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Original Article

Effects of sodium bicarbonate on hepatic injury after left lateral hepatectomy with inflow occlusion: a retrospective study

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Abstract: Ischemia-reperfusion injury induced by blocking the portal triad is a common clinical pathophysiological event during the hepatic lobectomy. We retrospectively investigated whether perioperative administration of sodium bicarbonate decreases occurrence of postoperative hepatic injury. 158 patients diagnosed with intrahepatic stone received left lateral lobectomy with inflow occlusion from Jan 2011 to Mar 2017. Control (n=124) and the sodium bicarbonate (n=34) groups were assigned depending on whether they intraoperatively received sodium bicarbonate or not. The data of alanine aminotransferase (ALT), aspartate transaminase (AST) and total Bilirubin, reflecting liver functions, on the pre-operative day, the first day and the third day after operation were collected and compared. Patients of two groups were well balanced for baseline characteristics. The AST level significantly decreased in the sodium bicarbonate group on the first day after operation compared with Control group (p=0.0058). 150 ml of intravenous sodium bicarbonate showed a significant attenuate in increased plasma AST, ALT and total Bilirubin levels at one day after operation compared with 50 and 100 ml (all $p < 0.05$), but not on the third day after operation ($p > 0.05$). Significant differences were found in BE, sodium, bicarbonate levels both one hour after occlusion and after surgery in the sodium bicarbonate group compared with Control group. And the number of patients treated with hepatic protective drugs on the second day after surgery declined significantly in the sodium bicarbonate group compared with Control group (p=0.0194). A particular volume of sodium bicarbonate can reduce hepatic injury after left lateral lobectomy of liver with inflow occlusion on the first day after operation and alleviate the burden of postoperative liver protective drugs usage.

Keywords: Sodium bicarbonate, hepatic ischemia-reperfusion injury, left lateral lobectomy

Introduction

Temporary portal triad clamping is one common methodology of reducing bleeding and transfusion during hepatic lobectomy since the early 20th century [1, 2]. Unfortunately, ischemia/reperfusion (IR)-induced ischemic injury in the remnant liver remains a frequent and major complication after portal triad clamping. It compromises liver function and increases postoperative morbidity, mortality, progress, recovery, and overall outcomes [3-5]. A great number of in-depth studies focused on the complicated mechanism underlying hepatic IR injury. It is now becoming clear that oxidative stress, inflammatory response, the impairment of mitochondria and vascular integrity and so on, play critical roles in hepatic IR injury [6-8]. And a variety of promising protective approaches have been explored to reduce the injury. Ischemic preconditioning, surgical strategies and pharmacological therapies with different targets play a predominant role in minimizing the hepatic IR injury in experimental animals and clinical [9, 10]. However, effective ways to prevent hepatic IR injury are not available so far [11].

Sodium bicarbonate was used to attenuate free radical formation and inhibit oxidase stress [12]. It has high accessibility and is a low-cost, easy-to-use drug in clinical. It's also suggested that sodium bicarbonate serves as a possible strategy for prevention of nephropathy

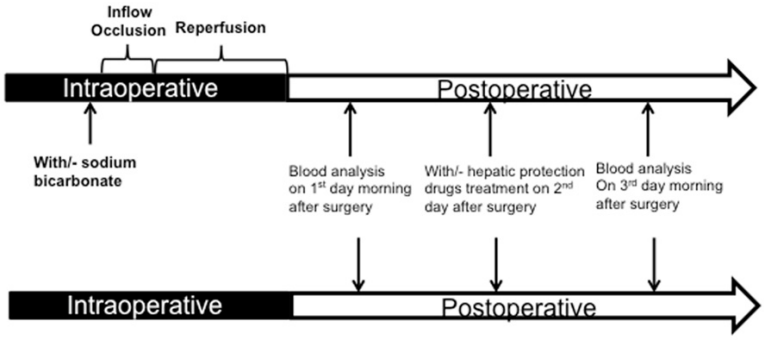

Figure 1. Protocol of surgical procedure and outcome measures.

