Acute Kidney Injury after Hepatic Surgery with Goal Directed Fluid Therapy

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Abstract

Background: Goal-directed therapy (GDT) has been shown to reduce perioperative complications. However, whether the restriction of fluid volume in goal-directed therapy causes acute kidney injury (AKI) remains to be determined. The aim of this study was to determine intraoperative risk factors for AKI after hepatic surgery with goal-directed therapy using restricted fluid volume.

Methods: Anesthesia and medical records of 67 patients who underwent hepatic resection were analyzed. Central venous pressure (CVP) and stroke volume variation (SVV) were monitored continuously by arterial contour analysis using a FloTrack sensor™ (Edwards life sciences LLC, CA, USA) for restrictive fluid management during portal triad clamping (PTC) with inferior vena cava (IVC) clamping. Low CVP (<5 cmH₂O) and high SVV (>12%) were achieved by restrictive fluid management during PTC. AKI was assessed using the AKI network definition.

Results: Eight patients developed stage-1 AKI (12%) after hepatic resection, but none of the patients required renal replacement therapy. The durations of anesthesia and PTC were longer in the AKI group than in the non-AKI group (P=0.006 and P=0.004). The IVC was clamped more frequently in the AKI group than in the non-AKI group (P=0.004). The amount of blood loss was larger and the necessity for blood transfusion was higher in the AKI group than in the non-AKI group (P=0.02 and P=0.001).

Conclusion: The duration of PTC with IVC clamping and blood loss affects the incidence of AKI after hepatic surgery using GDT with restrictive fluid volume management. We suggest that unstable hemodynamics during PTC with IVC clamping and blood loss contribute to AKI after hepatic surgery.

Key words
goal directed therapy (GDT), acute kidney injury (AKI), hepatic resection

Introduction

Perioperative renal failure has a large influence on postoperative complications and mortality. When an acute kidney injury (AKI) occurs, the risk of mortality rises after an operation. Impaired renal function, an existing disease (diabetes and heart disease), or advanced age are known as factors distinctive to the patients, while cardiovascular surgery, the use of contrast media, or massive bleeding and transfusion are considered as intraoperative factors. Several studies showed AKI in about 30% of cases after cardiovascular surgery. On the other hand, the occurrence of AKI was estimated at less than 10% after liver resection. Recently, Spolverato et al demonstrated that acute renal failure occurred in 4.2% of cases after hepatic surgery.

During hepatic resection, lowering the central venous pressure is effective in reducing blood loss. Thus, intraoperative restrictive fluids and clamping of
the portal triad (PTC) and inferior vena cava (IVC) are required to decrease central venous pressure. However, both restriction of the volume of fluids and PTC with clamping of IVC may decrease cardiac output, resulting in reduction of renal blood flow as well as causing postoperative AKI. Restricted fluids volume therapy during surgery has been advocated for the last decade and has shown better outcomes than conventional therapy. Furthermore, volume overload during fluid resuscitation worsens organ perfusion during AKI. Goal-directed therapy (GDT) is a strategy for administering fluids and cardiovascular drugs to help guide physicians with monitoring techniques. However, whether goal-directed and/or restricted volume therapy causes AKI has not been determined.

The aim of this retrospective study was to evaluate the intraoperative risk factors for AKI after hepatic surgery with goal-directed therapy using restricted volumes.

Methods

The ethical approval for this study (No. 2331) was provided by the Ethical Committee of St. Marianna University School of Medicine.

Patients with significant renal dysfunction (preoperative eGFR <60ml/min) and patients who received hemodialysis or emergency operation were excluded.

1. Study Design
Anesthesia and medical records of patients who underwent hepatic resection for liver tumors at St. Marianna University Hospital between August 2009 and July 2010 were studied.

