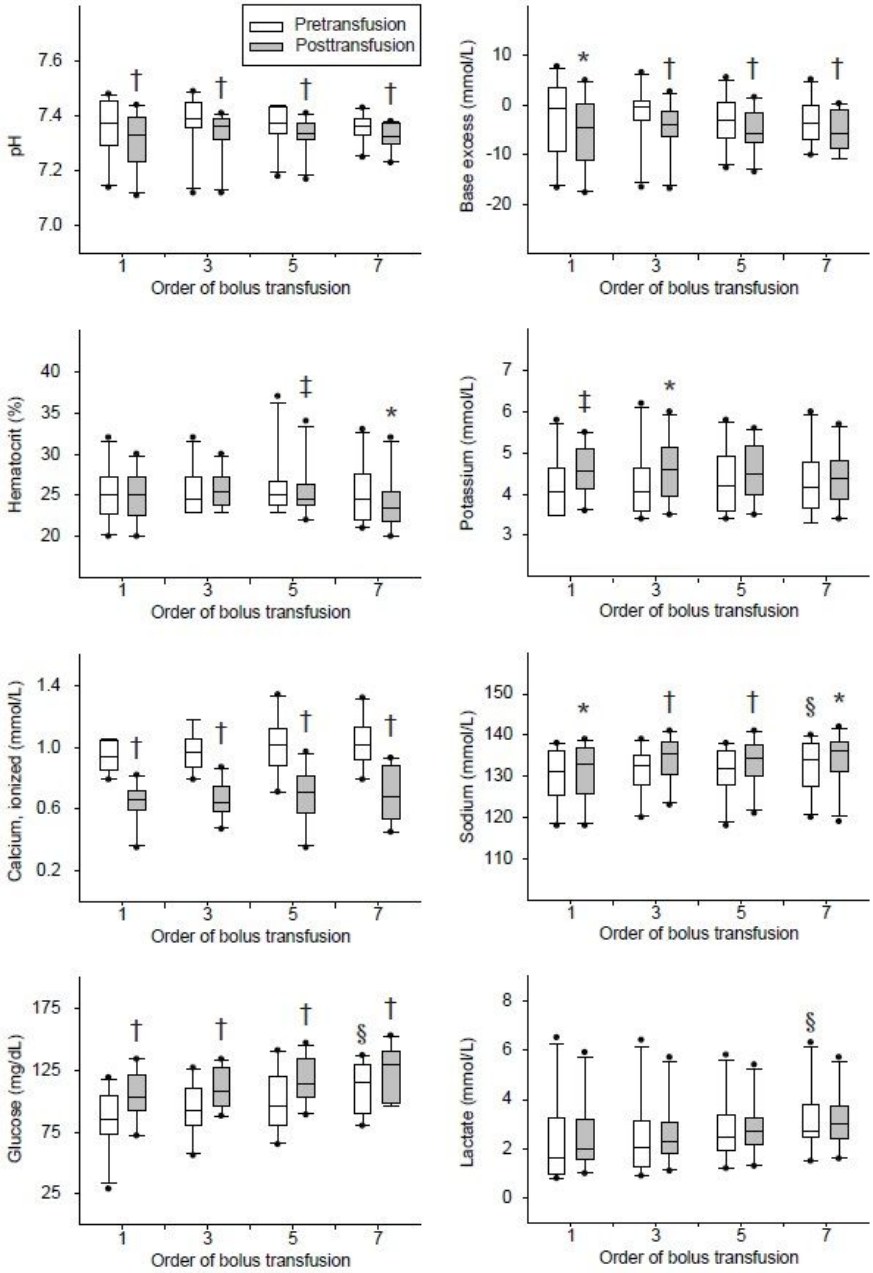
potassium and glucose) or increase (sodium) of values was also observed in the blood mixture during preservation.

Concentration of ionized calcium could not be measured (estimated concentration < 0.1 mmol/L), thus considered zero.

