Does Infusion Of Unbalanced Colloid Solutions Influence The Acid Base Status During Liver Transplantation?
A Mukhtar, A Elmasry, A Moniem, H Dahab, A Kamal, A Abdelaal, M Bahaa, M Elmeteini

Citation

Abstract
Background:The aim of the present study is to investigate the effects of two different unbalanced synthetic colloid solutions on acid-base equilibrium in patients undergoing living donor liver transplantation (LDLT)MethodsForty patients undergoing LDLT were prospectively randomized to receive either 5% human albumin ALB (n=20) or hydroxyethyl starch 6% 130/0.4 HES (n=20). PH, PaCO₂, and serum concentrations of sodium, potassium, chloride, lactate, ionized calcium, phosphate, and albumin were measured after induction of anaesthesia, anhepatic phase, and at admission to intensive care unit (ICU). Strong ion difference, strong ion gap, and corrected anion gap were calculated. Results
All Patients developed metabolic acidosis during anhepatic phase and at ICU admission. Factors that had contributed to metabolic acidosis were increase in lactate levels, unmeasured anions and hyperphosphatemia. In both groups; serum lactate levels had increased at anhepatic phase and ICU admission. Levels of unmeasured anions during anhepatic phase were 7.7±3.3 mEq/l, and 6.7±4.4 mEq/l among HES and ALB groups respectively). Hyperphosphatemia had occurred among both groups during anhepatic phase and at ICU admission. In HES group, significant decrease in strong ion difference with concomitant decrease in weak plasma acids compared to the albumin group was noticed. Conclusion Both HES 130/0.4 and albumin 5% had led to similar metabolic acidosis in patients undergoing liver transplantation but with great variation in Strong ion difference and weak plasma acid.

INTRODUCTION
The perioperative management of patients undergoing liver transplantation is challenging and fraught with many potential complications. Cardiovascular instability, significant blood loss and marked electrolyte, and haemostatic disturbances are all common during liver transplantation. One of the most challenging management problems during liver transplantation is to maintain patients’ acid-base status stable.

Acid base disturbance is frequently encountered during liver transplantation, because of increased lactate level, deficient hepatic clearance of acidic substance, and reduced perfusion which results in anaerobic metabolism [1].

Relying on bicarbonate centred approach to primary determine mixed acid-base disorders is not sufficient [2]. More recently Stewart [3] and Figge [4] approach; which depends on the principles of electro-neutrality and conservation of mass appear to provide more precise explanation than the bicarbonate-centred approach for acid–base changes specially in the critically ill population [5,6].

In Stewart’s approach³; pH and bicarbonate are no longer the independent variables, but the approach relies on three independent variables namely; a) PaCO₂, b) charge from weak acids (albumin and phosphate), and c) strong ion difference (SID).SID is the difference between all dissociated ions (positively and negatively charged strong ions in plasma).
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Colloid-containing solutions are commonly administered during liver transplantation, to maintain euvolemia, effective cardiac output and maintain plasma oncotic pressure.[4] No sharp guidelines regarding the optimal colloid solution, however albumin transfusion had shown improvements in the Sequential Organ Failure Assessment score and better fluid balance among hypoalbuminemic patients [7], more recently the use of HES 130/0.4 versus albumin in hypoalbuminemic patients undergoing liver transplantation showed comparable effects. [8] According to Stewart’s physico-chemical approach, colloid infusion can affect metabolic acid-base balance by either altering SID or by reducing weak acids. [9-11] None of the previous trials had demonstrated the impact colloid on acid-base changes. Thus it is questionable whether the nature of colloid can affect the acid base balance in patients undergoing liver transplantation with end stage liver disease that already possess various factors affecting their acid base status (e.g. hypoalbuminemia and hyponatremia) according to Stewart approach.

The aim of the current study was to primarily investigate the influence of colloid infusion on acid-base balance and to define the nature of acidosis in patients undergoing liver transplantation randomized to receive either hydroxyethyl starch 130/0.4 or albumin 5% as their colloid solution.

**METHODS**

After approval of the local Ethics and research Committee and obtaining written informed consents, the study was designed to recruit forty patients with end stage liver disease, scheduled for living donor liver transplantation.

Patients undergoing re-transplantation, those with previous upper abdominal surgery, Patients with portal vein thrombosis (diagnosed with preoperative duplex ultrasound), patients younger than eighteen years old, and those with primary renal dysfunction were excluded from the study.

We previously reported our anesthetic management of patients undergoing liver transplantation.[8]

Patients were randomized using closed envelope technique into two equal groups to have their volume replacement either with albumin 5% or HES 130/0.4 (Voluven; Fresenius-Kabi, Bad Hamburg, Germany), as their colloid solution during the perioperative period, with a maximum dose of 50 mL/kg/day.

In both groups, Ringer acetate was administered routinely at 10 mL/kg/hr. The patients received either 250 ml bolus of Voluven (HES group) or 250 ml of albumin 5% (ALB group) with a maximum of 50 mL/kg/day to maintain central venous pressure CVP between 5 and 7 mm Hg. For additional fluid; Ringer acetate was given. Blood transfusion was given based on a haemoglobin level (< 7 g/dl).

Arterial blood samples were collected at three specific times: immediately after induction of anaesthesia and before colloid infusion (baseline); thirty minutes after portal vein clamp (anhepatic phase), and at the ICU admission. For each time point, paired samples were simultaneously drawn. One sample was analyzed using a co-oximeter (ABL 700; Radiometer, Copenhagen, Denmark) to measure PH, partial pressure of carbon dioxide (PaCO₂), standard bicarbonate concentration (HCO₃⁻), lactate, and ionized calcium. The other sample was sent to hospital laboratory for measurement of serum sodium, potassium, chloride, magnesium, phosphate and albumin. From these data, standard bicarbonate concentration (HCO₃⁻), and anion gap (AG) were calculated. Apparent and effective SID (SIDa, SIDₑ), and strong ion gap (SIG) were determined by Stewart [3] and Figge [4] approach as follow:

**Figure 1**

\[ AG = Na^- - (chloride + HCO_3^-) \]

\[ SIDa = Na^+ + K^+ + Ca^{2+} + Mg^{2+} - (Cl^{-} + lactate^{-}) \]

\[ SIDe = 2.46 \times 10^8 \times PaCO_2 \times 10^{0.51} + [albumin] \times (0.123 \times pH - 0.51) + [PO_4^2-] \times (0.309 \times pH - 0.469) \]

\[ SIG = SIDa - SIDe \]

The anion gap was corrected for decreased albumin using the approach of Figge et al [12].

Corrected anion gap (mmol/L) = calculated anion gap + 0.25 X (42 – measured albumin [g/L]).

Other variables: heart rate, mean arterial blood pressure, pulmonary artery occlusion pressure (PAOP), CVP, and cardiac output (using a pulmonary artery catheter), volume replacement therapy including crystalloid and colloid infused, blood, and plasma transfusion were recorded at the same aforementioned 3 time points.

**STATISTICAL ANALYSIS**

Power analysis was performed using Student’s t-test for independent samples on corrected anion gap. Previous study showed that the mean (SD) of corrected anion gap in post liver transplant patients on ICU admission was 23(4.1) [13].
A sample size of 17 patients per group would allow detection of a difference of 20% in the corrected anion gap value in each infusion group with a power of 90% and a significance level ($\alpha$) of 0.05. A total of 20 patients in each group were included to compensate for possible dropouts.

Categorical variables were assessed using chi-square or Fischer exact test as appropriate. Normally distributed data are presented as mean (SD) and were analysed using Student’s t test and two-way analyses of variance with repeated measures and post hoc Dunnett test as appropriate. Data not normally distributed (tested by Kolmogorov-Smirnov test) are presented as median (range) and were analysed with Mann-Whitney U test or the Kruskal-Wallis test as appropriate. The software SPSS v15.0 for Windows (SPSS, Inc, Chicago, IL, United States) was used for statistical analysis.

RESULTS

All enrolled patients (40) had completed the study protocol. Patients characteristics, ischemia time, and operative time were comparable among both groups. (Table 1).

