Clinics in Pediatric Surgery

Review Article
Published: 14 Feb, 2020

Possible Risk Factors for Short-Term Massive Gastrointestinal Bleeding in Patients of Biliary Atresia after Kasai Portoenterostomy

Kai LI[1#], Gongbao LIU[1#], Shan ZHENG[1], Weili YAN[2]*, Xuexin LU[1], Zhen SHEN[1], Wei YAO[1], Qilei HAN[1] and Ying WU[1]*

[1]Department of Pediatric Surgery, Children's Hospital of Fudan University, China

[2]Department of Clinical Epidemiology, Children's Hospital of Fudan University, China

[#]Kai LI and Gongbao LIU are first co-authors

Abstract

Background: Short-Term Massive Gastrointestinal Bleeding (STMGB) after Kasai portoenterostomy is rarely happened but life-threatening in patients of biliary atresia. To find out risk factors and to predict risk is of importance.

Methods: Thirteen patients in bleeding group were those who presented STMBG in our institution from 2010-2016. Forty-one patients in control group were biliary atresia patients without STMGB in the same institution, and were chosen using propensity score according to a ratio of 4:1. Stepwise logistic regression model was performed to identify predictive risk factors of STMGB. ROC analysis was performed and point estimation and 95% CI of AUC were reported as evaluation of the accuracy of the fitted predictive model.

Results: STMGB occurred at an average of 13.70 d ± 4.12 d post-operatively. Eight cases needed blood transfusion from 75 ml to 900 ml. Three cases died. Stepwise logistic regression analysis identified four significant predictors, including the change in direct bilirubin level before and after surgery (OR=2.42, 95% CI: 1.21-4.87), as well as fever after surgery (OR=5.10, 95% CI: 0.69-37.5), WBC counts (OR=1.42 95% CI: 1.05-1.90), and platelet count (OR=0.99, 95% CI: 0.98-1.00) on postoperative day 12. The model established in study explained 42.8% of the variation of outcome risk (P<0.0001, AUC=0.883, 95% CI: 0.72-1.00).

Conclusion: STMGB is often seen around 13 days after KP. Sharp drop of bilirubin, postoperative fever, increased WBC and decreased platelet count on postoperative day 12 are identified as possible risk factors. The model established in this study has the potential of becoming a good tool to predict STMGB, but further studies are expected.

Keywords: Biliary atresia; