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Bilirubin adsorption for the treatment of severe hyperbilirubinemia after cardiac surgery: A retrospective cohort study

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Abstract

Objective: Severe hyperbilirubinemia after cardiac surgery increases in-hospital and 1-year mortality. Our present study aimed to analyze the safety and efficacy of bilirubin adsorption (BA) in patients with post-cardiac-surgery severe hyperbilirubinemia.

Methods: We retrospectively included patients who underwent BA due to severe hyperbilirubinemia after cardiac surgery in our center between January 2015 and December 2018. The change of serum bilirubin, alanine aminotransferase, aspartate aminotransferase, and 30-day and 1-year mortality were assessed as endpoints. Univariate and multivariate analyses were employed to identify the risk factors of patient 30-day mortality.

Result: A total of 25 patients with 44 BA treatments were included. One BA treatment reduced total bilirubin (TB) concentration from 431.65 ± 136.34 to 324.83 ± 129.44 μmol/L ($p < 0.001$), with a reduction rate of 24.8%. No clinically relevant thrombosis of the extracorporeal circuit occurred during the BA treatment. The 30-day and 1-year mortality rates were 68% ($n = 18$) and 84% ($n = 21$), respectively. Multivariate analysis identified that TB level before BA treatment (odds ratio [OR] 1.010, 95% confidence interval [CI] 1.000–1.019; $p = 0.043$) was an independent risk factor of 30-day mortality.

Conclusions: BA treatment should be considered as an effective and safe method for the reduction of serum bilirubin in patients with post-cardiac-surgery severe hyperbilirubinemia. Patients with higher TB level before BA treatment had a relatively increased risk of 30-day mortality. Further studies are needed to evaluate the timing of BA for severe hyperbilirubinemia after cardiac surgery.

Keywords

Hyperbilirubinemia, bilirubin adsorption, cardiac surgery

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Introduction

Over 2 million patients underwent cardiac surgeries worldwide per year.[1] Post-cardiac surgery hyperbilirubinemia is common, with an incidence of about 20–51%,[2–7] which may result from factors associated with cardiopulmonary bypass (CPB), such as hemolysis, hypoperfusion, and systemic inflammatory response, and also may be associated with secondary hepatic dysfunction due to heart failure or sepsis.[4,8] Post-cardiac-surgery hyperbilirubinemia is associated with

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longer hospital stay and a mortality of up to 30%. In patients with hepatic failure after cardiac surgery, the in-hospital mortality could be as high as 90%.[4,6,9] Study suggested that hyperbilirubinemia could aggravate infection, acute kidney injury (AKI),[10] and other operative complications. Additionally, severe hyperbilirubinemia has neurotoxic and encephalopathic effect.[11,12] Therefore, for patients with post-cardiac-surgery severe hyperbilirubinemia, the reduction of serum bilirubin concentration might be effective on the improvement of the patient outcome.

Bilirubin adsorption (BA) is a technique of therapeutic apheresis by using a bilirubin-adsorbing column. During BA treatment, the plasma is separated by the first column and then filtered by a bilirubin adsorption column before it is re-injected into the patient. BA is widely used due to its simplicity: (1) no infusion of exogenous plasma or albumin is required; (2) clotting factors or drugs could be preserved. In the last 15 years, BA has been reported as a treatment for patients with acute liver failure or acute-on-chronic liver failure caused by various etiologies, and could effectively reduce the bilirubin concentration and improve patient survival.[13–15] However, in post-cardiac-surgery hyperbilirubinemia patients, the bilirubin reduction efficacy of BA and the efficacy of BA on patient short- and long-term mortality were rarely reported.

Therefore, we sought to determine the efficacy of BA on the reduction of serum bilirubin and the 30-day and long-term mortality in post-cardiac-surgery patients with severe hyperbilirubinemia.

Patients and methods

Study design and patient selection

We retrospectively retrieved post-cardiac-surgery patients who had severe hyperbilirubinemia and received BA treatment in our institution between January 2015 and December 2018. Patients with age <18 years or missing data of the important variables were excluded. Our present study was approved by the ethics committee of our hospital. Because of the retrospective nature, the need for the informed consent from the eligible patients was waived by the ethic committee.