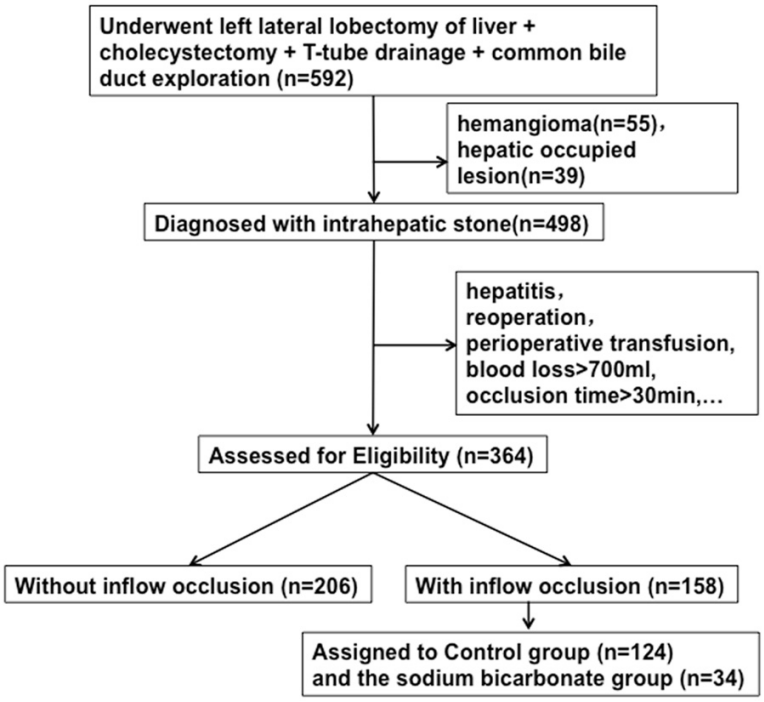

Figure 2. Study Flow and Distribution of participants through each stage of the retrospective study.

in patients undergoing coronary angiography or patients with systemic inflammatory response syndrome or sepsis and oliguria [13, 14]. But it has been rarely reported about the effect of sodium bicarbonate on hepatic IR injury induced by the hepatolobectomy with inflow occlusion. To address these issues, we retrospectively collected data to check whether intraoperative administration of sodium bicarbonate reduced hepatic injury in patients undergoing left lateral lobectomy of liver with inflow occlusion, with hopes of developing a simple and effective therapy to diminish the injury.

Material and methods

Patients

The de-identified data was retrospectively obtained from Jan 2011 to Mar 2017 from the structured hospital information system (HIS) and Anesthesia system of our institute, in accordance with local ethical committee approval. 364 ASA physical status I/II/III adult patients, who were diagnosed as intrahepatic bile duct stone and underwent left lateral lobectomy of liver + cholecystectomy + T-tube drainage + common bile duct exploration with or without inflow occlusion. The exclusion criteria were (1) diabetes mellitus; (2) preoperative hepatic dysfunctions; (3) hemangioma; (4) hepatic occupied lesion; (5) hepatitis; (6) scheduled resection not requiring hepatic portal occlusion; (7) reoperation; (8) perioperative transfusion; (9) administration of hepatic protective drugs on the first day after operation; (10) blood loss in operation > 700 ml; (11) occlusion time > 30 min. And in the patients with inflow occlusion during surgery, the control and sodium bicarbonate groups were assigned depending on whether they preoperatively received sodium bicarbonate or not. And in the sodium bicarbonate group, 50 ml up to 150 ml of sodium bicarbonate was intravenous once within 20 minutes before occlusion during surgery (**Figure 1**). And the volume of sodium bicarbonate infused perioperatively was depending on the anesthetists' experiences and decision.

Anesthesia management

All the patients were under general anesthesia with tracheal intubation. They were given midazolam (0.1-0.15 mg/kg), propofol (1.5-2 mg/

kg), sulfentanil (0.5-0.8 μg/kg) and cisatracurium (0.15 mg/kg) for routine anesthesia induction. Anesthesia was all maintained with propofol, cisatracurium, remifentanil and sevoflurane. All the patients were treated with arterial radialis puncture for direct manometric method and arterial blood gas analysis. A central venous catheter was indwelled for monitoring the central venous pressure and infusing of fluids or transfusion. In addition, ECG, blood pressure, SpO_2, $EtCO_2$ and urine volume were checked continuously as a routine during surgery. Arterial blood gas analysis in the patients with hepatic portal interdiction during surgery were carried out at least three times: preoperatively, immediately after surgery and 24 hours after surgery. Patients were extubated once awake in PACU.