* Bonferroni corrected $P < 0.05$ between values

† Bonferroni corrected $P < 0.01$ between values

Figure 2. Biochemical changes in the arterial blood during rapid transfusion of blood mixture.



Immediate posttransfusion changes in the arterial blood were observed during early (potassium), late (hematocrit), and entire (pH, base excess, ionized calcium, sodium and glucose) periods of transfusion. Significant cumulative effects were observed in sodium, glucose and lactate concentrations.

* $P < 0.05$ *vs* pretransfusion value

† $P < 0.01$ *vs* pretransfusion value

‡ $P = 0.054$ and $P = 0.058$ compared with pretransfusion values of hematocrit and potassium, respectively

§ $P < 0.05$ *vs* the 1st pretransfusion value

Table 1. Patient characteristics

Sex (M/F)		8/2
Age (years)		55 (36-71)
Weight (kg)		60 (46-67)
Height (cm)		165 (150-174)
Model for end-stage liver disease score		23 (6-42)
Diagnosis (acute liver failure/ hepatocellular carcinoma/ alcoholic liver cirrhosis/ non-alcoholic liver cirrhosis)		1/3/2/4
Type of donor (living/ deceased)		8/2
Operation time (min)		465 (300-620)
Estimated blood loss (ml)		6160 (2580-11000)
Transfused blood units	Red blood cell	14 (6-30)
	Fresh frozen plasma	14 (6-28)
	Platelet concentrate	0 (0-12)
Infused fluids (ml)	Normal saline	4750 (2500-8000)
	20% Albumin	300 (0-300)
Drugs administered during study period	Ephedrine (mg)	10 (0-40)
	Calcium chloride (mg)	1200 (600-1800)
	Sodium bicarbonate (mEq)	30 (0-240)

Values are expressed as absolute number or median (range).

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초록

간이식 환자에서 혼합혈액의 급속 수혈

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배경

저장소에 미리 채운 혼합 혈액을 급속주입기계를 이용하여 수혈을 할 때 나타나는 변화들에 대해 정보가 부족하다. 본 연구는 간이식 환자에게서 혼합 혈액을 급속 주입하였을 때 나타나는 급성 생화학적 변화들을 설명하고자 한다.

방법

간 이식 수술을 받는 중, 간의 박리 과정에서 대량 수혈을 받는 10 명의 환자를 대상으로 하였다. 혼합 혈액은 냉동 적혈구 10 단위, 신선 동결 혈장 10 단위, 생리 식염수 800ml 로 구성하여 출혈을 대비하여 저장소에 준비하였다. 대량 수혈은 300ml 의 혼합 혈액을

500ml/분으로 주입하도록 하였으며, 혈액 샘플은 1, 3, 5, 7 번째 수혈 시 채취하였다. 매 수혈마다 환자에게 주입되는 혼합 혈액과 환자의 동맥혈에 수혈 전후로 채취하여, 각각 pH, 염기 지수, 적혈구 용적, 칼륨, 나트륨 및 이온화 칼슘, 포도당, 젖산의 농도를 측정하고 분석하였다 .

결과

칼륨의 현저한 증가와 적혈구 용적의 감소가 수혈의 전반을 통틀어 관찰되었다. 저칼슘혈증과 산증은 모든 주입마다 즉각적인 교정이 필요하였다. 하나의 저장소의 혼합혈액을 주입한 후, 유의한 변화가 혈장 나트륨, 포도당, 젖산 농도에서 나타났으며 임상적인 유의성은 미미하였다.

결론 및 고찰

급성 수혈동안 급성 저칼슘혈증과 산증은 즉각적인 교정을 요구한다. 급성 고칼륨혈증과 빈혈 및 지연성 고혈당증은 잠재적인 위험이 된다. 본 연구에 따라, 간 이식 수술 중 세심한 주의와 적극적인 교정이 동반된다면 혼합 혈액의 기계를 이용한 급속 주입이 대체로 안전하다고 생각된다.

주요어 : 간이식, 대량 수혈, 급속 수혈

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