BA treatment

Temporary vascular access was created by the insertion of a dual lumen catheter into the femoral or jugular vein. Each patient received 2–3 h BA per day. BA was performed by using the Diapact continuous renal replacement therapy (CRRT) machine (Baxter, U.S) with blood flow rate 150 mL/min. BA was performed according to the manufacturer's instructions. In short, plasma was separated by a disposable membrane plasma separator (BBraun Medical, Germany) and then passed a disposable plasma bilirubin adsorption column (BS330, Jafron Biomedical). Before the BA treatment, 5 mg dexamethasone was administered to prevent allergy. Vital signs and adverse events were monitored during the BA treatment. Blood chemistry was evaluated before and immediately after the BA therapy. All patients were informed about the benefit and risk of BA and an informed consent was signed before the BA treatment.

Data collection

Data was retrospectively collected by using a predefined Excel table from the patients' medical records. Baseline characteristics, including demographic and operative data were recorded. Laboratory parameters, including routine blood tests, blood biochemical testes, and blood gas analyses were recorded before and after BA treatment. Illness severity was scored by using the acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA) score, European system for cardiac operative risk evaluation II (EuroSCORE II), and model for end-stage liver disease (MELD) score before and after cardiac surgery. Postoperative outcomes, including amount of blood transfusion, hospitalization duration, ICU stay time, the number of BA treatment, mechanical ventilation time, the need for continuous renal replacement therapy (CRRT), and treatment-associated complications, were recorded. For survival patients after the hospital discharge, long-term prognosis was acquired by telephone follow up.

Outcomes and definitions

Thirty-day mortality was defined as death occurred within 30 days after cardiac surgery. Kidney disease improving global outcomes (KDIGO) criteria, based on serum creatinine (SCr) concentration and urine output, were used to diagnose and categorize AKI.[16] Preoperative SCr level nearest to the time of cardiac surgery was considered as the baseline SCr. Main indications for CRRT were progressive AKI, fluid overload, hyperkalemia, and severe metabolic acidosis.[17] Indications for BA treatment included serum total bilirubin concentration $\geqslant 340$ μmol/L or rapidly progressing of hyperbilirubinemia (bilirubin concentration increased by more than 34 μmol/L per day for five consecutive days).[14]

Statistical analyses

The results are showed as the mean $\pm$ SD for continuous variables and proportions for categorized variables. To evaluate the efficacy of each BA treatment, all of BA sessions were pooled and analyzed as an independent sample. Student's paired *t*-test was used to evaluate the change of parameters before and after BA treatment. The variables identified by univariate analysis and the clinical important

parameters were included in multivariate Logistic regression analysis to identify the independent risk factors of patient 30-day mortality. $P \leqslant 0.05$ was considered as statistically significant. All statistical tests were two-sided. All of the data analyses were performed by using SPSS software (version 22.0, IBM).

Results

Patient characteristics

After screening, our present study included 25 patients who accepted BA treatment due to post-cardiac surgery severe hyperbilirubinemia. Of the included patients, 20 (80%) were male and the mean age was 51.76 ± 11.48 years. Additionally, of the included patients, 12 (48%), 10 (40%), 1 (4%), 1 (4%), and 1 (4%) received aortic dissection surgery under deep hypothermic circulatory arrest, valve replacement surgery under CPB due to heart valve disease, orthotopic heart transplantation under CPB due to dilated cardiomyopathy, off pump coronary artery bypass grafting due to coronary heart disease, and valve replacement and patent ductus arteriosus occlusion under CPB due to congenital heart disease, respectively. Patient characteristics are shown in Table 1.

Patient outcomes are shown in Table 2. At the beginning of BA treatment, all patients had AKI according to the KDIGO criteria. Two (8%) patients each, were classified as stage 1 and stage 2 AKI, while 21 (84%) were classified as stage 3 AKI. Eighteen patients (72%) accepted CRRT. Totally, the included patients accepted 44 BA treatments and the median BA treatment was 1 (1, 6). The median follow-up time was 0.57 (0.17–49.27) months, and no patient was lost to follow-up.

The change of laboratory variables after BA treatment

The mean TB concentration and conjugated bilirubin (CB) concentration before BA treatment were 431.65 ± 136.34 μmol/L and 321.94 ± 94.24 μmol/L, respectively. After a BA treatment, the TB and CB were reduced to 324.83 ± 129.44 μmol/L ($p < 0.001$) and 263.25 ± 137.59 μmol/L ($p < 0.001$), respectively. The averaged reduction rates of TB and CB after a BA treatment were 24.8 ± 19.92% and 18.1 ± 25.63%, respectively. Significant decreases of aspartate aminotransferase (AST, $p < 0.036$) and alanine transaminase (ALT, $p < 0.002$) levels were observed after a BA treatment. Additionally, hemoglobin concentration was found to be significantly decreased after a BA treatment ($p < 0.007$). No significant change was observed in kidney function parameters, including SCr concentration and blood urea nitrogen (BUN) concentration (Table 3). No thrombosis of the extracorporeal circuit occurred during BA treatment.