Study outcomes

Basic characteristics such as ASA, sex, and age were gathered and compared between the groups. The operation time, blood loss, occlusion time, urine outputs, anesthesia management and number of patients requiring vasopressin were also compared. The comparison of anesthesia management included dosages of different anesthetic drugs including sufentanil, sevoflurane and so on. Postoperative conditions including the hospital stay time, incidence of acute liver failure, pulmonary infection, number of patients who had postoperative controlled intravenous analgesia (PCIA) and number of patients received hepatic protective drugs on the second day after surgery were also compared.

The primary study outcome was the variables reflecting the liver and renal functions, including alanine aminotransferase (AST), aspartate transaminase (ALT), total Bilirubin, Blood urea nitrogen (BUN), and creatinine on the day before operation, the first day and third day after operation. Especially, plasma pH, the concentrations of K^+, Na^+, and HCO_3^- were also measured and compared by blood gas analysis preoperatively, 1 h after occlusion and immediately after surgery.

Statistical analysis

Results are expressed as mean ± standard deviations (SD). Student's t tests or nonparametric tests were used to compare quantitative variables, and Fisher's exact tests were used for categorical variables. Results were assessed using one-way analysis of variance (ANOVA) followed by Student's t-test. Statistical analysis was implemented with Prism 6 (GraphPad Software, Inc., CA, USA), during which *p* values less than 0.05 were considered statistically significant.

Results

We conducted a single-center, retrospective study of hospitalized adults from Jan 2011 to Mar 2017. In total, 592 patients who underwent left lateral lobectomy of liver + cholecystectomy + T-tube drainage + common bile duct exploration were considered potential candidates. We identified 498 subjects in the structured hospital information system (HIS) of our institute who were diagnosed with intrahepatic stone. 94 patients were excluded with a discharge diagnosis of 'haemangioma' or 'hepatic occupied lesion' and so on. And another 134 patients were next ruled out, as they had hepatitis, reoperation, perioperative transfusion, blood loss > 700 ml, occlusion time > 30 min. Finally, 364 patients underwent the operations with (B and C groups, n=158) or without hepatic portal interdiction (A group, n=206) were assessed for eligibility. And 158 patients of them enrolled were divided into the sodium bicarbonate group (C group, n=124) who received intravenous sodium bicarbonate intraoperatively, and Control group (B group, n=34) (**Figure 2**). A detailed description of baseline demographic characteristics of enrolled patients is given in **Table 1**. No significant differences were found between the groups (B *vs.* A group, C *vs.* B group) in ASA, age, sex, and BMI (all $p > 0.5$) (**Table 1**). Similarly, Intraoperative data, including blood loss, occlusion time, operation time, urine output, number of patients requiring vasopressin and anesthesia management, were shown no differences between groups (B *vs.* A group, C *vs.* B group) (all $p < 0.5$) (**Table 1**). In the patients with inflow occlusion, the mean occlusion times of B and C groups were 15.04 minutes and 15.29 minutes, respectively. The mean dose of sodium bicarbonate was 116.2 ml (Data not shown). Postoperative data, including hospital stay, PACU time, PCIA numbers, incidence of myocardial infarction, pulmonary infection, liver failure, and mortality, were also comparable between

Table 1. Preoperative, perioperative and postoperative characteristics and data

Parameter	Without inflow occlusion			*p1 (B vs. A)*	*p2 (C vs. B)*
	Without inflow occlusion (A)	Control (B)	Sodium bicarbonate (C)		
Preoperative					
Sample	206	124	34		
ASA	I-III	I-III	I-III	> 0.05	> 0.05
Sex	F 125, M 81	F 77, M 47	F 22, M 12	0.8165	0.8434
AGE	49.12±0.5809	51.17±0.7121	51.91±1.762	0.154	0.652
Intraoperative					
Total infused (ml)	3224±70.88	3277±76.43	3558±140.8	0.656	0.088
Blood Loss (ml)	427.3±12.2	435.1±17.72	433.8±30.20	0.771	0.973
Occulsion time (min)	-	15.04±0.6650	15.29±1.168	-	0.857
Operation time (h)	3.329±0.0805	3.347±0.1029	3.068±0.1210	0.8911	0.179
Urine output (ml)	939.3±27.76	951.6±41.67	1089±84.63	0.7543	0.135
Number of patients requiring vasopressin	119 (87)	66 (58)	20 (14)	0.4256	0.6979
Anesthesia management					
Sufentanil (μg)	79.54±1.093	79.25±1.562	77.06±3.067	0.8785	0.516
Sevoflurane (ml)	22.06±0.5506	23.47±0.721	24.35±1.668	0.1236	0.587
Propofol (mg)	664.7±15.35	620.9±20.96	609.4±42	0.0887	0.801
Remifentanil (mg)	1.215±0.0255	1.163±0.335	1.271±0.102	0.2172	0.197
Postoperative					
Hospital stay (d)	19.13±0.3592	19.66±0.5399	21.21±1.152	0.3963	0.198
PACU time (h)	81.18±1.977	76.91±6.32	84.18±3.26	0.4035	0.3
PCIA	188 (18)	118 (6)	32 (2)	0.2734	0.6819
Myocardial infarction	0	0	0	> 0.05	> 0.05
Pulmonary infection	0	0	0	> 0.05	> 0.05
Death	0	0	0	> 0.05	> 0.05
Liver failure	0	0	0	> 0.05	> 0.05
Bile Leakage	0	0	0	> 0.05	> 0.05
No. of patients received hepatic protective drugs on the 2nd day after operation	71 (135)	57 (67)	8 (26)	0.0472	0.0194

Values are presented as median or number (%). PCIA, postoperative controlled intravenous analgesia.

the groups (B *vs.* A group, C *vs.* B group) (all p > 0.5). No patients had myocardial infarction, pulmonary infection and acute liver failure after surgery in all the groups. However, the number of patients treated with hepatic protective drugs on the second day after surgery declined significantly in the sodium bicarbonate group compared with Control group (C *vs.* B group, p=0.0194). And this number in B group were significantly more than in A group (B *vs.* A group, p=0.0472) (**Table 1**).

The plasma levels of different biomarkers reflecting liver (AST, ALT, total Bilirubin), and renal functions (BUN, creatinine) in all the patients were also harvested before operation, one and three days after operation. To investigate the influence of hepatic portal interdicting on haptic and renal functions after surgery, the levels of plasma ALT, AST, total bilirubin, BUN and creatinine of patients in A and B group were separately compared. A significant increase of AST and ALT were shown in B group at one day after operation (B *vs.* A group, p= 0.0155, p=0.0484, respectively). But no significantly differences were found in the levels of AST, ALT or total bilirubin between A and B group at three days after operation (B *vs.* A group, p=0.9193, p=0.9788, p=0.7644, respectively) (**Table 2**). Then by comparing the two groups of patients with hepatic portal interdiction during surgery, we found patients in C group experienced a significantly attenuation in their absolute and relative increase in plasma AST on the first day after operation compared to the patients in B group (C *vs.* B group, p=0.0058). Both plasma ALT and total bilirubin levels showed obviously attenuate in their increase, but not so significantly (C *vs.* B group, p=0.072, p=0.608, respectively). All the plasma levels of AST, ALT and total bilirubin in both groups increased on the first day after operation, but returned to the same levels as control

group by three days after operation. But for the renal function, no significant differences of the BUN and creatinine levels were found between the groups before operation, 1 day or 3 days after operation (B *vs.* A group, C *vs.* B group, all $p > 0.05$) (**Table 2**). According to the different volume of intravenous sodium bicarbonate in C group, the low volume (50 or 100 ml, n=11) and high volume (150 ml, n=23) groups were separated. Interestingly, the high volume group showed remarkable attenuation in increased plasma AST, ALT and total Bilirubin levels level at one day after operation compared to Control group ($p < 0.001$, $p=0.0043$, $p=0.0487$) (**Figure 3**), but not in the low volume group ($p=0.573$, $p=0.347$, $p=0.645$) (data not shown).

Arterial blood gas analyses were made preoperatively, 1 h after occlusion and immediately after operation in B and C groups, to observe the effect of intravenous sodium bicarbonate on arterial pH, BE, lactate, sodium, bicarbonate and so on. All the preoperative plasma biochemical variables were comparable between the two groups ($p > 0.5$) (**Table 3**). The arterial blood gas analysis showed significant differences in the levels of PH, BE, sodium, bicarbonate levels both 1 h after occlusion and after surgery in the sodium bicarbonate group compared with Control group (all $p < 0.5$) (**Table 3**).