2. Anesthesia
Premedication was not administered to all patients. However, all patients received epidural anesthesia before surgery. An epidural catheter was inserted in the vertebral interspace via either Th9/10 or Th10/11. General anesthesia was induced with propofol 1–2 mg/kg and remifentanil 0.5 mcg/kg/min. Tracheal intubation was facilitated with rocuronium 0.9 mg/kg. Anesthesia was maintained with 1–1.5% sevoflurane and oxygen-air mixture and remifentanil. Levobupivacaine 0.125% or 0.25% was administered via epidural catheter during and after surgery for perioperative analgesia.

All patients underwent controlled mechanical ventilation with oxygen and air.

After the induction of anesthesia, either the left or right radial artery was cannulated.

Then central venous catheter was introduced via the right internal jugular vein.

3. Goal-directed and Fluid Management During Surgery
Radial arterial pressure and central venous pressure catheter were connected to a hemodynamic monitor, recording arterial pressure and CVP.

CVP and stroke volume variation (SVV) were monitored continuously by arterial contour analysis using the FloTrac sensor™ and the Vigileo™ monitor (Edwards lifesciences LLC, CA, USA) for restrictive fluid management during PTC.

PTC with inferior vena cava clamping was performed for 15 minutes followed by several periods of unclamping for 5 minutes each.

Both low CVP (5 cm H2O) and high SVV (12%) during PTC were achieved by restricting fluid volume. Fluid management was achieved with standard approach for liver resection. Restricting fluid volume management (less than 5ml/kg/h) was applied from the start of operation to completion of hepatic resection. After hepatic resection, maintenance fluids were infused to achieve the assumed fluid requirement (over 10ml/kg/h). After this fluid therapy, if either systolic blood pressure was <80 mmHg or SVV was <12%, additional fluid boluses either colloid or crystalloid were given. Packed blood cells were included in resuscitation if the hemoglobin level was <7 g/dl.

4. Definition of AKI and Group Classification
AKI was assessed using the AKI network definition. The AKI and non-AKI groups were differentiated by the level of serum creatinine (SCr) after surgery.

Group AKI: Patients who showed a post-operative SCr of more than or equal to 0.3 mg/dl or an increase of more than or equal to 150% to 200% from the baseline with in a 48 hour postoperative period (stage 1), or patients who showed that a post-operative SCr increase to more than 200 to 300% from the baseline (stage 2), or patients who showed a post-operative SCr increase of more than 300% from the baseline or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl (stage3).

Group non-AKI: Patients who showed a post-operative SCr of less than 0.3 mg/dl with in a 48 hour
postoperative period.

5. Data Analysis

The patients’ demographic data, duration of surgery, anesthesia, and PTC, intraoperative fluid volume, amount of blood loss and blood transfusion urinary output and frequency of IVC clamping were investigated.

The preoperative and postoperative SCr values for the AKI and non-AKI groups were also studied. Finally, the relationship between the increase of SCr and duration of surgery, anesthesia and PTC was analyzed.

6. Statistical Analysis

Continuous variables were presented as medians (IQR: interquartile range). Categorical variables were presented as percentages (%). All data were analyzed with SPSS Statistics software, version 18.0 (IBM, Chicago, IL, USA).

Statistical analyses included Mann-Whitney U-test, Fisher’s exact test, Pearson correlation, and multiple logistic regression analysis. P<0.05 was considered significant.

Results

Between August 2009 and July 2010, hepatic resection for liver tumor was performed on 67 consecutive patients. Eight patients developed stage-1 AKI (12%) after surgery, but none required renal replacement therapy.

There were no differences in preoperative SCr between the AKI and non-AKI groups (median; 0.79 vs 0.73 mg/dl, IQR; 0.67–0.84 vs 0.56–0.84). Postoperatively, SCr in the AKI group was larger (median; 1.25 mg/dl, IQR; 1.04–1.34) than in the non-AKI group (median; 0.80 mg/dl, IQR; 0.65–0.93) (P=0.001, Figure 1).