Table 1. The characteristics of study patients.

Variables	Value
Preoperative	
Age (years)	51.76 ± 11.48
Gender	
Male, *n* (%)	20 (80)
Female, *n* (%)	5 (20)
Hypertension, *n* (%)	8 (32)
Type of diseases	
Aortic dissection, *n* (%)	12 (48)
Valve heart disease, *n* (%)	10 (40)
Dilated cardiomyopathy, *n* (%)	1 (4)
Congenital heart disease, *n* (%)	1 (4)
Coronary heart disease, *n* (%)	1 (4)
APACHE II score	7.52 ± 2.50
EuroSCORE II score	6.92 ± 2.86
SOFA score	2.40 ± 2.36
MELD score	11.60 ± 7.51
AST (U/L)	173.08 ± 729.49
ALT (U/L)	166.92 ± 682.73
TB (μmol/L)	34.06 ± 34.11
CB (μmol/L)	15.10 ± 20.77
SCr (μmol/L)	108.53 ± 43.27
PLT (10^9/L)	160.96 ± 58.72
WBC (10^9/L)	9.64 ± 5.26
Hb (g/L)	134.71 ± 20.49
Intraoperative	
Duration of operation (min)	343.52 ± 127.48
CPB time (min)	206.25 ± 76.10
ACCT (min)	100 ± 27.42
The amount of blood transfusion (*U*)	12.14 ± 12.43
Postoperative	
APACHE II score	17.08 ± 2.12
SOFA score	11.96 ± 2.59
MELD score	18.12 ± 6.20
AST (U/L)	256.36 ± 294.22
ALT (U/L)	280.04 ± 590.24
TB (μmol/L)	78.79 ± 43.45
CB (μmol/L)	37.25 ± 20.34
SCr (μmol/L)	158.48 ± 42.59
PLT (10^9/L)	113.52 ± 56.68
WBC (10^9/L)	15.52 ± 6.52
Hb (g/L)	118.44 ± 23.02

ACCT: aortic cross-clamp time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APACHE II: acute physiology and chronic health evaluation II; CB: conjugated bilirubin; CPB: cardiopulmonary bypass; Hb: hemoglobin; MAP: mean arterial pressure; MELD: model for end-stage liver disease; min: minute; SCr: serum creatinine; SOFA: sequential organ failure assessment; PLT: platelet; PT: prothrombin time; WBC: white blood cell.

The prognosis and risk factors of 30-day mortality after surgery

Six patients died after discharge and two patients had dialysis-dependent end-stage renal disease. The 30-day and 1-year mortality were 68% and 84%, respectively (Table 2).

Table 4 shows the risk factors of 30-day mortality after cardiac surgery. Univariate analysis revealed that TB concentration before and after BA treatment were the risk factors of 30-day mortality. After the adjustment of the important clinical parameters (age, CPB time, and the number of BA treatment), only TB concentration before BA treatment was identified as the independent risk factor of 30-day mortality (OR 1.010, 95% CI 1.000–1.019; $p=0.043$).

Discussion

High serum bilirubin is suggested to be cytotoxic, which can cause mitochondrial dysfunction and organ system dysfunction, and could be life threatening.[11,12] Thus, excessive bilirubin should be urgently cleared to prevent the organ injury caused by severe hyperbilirubinemia. BA was suggested to be an efficacy method for bilirubin reduction in acute liver failure patients.[13–15] However, the data of BA in cardiac patients with severe hyperbilirubinemia after surgery was limited. In our present study, the main findings are following: (1) BA treatment could effectively reduce TB, CB, ALT, and AST concentration and was relatively safe for post-cardiac-surgery patients with severe hyperbilirubinemia; (2) Post-cardiac-surgery severe hyperbilirubinemia patients treated with BA had a poor prognosis; (3) TB concentration before BA treatment was an independent risk factor of 30-day mortality.

Table 2. Outcomes of patients.

Variable	Value
Reoperation, *n* (%)	8 (32)
AKI, *n* (%)	25 (100)
Stage of AKI	
Stage 1, *n* (%)	2 (8)
Stage 2, *n* (%)	2 (8)
Stage 3, *n* (%)	21 (84)
CRRT, *n* (%)	18 (72)
Number of BA, *n* (%)	44
Hospital stay (*d*)	29.80 ± 19.41
Length of ICU stay (*d*)	16.12 ± 13.30
Postoperative blood transfusion (*U*)	112.31 ± 87.02
Duration of postoperative mechanical ventilation (*d*)	7.00 ± 14.45
30-day mortality, *n* (%)	17 (68)
1-year mortality, *n* (%)	21 (84)

AKI: acute kidney injury; BA: bilirubin adsorption; CRRT: continuous renal replacement treatment; ICU: intensive care unit.