Discussion

To investigate the influence of hepatic portal interdicting on intraoperative and postoperative data, total infused, blood loss and so on were separately compared between A and B group. And no significant differences were found.

It should be noted that hepatic portal interdiction was not found to decrease the amount of blood loss, which was different from the previous reports [14, 1, 2]. The possible reason is that we excluded the patients whose blood loss was more than 700 ml during the surgery, considering that massive blood loss may lead to hepatic injury, severe unbalance of electrolyte and so on. Thus, differences between the two groups were not significant because of the data deficiency. In addition, a significant increase of ALT, AST levels in plasma were shown in B group at one day after operation compared with A group. The results obtained are consistent with previous studies in confirming that hepatic portal interdiction caused liver injury of ischemia reperfusion [3-5].

Our study showed a significantly better postoperative profile regarding AST levels for the sodium bicarbonate group at one day after operation. Although we found a slightly better postoperative operative profile regarding ALT and total bilirubin levels in the sodium bicarbonate group, the differences were not statically significant. This inconsistency of AST and ALT levels were also found in Henrik Petrowsky's study [14]. In their prospective research, intermittent clamping resulted in lower AST values than ischemic preconditioning whereas the opposite constellation was found for peak ALT after operation in patients undergoing major liver resection, although these differences were not statistically significant [14]. There may be some explanations for it. It's known that both AST and ALT are highly concentrated in the liver, but AST is also diffusely presented in the heart, skeletal muscle, kidneys and red blood cells [15]. Thus, an increase in AST serum levels is more sensitive for acute injury, including liver, kidney injury and so on compared with ALT. Another possibility is that in ischemic liver injury, AST levels usually peak before those of ALT because of the aminotransferase's peculiar intralobular distribution [16]. In particular, the plasma level of total bilirubin is very low [17]. Therefore, it is important to stress that the pattern of enzyme alteration may vary and occasionally appear similar if only one or two observation points are taken into consideration.

Numerous factors contribute to hepatic IRI, including impairment of sinusoidal endothelial cells, disturbance of microcirculation, oxidative stress, up regulation of proinflammatory cytokine signaling and so on [6-8, 18]. Hence, many surgical methods, ischemic preconditioning, gene therapy, additives in preservation solutions and pharmacological therapies with different targets have predominated in the research on novel strategies to minimize the injurious effects of warm I/R [9, 10, 19]. There is growing evidence that sodium bicarbonate could play an important role in its ability to markedly attenuate oxidative injury due to hypoxia/reoxygenation [11, 20]. The mechanism may mainly involve in the bicarbonate-dependent acid–base transporters called Na^+/

Table 2. Variations in the liver and renal function

Parameter	With Inflow Occlusion			*p1 (B vs. A)*	*p2 (C vs. B)*
	Without inflow occlusion (A)	Control (B)	Sodium bicarbonate (C)		
AST					
Before operation	31.44±0.9570	30.21±1.161	32.76±2.257	0.4211	0.3102
1 day after operation	150.9±5.573	175.8±9.416	122.9±11.01	0.0155	0.0058
3 days after operation	39.77±1.347	39.53±1.905	32.97±2.540	0.9193	0.0925
ALT					
Before operation	43.98±1.995	39.75±2.770	50.15±7.079	0.2085	0.108
1 day after operation	136.7±5.003	157.7±10.86	119.1±10.11	0.0484	0.0717
3 days after operation	80.89±3.035	81.03±4.565	78.03±9.209	0.9788	0.7609
Total Bilirubin					
Before operation	25.19±1.410	22.28±1.899	21.80±3.051	0.2159	0.9031
1 day after operation	25.03±1.097	26.94±2.172	25.25±1.712	0.3823	0.6077
3 days after operation	32.04±2.261	30.91±3.053	25.28±1.862	0.7644	0.3361
BUN					
Before operation	4.158±0.1113	4.114±0.1571	3.580±0.1488	0.8134	0.0832
1 day after operation	3.886±0.09366	3.672±0.1316	3.864±0.2314	0.1798	0.444
3 days after operation	4.137±0.1207	3.833±0.1741	4.239±0.2394	0.1485	0.2263
Creatinine					
Before operation	62.90±1.445	60.32±2.067	60.02±2.325	0.3053	0.928
1 day after operation	58.20±1.391	54.60±1.818	55.42±2.399	0.1305	0.788
3 days after operation	54.80±1.387	50.63±2.148	55.54±2.462	0.1057	0.142

Values are presented as mean ± standard deviations (SD). AST, aspartate transaminase; ALT, aminotransferase; BUN, Blood urea nitrogen.