At the end of surgery the amount of colloid (3100± 625 versus 3220± 523 ml) had been administered in the ALB group and the HES group respectively. Intraoperative infusion of crystalloids, PRBCs, and FFP did not differ between the two groups. (table2)

Figure 3

TABLE 2: Infused volumes. Data are mean ± SD; Median (range)

<table>
<thead>
<tr>
<th></th>
<th>ALB (n=20)</th>
<th>HES (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloids (mL)</td>
<td>3100± 625</td>
<td>3220± 523</td>
</tr>
<tr>
<td>Crystalloids (mL)</td>
<td>4523± 992</td>
<td>4723± 854</td>
</tr>
<tr>
<td>PRBCs (units)</td>
<td>2 (0-6)</td>
<td>2 (0-6)</td>
</tr>
<tr>
<td>FFP (units)</td>
<td>2 (0-6)</td>
<td>0 (0-8)</td>
</tr>
</tbody>
</table>

ALB: albumin, HES: hydroxyethyl starch, PRBCs: packed red blood cells, FFP: fresh frozen plasma.

Hemodynamic variables were comparable among both groups (table3).

Figure 4

TABLE 3: Intraoperative Hemodynamic Data. Values are mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Anhepatic Phase</th>
<th>ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (b/min)</td>
<td>90 ± 9.5</td>
<td>101 ± 15</td>
<td>94 ± 11</td>
</tr>
<tr>
<td>ALB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HES</td>
<td>88 ± 12.2</td>
<td>99 ± 20</td>
<td>96 ± 14</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALB</td>
<td>87.5 ± 6</td>
<td>82 ± 11</td>
<td>84 ± 13</td>
</tr>
<tr>
<td>HES</td>
<td>94.4 ± 19.6</td>
<td>83 ± 13</td>
<td>81 ± 13</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALB</td>
<td>9 ± 2</td>
<td>5 ± 2.2</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>HES</td>
<td>8 ± 3</td>
<td>4.6 ± 1.9</td>
<td>5.7 ± 2.3</td>
</tr>
<tr>
<td>PAO2 (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALB</td>
<td>12 ± 5.1</td>
<td>8 ± 3</td>
<td>9 ± 3.1</td>
</tr>
<tr>
<td>HES</td>
<td>11 ± 4.1</td>
<td>7 ± 2.6</td>
<td>8.3 ± 2.2</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALB</td>
<td>7.2 ± 2.3</td>
<td>6.5 ± 1.6</td>
<td>9.3 ± 2.9</td>
</tr>
<tr>
<td>HES</td>
<td>7.3 ± 2.9</td>
<td>6.7 ± 2.1</td>
<td>10.1 ± 5.1</td>
</tr>
</tbody>
</table>

ALB: albumin, HES: hydroxyethyl starch, HR: heart rate; MAP: mean arterial pressure; CVP: central venous pressure; PAO2: Pulmonary artery occlusion pressure; CO: cardiac output.

All our patients developed metabolic acidosis, during anhepatic phase, and ICU admission. Both groups had a significant decrease in PH during anhepatic phase, and ICU admission compared to baseline, without significant difference between the two groups (table 4).
TABLE 4: Acid base variables during liver transplantation. Data are presented as mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>HES (N=20)</th>
<th>ALB (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>7.42±0.06</td>
<td>7.43±0.08</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>33±1.0</td>
<td>33±1.8</td>
</tr>
<tr>
<td>HCO₃ (mEq/L)</td>
<td>29.4±3.6</td>
<td>31.6±3.8</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>134±6.1</td>
<td>136±6.3</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>108±4.5</td>
<td>107±6.7</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.8±0.4</td>
<td>4.6±0.3</td>
</tr>
<tr>
<td>Magnesium (mEq/L)</td>
<td>1.0±0.2</td>
<td>1.0±0.9</td>
</tr>
<tr>
<td>Calcium(mEq/L)</td>
<td>1.1±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>Lactate (mEq/L)</td>
<td>2.1±0.3</td>
<td>3.4±0.6</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>2.4±0.7</td>
<td>2.4±0.7</td>
</tr>
<tr>
<td>Phosphate (mEq/L)</td>
<td>1.0±0.4</td>
<td>1.0±0.5</td>
</tr>
<tr>
<td>SIDa (mEq/L)</td>
<td>20±4.6</td>
<td>20±4.6</td>
</tr>
<tr>
<td>SIG (mEq/L)</td>
<td>3.0±1.7</td>
<td>3.0±1.7</td>
</tr>
<tr>
<td>Corrected gap</td>
<td>13±4.6</td>
<td>13±4.6</td>
</tr>
</tbody>
</table>

SIDa: strong ion difference apparent; SIDe: strong ion difference effective; SIG: strong ion gap. * denotes significance relative to baseline; † denotes significance relative to the other group. P<0.05

PaCO₂ values were comparable among both groups and at all study points (Table 4). Serum standard bicarbonate concentrations were comparable among both groups at all study points. In the HES and ALB groups, the serum standard bicarbonate concentration decreased significantly during anhepatic phase and at ICU admission compared to baseline (P<0.001) (table 4).