The efficacy and safety of BA treatment

In our present study, we observed statistically significant reduction in TB, CB, ALT, and AST concentration after a BA treatment in patients with post-cardiac surgery severe hyperbilirubinemia. The observed TB level reduction rates were comparable to the reduction rates reported in previous studies using other extracorporeal detoxification systems, including plasma exchange (PE) and molecular adsorbent recirculating system (MARS).[14,15] This observation reinforces the suggestion by Viggiano et al.[18] that PE, BA, and MARS have similar bilirubin lowering efficiencies. A study by Senf et al.,[14] involving 23 patients, reported a bilirubin reduction rate of 24% using BA treatment. A study on 11 patients by Keklik et al.[15] reported a bilirubin reduction rate of 38% using PE treatment. While a study on seven patients by McIntyre et al.[19] reported a bilirubin reduction rate of 40% using MARS treatment. Here, we observed a bilirubin reduction rate of 24.8%. The reduction of TB levels during a single BA treatment appeared to be relatively low, which might result from the large bilirubin distribution volume. Addition to the intravascular space, bilirubin distributes in the extravascular compartments. Therefore, redistribution of bilirubin may contribute to the relatively lower reduction of bilirubin by

Table 3. Laboratory data before and after 44 treatments of BA with 30 days after surgery.

Variable	Before treatment	After treatment	Paired difference	*p* value
AST (U/L)	182.16 ± 384.03	104.64 ± 167.32	77.52 ± 236.94	0.036
ALT (U/L)	229.39 ± 376.81	129.52 ± 195.23	99.87 ± 205.74	0.002
TB (μmol/L)	431.65 ± 136.34	324.83 ± 129.44	106.82 ± 86.11	<0.001
CB (μmol/L)	321.94 ± 94.24	263.25 ± 137.59	58.68 ± 82.50	<0.001
Albumin (g/dL)	35.34 ± 6.53	45.59 ± 67.64	−10.25 ± 68.00	0.323
TP (g/dL)	58.49 ± 9.90	68.62 ± 52.71	−10.13 ± 52.74	0.21
BUN (μmol/L)	26.82 ± 14.86	25.42 ± 15.05	1.40 ± 8.36	0.384
SCr (μmol/L)	189.92 ± 127.82	193.19 ± 134.47	−3.27 ± 71.30	0.80
CysC (μmol/L)	3.02 ± 1.79	2.60 ± 1.54	0.42 ± 1.32	0.09
PLT (10^9/L)	67.50 ± 54.46	65.38 ± 60.09	2.12 ± 23.29	0.559
WBC (10^9/L)	16.91 ± 7.51	17.84 ± 8.48	−0.93 ± 4.64	0.201
Hb (g/L)	109.43 ± 12.09	105.33 ± 13.91	4.10 ± 9.42	0.007
MELD score	26.56 ± 7.95	26.51 ± 6.60	0.05 ± 6.10	0.966

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CB: conjugated bilirubin; CysC: cystatin C; Hb: hemoglobin; MELD: model for end-stage liver disease; PLT: platelet; TB: total bilirubin; TP: total protein.

Table 4. Logistic regression analysis for 30-day mortality.

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (years)	0.985 (0.913–1.064)	0.706		
preoperative APACHE II score	1.404 (0.905–2.178)	0.129		
preoperative EuroSCORE II score	0.827 (0.597–1.144)	0.251		
preoperative TB	0.997 (0.973–1.021)	0.795		
preoperative SCr	0.995 (0.976–1.014)	0.577		
CPB time	1.009 (0.993–1.026)	0.271		
CRRT	0.800 (0.118–5.404)	0.819		
The number of BA	1.104 (0.592–2.060)	0.755		
TB before BA (μmol/L)	1.009 (1.000–1.018)	0.044	1.010 (1.000–1.019)	0.043
TB after BA (μmol/L)	1.013 (1.002–1.025)	0.023		
SCr before BA (μmol/L)	0.998 (0.990–1.007)	0.688		
SCr after BA (μmol/L)	1.001 (0.991–1.011)	0.890		

APACHE II: acute physiology and chronic health evaluation II; BA: bilirubin adsorption; CPB: cardiopulmonary bypass; EuroSCORE II: European system for cardiac operative risk evaluation II; SCr: serum creatinine; CRRT: continuous renal replacement therapy; TB: total bilirubin.
The Model was adjusted for TB before BA, age, CPB time, and the number of BA treatment.