HCO_3^- co-transporters on the cell membrane. It is involved not only in intracellular pH regulation in cells but also plays a critical role in maintaining ionic homeostasis and water balance between the intra- and extra-cellular space [21, 22]. Emerging evidences indicate that sodium bicarbonate can slow pH-dependent Haber-Weiss free radical production [6], and directly lead to scavenging of reactive nitrogen or oxygen [23]. Although not referred in our research, it can be postulated that sodium bicarbonate administrated to patients exposed to ischemia-reperfusion protects the liver from oxidation and peroxidative injury acting as an antioxidant compound.

However, the exact volume of sodium bicarbonate for preventing hepatic injury in patients undergoing left lateral lobectomy of liver with inflow occlusion is rarely known. An unanticipated finding in our study was that the high volume of sodium bicarbonate conferred a high degree of protection while this effect was lost in the low volume. In our research, three doses of sodium bicarbonate, i.e. 50, 100 and 150 ml were intravenously administrated in the sodium bicarbonate group. Then the low (50 and 100 ml) and high volume (150 ml) groups were separated. And another important finding of our research was that the patients administrated with 150 ml of intravenous sodium bicarbonate experienced a significantly reduced hepatic injury (plasma AST, ALT and total Bilirubin levels) with respect to 50 and 100 ml on one day after operation. In this respect, 150 ml of intravenous sodium bicarbonate may be expected to reduce hepatic reperfusion injury or stunning after left lateral lobectomy of liver with inflow occlusion rather than 50 or 100 ml. This raises the possibility that the higher volume of sodium bicarbonate may be the more propitious to prevent the hepatic IR injury. Nonetheless, the exact volume of sodium bicarbonate that should be administrated for preventing the hepatic injuries needs to be further investigated. In addition, 150 ml of sodium bicarbonate administration can reduce hepatic injury left lateral lobectomy of liver with inflow

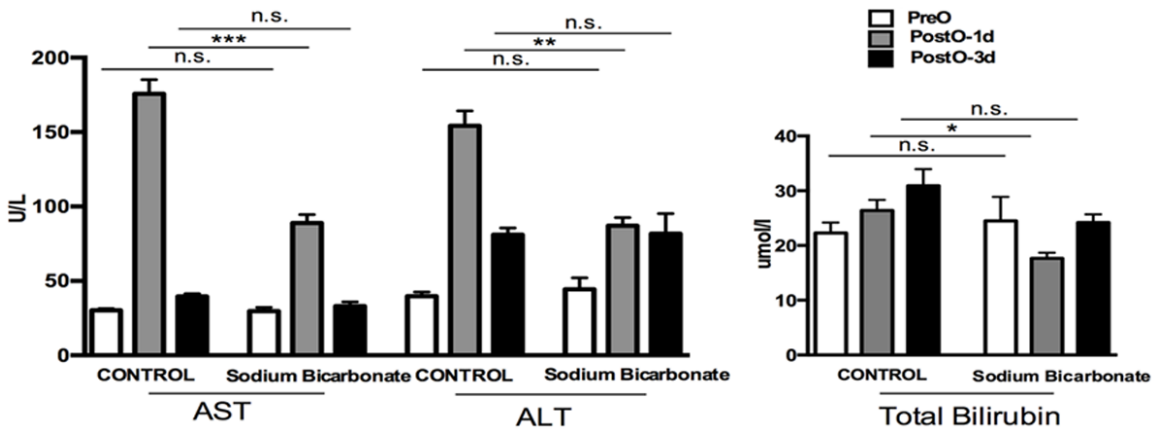

Figure 3. 150 ml of sodium bicarbonate showed remarkable attenuation in increased plasma AST (vs. Control group, $p < 0.001$), ALT (vs. Control group, $p=0.0043$) and total Bilirubin (vs. Control group, $p=0.0487$) levels at one day after operation. All the plasma levels of AST, ALT and total bilirubin in both groups increased at one day after operation, and then recovered by three days after operation. $^{*}p < 0.05$, $^{**}p < 0.01$, Data are presented as mean ± SD.