The triad of SIDa, weak acids (albumin and phosphate), and unmeasured anions had altered significantly among both groups during the study (Table 4). In HES group, serum chloride concentration increased significantly during anhepatic phase and at ICU admission compared to baseline (p=0.002 and 0.004 respectively), whereas no changes were observed in the ALB group. Additionally, the albumin concentration was markedly decreased in HES group, in contrast to the ALB group, in which albumin concentration increased. (Fig 1-3), Table (4).
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**Figure 8**

Figure 3: Anionic and cationic change in the study groups at ICU admission. SIDa: strong ion difference apparent; Alb: albumin effect; PO4 –: phosphate effect; CO2: CO2 effect; SIG: strong ion gap (effect due to unmeasured anions)

In the HES group, SIDa decreased significantly from 36.5±3.6 at baseline to 30.4±5.4 during anhepatic phase and 29.4±3.6 meq/L at ICU admission (P=0.006 and 0.001 respectively), while SIDa did not vary with time in the ALB group (table 4). However SIDa had varied significantly among ALB and HES groups during both anhepatic phase and at ICU admission (p=0.02 and 0.003 respectively). By the same token, due to hypoalbuminemia associated with the HES group, SIDe had significantly decreased from 30.8±3.7 at baseline to 22.6±3.1 during anhepatic phase and 24.4±3.9 meq/L at ICU admission (P<0.0001). SIDe in the ALB group had decreased from 31.6±3.0 at baseline to 28.3±3.6 during anhepatic phase and 28.3±2.2 meq/L at ICU admission (p=0.01 and 0.001 respectively). SIDe was significantly lower in HES group compared to ALB group during anhepatic phase and at ICU admission (p=<0.0001 and 0.003 respectively) (Fig 1-3), (Table 4). In both groups, SIG, representing the unmeasured anion, increased significantly during anhepatic phase, and returned to baseline at ICU admission. (Table 4).

Analysis according to the Stewart-Figge model revealed that metabolic acidosis during liver transplantation was primarily related to changes in a) SIDa, b) charges due to albumin (Prot-) and serum phosphate and c) accumulation of additional unmeasured anions (SIG). Accordingly, hyperphosphatemia and unmeasured anions contributed an excess of 1.0 mEq/l and 2.5 mEq/l of acidifying anions, respectively. However, In the HES group, SIDa decreased by a mean of 6.0 mMol, and did not change in ALB group (0.6 mMol). As a result of profound hypoalbuminemia, (Prot`) decreased by about 3.45 mMol in the HES group, in contrast to the ALB group, in which (Prot`) increased by about 1 mMol. (Figure 1-3), (Table 5)

**Figure 9**

TABLE 5: Contribution of various components of the plasma to bicarbonate change according to Stewart approach.

**DISCUSSION**

The main finding from the current study is that patients undergoing liver transplantation developed metabolic acidosis irrespective of the used colloid solution; however the pathogenesis of underlying acid-base disturbance can vary greatly according to the nature of colloid infused.

To define and quantify the pathogenesis of this acidosis, we applied the physico-chemical approach described by Stewart [3], and then modified by Figge. [4] Stewart concluded [3] that the acid–base status of body fluids is controlled by three independent factors: SID; weak acids; and the partial pressure of carbon dioxide.

After hydroxyethyl starch administration, the serum chloride increased, which caused decrease in SIDa; however, in the albumin group, no significant change in SIDa was seen. According to Stewart, a decrease in SIDa should have an acidic effect. These acidifying disorders were attenuated by a concomitant decrease in weak acid, which was essentially secondary to hypoalbuminemia.

In agreement with our findings, Rehm et al. [11] randomized 20 female patients to receive either albumin 5% or hydroxyethyl starch. They found that, despite three-time larger decrease in strong ion difference with infusion of 6% hydroxyethyl starch solution, the decrease in pH was nearly the same in both groups.