a BA treatment. We found out that the serum TB concentrations of some patients were tested on the day after the BA treatment instead of the time right after BA treatment, which might under-estimate the serum bilirubin reduction rate as well. Additionally, we observed that the averaged AST concentration reduction rate was 42% after a BA treatment, which was comparable to PE therapy (39%).[15]

However, we observed a statistically significant reduction in hemoglobin concentration after BA treatment. Previous studies reported that hemoglobin levels were almost unaffected by BA treatment.[14,15] In our present study, the hemoglobin concentrations of four patients continued to decrease due to surgical wound oozing and/or gastrointestinal bleeding before BA treatment. When we excluded these patients from the paired analysis, there was no significant change in hemoglobin concentration after BA treatment. Most likely, the reduction in hemoglobin level in our present study was caused by the bleeding from surgical wounds and/or gastrointestinal bleeding after surgery, rather than the BA treatment.

Additionally, to prevent allergy, 5 mg dexamethasone was administered by injection before BA treatment, which is safe because of relatively small doses. No clinically relevant extracorporeal circuit thrombosis occurred during BA treatment. The results of our present study suggested that BA was effective and relatively safe for the management of post-cardiac surgery severe hyperbilirubinemia.

The prognosis of post-cardiac-surgery severe hyperbilirubinemia patients treated with BA

A previous systematic review by Kjaergard et al.[20] showed that relative to standard medical therapy, artificial support systems reduced acute-on-chronic liver failure mortality. In our present study, the 30-day and 1-year mortality for post-cardiac-surgery severe hyperbilirubinemia patients treated with BA were about 68% and 84%, respectively, which was comparable with studies of Komardina et al.,[21] Senf et al.,[14] and Keklik et al.[15] Although BA treatment effectively reduced the bilirubin levels, the overall 30-day mortality of our present cohort remains high. Of the included patients, some (56%) had severe hepatic dysfunction. Additionally, AKI was present in all patients and 18 (72%) patients received CRRT. These results indicated that the included patients had very critical situation and less possibility for reversibility. And, the initiation of BA treatment might be relatively late. Nevertheless, whether artificial liver therapy can significantly improve the prognosis of patients with severe hyperbilirubinemia after cardiac surgery is still controversial. Further researches are needed on this field.

The risk factors of 30-day mortality

Notably, we found TB concentration before BA treatment was an independent risk factor of 30-day mortality for post-cardiac-surgery severe hyperbilirubinemia patients treated with BA. Most likely, early initiation of BA treatment for severe hyperbilirubinemia patients could prevent hepatic failure progression and damage of other organs caused by hyperbilirubinemia. These findings are consistent with the study by Keklik et al.,[15] which found that two patients with mushroom poisoning recovered completely after PE treatment, and suggested that earlier treatment correlates with better patient outcomes. Up to date, the ideal timing of BA initiation remains uncertain and the timing of artificial liver initiation is controversial. For example, in the study of Senf et al.,[14] BA treatment be initiated when bilirubin levels exceed 340 μmol/L or daily bilirubin increase >34 μmol/L. Another study proposed that prometheus therapies was started when serum bilirubin was $\geqslant 180$ μmol/L.[21] However, the above-mentioned studies failed to investigate the timing of BA treatment on patient prognosis. The ideal timing of BA initiation for patients with severe hyperbilirubinemia requires further investigations.

Study limitation

Our present retrospective study has several limitations. At first, the sample size was small and the included patients were heterogeneous, which might reduce statistical power. However, since there are fewer studies on the effect of BA on patients with post-cardiac surgery severe hyperbilirubinemia, we believe that our present study could provide useful information for clinicians and clinical researchers. Nevertheless, large, prospective, randomized, controlled clinical studies are needed to further explore the clinical efficacy of BA for the treatment of patients with post-cardiac surgery severe hyperbilirubinemia. Secondly, there are many uncertainties on the ideal timing of BA initiation due to lack of relevant guidelines. Therefore, there is heterogeneity on the timing of BA initiation among the included patients. However, this heterogeneity offers us opportunity to analysis the role of bilirubin concentration before BA on patient mortality.

Conclusions

In conclusion, BA could effectively reduce serum bilirubin concentration and have low risk of serious treatment-associated complications in patients with post-cardiac surgery severe hyperbilirubinemia. Patients with lower TB level before BA treatment had a relatively better prognosis. The timing of BA treatment needs further evaluation.

Declaration of conflicting interests

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