In the AKI group, there were fewer female than male patients (P=0.002). More patients were compromised with hypertension and diabetes mellitus in the AKI group than in the non-AKI group (P=0.02, Table 1). The range of hepatic resections performed was larger in the AKI group than in the non-AKI group (P=0.001, Table 1).

The durations of anesthesia and PTC were more prolonged in the AKI group than in the non-AKI group (P=0.006 and P= 0.004, Table 2). The clamping of IVC was performed more frequently in the AKI group than in the non-AKI group (P= 0.004).

There were no differences in fluids infusion rate and urinary output between the two groups.

There were no differences in fluids infusion rate and urinary output between the two groups.

Although the increase of SCr correlated weakly with the duration of anesthesia and PTC(r=0.33, P=0.008 and r=0.30, P=0.013, Figure 2A and 2B), the correlation with the duration of surgery was not statistically significant.

Finally, multiple logistic regression analysis for the duration of anesthesia, and PTC and, volume of blood loss and total fluids showed no differences between the AKI and non-AKI groups (Table 3).

Discussion

The incidence of AKI after hepatic surgery in the present study was 12%. This agrees with the results of Slankamenaec et al(16) who reported an incidence of 15.1% which was highly associated with mortality (23.2%). In our study, the degree of renal dysfunction was less than in the study of Slankamanaec et al. All of the AKI patients in our study were stage-1 and no patients received renal replacement therapy or passed away. This discrepancy may be partly explained by the difference of pre-existing comorbidity. Although any patients with renal dysfunction was excluded in our study, patient with preexisting chronic renal failure (32.6%) were included in the study of Slankamanaec et al.

Our findings are congruent with those reported by Correa-Gallego(17). They reported that low central venous pressure-assisted hepatectomy was associated with AKI (17%). They also reported that 13% of patients had been at risk, 2% experienced injury and 1% experienced failure in RIFLE (risk-injury-failure-loss-end-stage) criteria(18).

Fluids management during abdominal surgery has changed in the last decade. Traditional approaches to perioperative fluid therapy are based on historical estimates of fluid requirements during fasting and during episodes of excess loss. In this approach, the large volume of fluids must be administered during the perioperative period and is associated with increased postoperative morbidity(19). Fluid overload can cause edema formation in several organs. Edema can leads to myocardial dysfunction and heart failure. Pulmonary edema impairs gas exchange in the lungs. Interstitial edema also affects recovery of gastrointestinal function and wound heal-
Figure 1. Changes of serum creatinine (SCr) in AKI and non-AKI group. Boxes represent median and interquartile range.

Pre: preoperative level of SCr. Post: postoperative level of SCr

Right: change of SCr in non-AKI group. Left: change of SCr in AKI group

There were no differences between preoperative level and postoperative level in non-AKI group. Preoperative SCr: 0.73mg/dl (0.56–0.84), postoperative SCr: 0.80mg/dl (0.65–0.93). Values are median (IQR). As a result, SCr increased significantly after hepatic resection in AKI group (P=0.012).

Preoperative SCr: 0.79 mg/dl (0.67–0.84), postoperative SCr: 1.25 mg/dl (1.04–1.34). Values are median (IQR).

Table 1. Patient Demographic

<table>
<thead>
<tr>
<th></th>
<th>AKI Group</th>
<th>Non-AKI Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=8)</td>
<td>(n=59)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69 (62-77)</td>
<td>68 (62-74)</td>
<td>0.349</td>
</tr>
<tr>
<td>Gender (male / female)</td>
<td>6/ 2*</td>
<td>39/ 20</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 (157-167)</td>
<td>161 (156-168)</td>
<td>0.983</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>63 (58-67)</td>
<td>58 (50-67)</td>
<td>0.426</td>
</tr>
<tr>
<td>BMI</td>
<td>23 (23-25)</td>
<td>22 (20-24)</td>
<td>0.06</td>
</tr>
<tr>
<td>ASA (1 / 2 / 3)</td>
<td>0 / 8 / 0*</td>
<td>1 / 53/ 5</td>
<td>0.010</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (75%)*</td>
<td>20 (34%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>3 (38%)*</td>
<td>14 (24%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>partial resection</td>
<td>2 (25%)</td>
<td>26 (44%)</td>
<td></td>
</tr>
<tr>
<td>segmentectomy</td>
<td>5 (63%)*</td>
<td>22 (37%)</td>
<td>0.001</td>
</tr>
<tr>
<td>lobectomy</td>
<td>1 (12%)</td>
<td>11 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (IQR) or number (%). AKI: acute kidney injury, *: P<0.01 vs. Non-AKI group