In the current study, SIDa decreased in the HES group by about 6 mMol, however, decrease in serum albumin concentration was responsible for the subtraction of
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approximately 3.5 mEq/l of acid from the circulation. In ALB group, (Prot ) increased slightly while SIDa decreased by about 0.6 mMol (table 5). The other ion effect on bicarbonate concentration was a decrease of about 3.5mmol/L. About 1mMol/L of that was due to hyperphosphatemia. The other 2.5 mMol/L difference was caused mainly by unmeasured anion, as shown by strong ion gap.

In the present study, both transplant groups had increased corrected anion gap. Lactic academia may be part of this effect. Several mechanisms underlie the development of lactic acidosis during liver transplantation. First, clearance of a lactate challenge is prolonged in patients with cirrhosis because of impaired reserve capacity of the liver. [14]

Second, surgical manipulation may cause visceral ischemia, concomitantly increasing endogenous lactic acid production and compromising its hepatic and renal uptake. Finally blood transfusion is an exogenous source of lactate. [15]

The application of physico-chemical approach also reveals the importance of a previously neglected contributor to the acidosis during liver transplantation namely Phosphate level. In the current study we were able to demonstrate approximately 1mEq/L of acidifying anions contributed to increased serum phosphate levels. Such increase in serum phosphate levels among patients undergoing liver transplantation is not clear. We believe that associated hyperphosphatemia is of multifactorial origin that affects both proper elimination and utilization of phosphorus. Phosphorus is mainly eliminated via renal system and such elimination may be affected due to transient deterioration of renal function [16] that can be faced during anhepatic phase. Another factor is phosphate underutilization due cessation of phosphate flux to liver (anhepatic phase). During normal conditions phosphate is one of the most important elements in ATP synthesis via liver tissues. [17]

In our population, the SIG measured at baseline was about 5 mEq/L. Results from studies in normal animals [18,19] and from values derived from published data in exercising humans [20] revealed normal SIG near zero. Most studies [21-23] found that the SIG is about 5 mEq/L for critically ill subjects. Hepatic dysfunctions [18] are known to result in accumulation of unmeasured anions that resulted in an increased SIG. In the present study, unmeasured anions increased during anhepatic phase, however, the exact nature of these anions remain elusive. [24]

The 5% albumin solution used in this study contained sodium caprylate, and acetyltryptophanate as thermal stabilizers. These might represent a potential source of unmeasured anions that contributed to the relative increase in SIG among ALB group at ICU admission despite that SIG was comparable among both groups.

Metabolic acidosis observed in patients undergoing liver transplantation is a consistent finding, [1] however contributing factors for such acidosis were usually attributed to accumulation of lactic acid, indicating that the major aetiology is lactic acidosis. [15] In the current study we were able to demonstrate the role of various components of the plasma to the acid-base changes seen during liver transplantation beside the traditional lactate mechanism.

In the present study, we were able to demonstrate that, large volume infusion of unbalanced colloid solution (HES 130/0.4) resulted in minimal alteration of acid base status in patients undergoing liver transplantation.

Concerns have been raised about the risks of hyperchloremic metabolic acidosis associated with large-volume administration of 0.9 % saline and of colloids dissolved in isotonic saline [25-27]. However in this particular group of patients with preoperative hypoalbuminemia; the use of albumin free colloid solutions resulted in severe degree of hypoalbuminemia that may potentially ameliorate the degree of hyperchloremic metabolic acidosis associated with administration of unbalanced colloid solution. Other studies are warranted to compare the acid base effect of administration of new plasma-adapted colloid solution with those of unbalanced colloid in patient undergoing liver transplantation.

In conclusion, the pathogenesis of metabolic acidosis during liver transplantation is multi-factorial. Metabolic acidosis and lactate levels were commonly used interchangeably; however from the current study we can highlight that the triad of serum lactate, unmeasured anions and phosphate levels can precisely document contribution of various plasma components to metabolic acidosis. Metabolic acidosis had occurred with both colloids; however contribution of colloid to metabolic acidosis were different according to Stewart-Figge approach.

References
2. David A. Story BH. Acid-base balance revisited: Stewart and strong ions. Seminars in Anesthesia, Perioperative
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