Table 3. Changes in Plasma Biochemical Variables

Parameter	Control	Sodium bicarbonate	*p*
pH			
Preoperative	7.378	7.372	0.4522
1 h after Occulsion	7.33	7.41	< 0.01
After surgery	7.33	7.39	< 0.01
Hemoglobin, g dl^{-1}			
Preoperative	11.52	11.77	0.2979
1 h after Occulsion	11.13	11.01	0.6261
After surgery	10.07	10.49	0.0981
Bicarbonate, mmol/l			
Preoperative	23.10	22.97	0.6784
1 h after Occulsion	22.15	25.04	< 0.01
After surgery	22.6	24.2	< 0.01
Base excess			
Preoperative	-1.68	-1.8	> 0.05
1 h after Occulsion	-4	-2.8	0.0403
After surgery	-3.3	-0.8	< 0.01
Lactate, mmol/l			
Preoperative	0.72	0.69	> 0.05
1 h after Occulsion	1.87	2.01	> 0.05
After surgery	2.89	2.11	0.0496
Sodium, mmol/l			
Preoperative	137.2	138.5	> 0.05
1 h after Occulsion	136.5	138.2	0.078
After surgery	136	139.6	0.0014

Values are presented as median.

occlusion only at one day after surgery by attenuating the rise of AST, ALT and total bilirubin but not at the third day. Actually, the doctors postoperatively had given the patients hepatic protective drugs mostly depending on the levels of AST, ALT and total bilirubin of one day after surgery. Interestingly, the number of patients treated with hepatic protective drugs on the second day after surgery declined significantly in the sodium bicarbonate group compared with Control group. Surely, administration of hepatic protective drugs on the second day after surgery could accelerate the amelioration of liver function on the third day. This may explain why the sodium bicarbonate administration can reduce hepatic injury only at one day after surgery but not at the third day.

Considering that sodium bicarbonate infusion might be effective in preventing hepatic injury, kidney function was also checked. The BUN and creatinine levels were compared between B and C groups. As expected, perioperative infusion of sodium bicarbonate did not show postoperative kidney protection. But it is known that sodium bicarbonate can decrease the acidification of urine and renal medulla, which might limit the urinary excretion rate of complement activation products and protect the kidney from injury [24, 25]. The main explanation for the discordance may be that we did not consider or exclude patients pre-existing chronic or acute renal disease. And also few studies have reported have found the renal damage induced by hepatic IRI. Accordingly, it is difficult to associate the renal injury with hepatic IRI from the current results.

This study is still subject to the following limitations. Firstly, the number enrolled is limited. Especially, only 34 patients were collected in the sodium bicarbonate group since 2011. It remains possible that greater subject yield different outcomes. So larger RCT studies providing for higher level of evidence and more investigations for the precise mechanism underlying postoperative IRI in patients undergoing hepatic lobectomy with inflow occlusion are required for further works. As it was not completely realized the importance of preventing hepatic ischemic injury in our operation room, the volume of sodium bicarbonate infused definitely depended on the anesthetists' experiences and decision but not the stark evidences or guidelines. Thus, it may provide favorable evidence for emphasizing the significance of the administration of sodium bicarbonate and its routine use perioperatively. In addition, the levels of AST, ALT and the total bilirubin decreased on one day after surgery may have no beneficial clinical consequences at all. And the hepatic damage caused by the short blocking time may be much less compared to surgical operation of the lateral lobectomy. But in our study, the postoperative level of transaminases could guild the clinical medication, especially the use of the liver protective drugs. Lastly, we only collected the number of patients treated with hepatic protective drugs on the second day after surgery in our study. The types, dosages of drugs and medication course were not included.

Conclusions

Based on these observations, we concluded that a particular volume of sodium bicarbonate has the potential to improve hepatic function in liver surgery with inflow occlusion involving ischemic stress and reperfusion. And it can also alleviate the burden of postoperative liver protective drugs usage postoperatively. Further studies are necessary to confirm our findings and allow a better appreciation of their clinical value.

Disclosure of conflict of interest

None.

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