Furthermore, edema of the kidney increases interstitial pressure, decreases renal blood flow, and may cause AKI\(^1\)\(^1\).

On the other hand, restrictive fluid therapy may cause hypovolemia and also disturbs hemodynamic stability during anesthesia. Both hypovolemia and hypotension during anesthesia reduce cardiac output, hence reducing renal blood flow. Restrictive fluid therapy may contribute to the progress of AKI. However, there are no reports that restrictive fluid therapy during anesthesia causes AKI. Many studies have had better outcomes with restrictive fluid management than liberal fluid management\(^9\).

Several studies have shown that goal-directed therapy (GDT) has a benefit in reducing perioperative risk\(^2\)\(^0\). On the other hand, Pearse et al. showed that
Table 2. Operative Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AKI Group (n=8)</th>
<th>Non-AKI Group (n=59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anesthesia (min)</td>
<td>493 (418-556)*</td>
<td>363 (308-436)</td>
<td>0.006</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>375 (328-410)</td>
<td>275 (225-360)</td>
<td>0.097</td>
</tr>
<tr>
<td>Duration of PTC (min)</td>
<td>115 (141-163)*</td>
<td>61 (45-90)</td>
<td>0.004</td>
</tr>
<tr>
<td>Clamping of IVC</td>
<td>8 (100%)*</td>
<td>22 (37%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total fluids volume (ml)</td>
<td>5150 (3950-5638)*</td>
<td>3400 (2825-4525)</td>
<td>0.038</td>
</tr>
<tr>
<td>Fluids infusion rate (ml/kg/h)</td>
<td>9 (7-13)</td>
<td>10 (9-12)</td>
<td>0.709</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>5 (55%)*</td>
<td>12 (21%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>1368 (1157-1644)*</td>
<td>581 (326-1033)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total urine volume (ml)</td>
<td>770 (743-823)</td>
<td>500 (285-965)</td>
<td>0.331</td>
</tr>
<tr>
<td>Urinary output (ml/kg/h)</td>
<td>1.5 (1.3-1.8)</td>
<td>1.4 (1.0-2.0)</td>
<td>0.869</td>
</tr>
</tbody>
</table>

Values are median (IQR) or number (%). AKI: acute kidney injury, PTC: Portal triad clamping, IVC: Inferior vena cava
*; P<0.01 vs. Non-AKI group

Figure 2. Relationship between increase of SCr and duration of PTC or anesthesia.

**Figure A:** relationship between increase of SCR and duration of PTC

**Figure B:** relationship between increase and duration of anesthesia

SCr: serum creatinine, PTC: portal triad clamping

Increase of SCr correlated weakly duration of PTC (**Figure A**, r=0.331, P=0.008) or anesthesia (**Figure B**, r=0.300, P=0.013)

Table 3. Multiple logistic analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anesthesia</td>
<td>0.99</td>
<td>0.95-1.02</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration of PTC</td>
<td>0.91</td>
<td>0.82-1.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Total fluids volume</td>
<td>0.99</td>
<td>0.99-1.00</td>
<td>0.35</td>
</tr>
<tr>
<td>Total blood loss</td>
<td>1.00</td>
<td>1.00-1.02</td>
<td>0.21</td>
</tr>
</tbody>
</table>

there was no difference between GDT and usual care by meta-analysis(21). Thus the issue of whether or not GDT reduces postoperative complication is still unsolved. However, Prowle et al. showed a meta-analysis that the incidence of AKI on GDT-based fluid resuscitation decreases AKI in surgical patients(10). In

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hepatic surgery, intraoperative hemorrhage is a crucial complication. The massive bleeding and blood transfusion affect the patients’ prognosis. Control CVP during PTC is well accepted to reduce blood loss during liver resection and has been shown to have no side effect on renal function by meta-analysis.\(^5\)

In a previous report, we showed that PTC with IVC clamping causes significant reduction of cardiac output during hepatic resection.\(^2\) In the present study, we found that PTC combined with IVC clamping deteriorates renal function. Renal injury on PTC with IVC clamping can be caused by three different mechanisms. First, PTC with IVC clamping reduces cardiac output by a decrease of venous return and then reduces renal blood flow. The second mechanism is a hormonal change by PTC with IVC clamping. PTC and IVC clamping activates arginine vasopressin and the sympathetic system.\(^2\)\(^3\)\(^4\). These endocrine substances strongly decreases renal blood flow. Third, although IVC clamping decreases hepatic venous pressure, it increases CVP at the distal clamping site. The increased renal venous pressure decreases renal perfusion pressure and also reduces renal blood flow. These three mechanisms may contribute to AKI.

In this study we also demonstrated that the amount of blood loss was greater in the AKI group than in the non-AKI group, resulting in a greater necessity for blood transfusion in the former. This indicated that anemia and blood transfusion affects renal injury during surgery.

Anemia appears to have a crucial role in AKI. In cardiac surgery with cardiopulmonary bypass, several studies suggest that perioperative blood transfusion is independently associated with a 10–20% increase in the risk of AKI after surgery.\(^2\)\(^5\). In hepatic surgery, anemia ensues when oxygen delivery is compromised by hemodynamic change due to PTC with IVC clamping.

In this study, the total fluid volume in the AKI group was larger than that in the non-AKI group. The reason may have been that the operative procedure in the AKI group was more difficult than that in the non-AKI group, prolonging the duration of anesthesia and requiring more fluid volume. It was not clear whether the increase in fluid volume affected kidney injury in our study.

There are several limitations in this study. We could not determine intraoperative risk factors with multiple logistic analyses. Because the present study was a retrospective analysis, the result may have been affected by unknown factors.

Furthermore, the sample size was too small to detect significant differences between the AKI and non-AKI groups on logistic regression analysis. Strictly speaking, GDT with restrictive fluid management in the present study was different from standard GDT. Many studies have used the stroke volume index or cardiac index as the goal of fluid management throughout surgery. We used SVV and CVP as the goal of fluid management during PTC, as opposed during surgery. As a result, the total fluid volume was the same in both the AKI and non-AKI groups. Still, SVV is a good predictor of fluid responsiveness in hypovolemic patients, so continuing to measure by SVV may help to evaluate the volume status during restrictive fluid management.\(^2\)\(^6\)\(^7\). However, we did not compare GDT with restrictive fluid management and with liberal fluid management. Therefore, no conclusion can be made regarding whether GDT with restrictive fluid management or liberal fluid management is better for postoperative AKI after hepatic surgery. Further study and a larger investigation are needed to define the intraoperative risk factors for AKI after hepatic surgery with goal directed and restricted volume therapy.

We conclude that the duration of PTC with IVC clamping and blood loss affect the incidence of AKI after hepatic surgery using GDT with restrictive fluid volume management. The unstable hemodynamic during PTC with IVC clamping and blood loss appears to be involved in AKI after hepatic surgery. We recommend that early inotropic support and blood transfusion are essential for preventing AKI during hepatic resection with goal directed and restricted volume therapy.

**Conflict of Interests**

The authors declare that they have no conflicting interests.

**References**


25) Zhang Z, Lu B, Sheng X, Jin N. Accuracy of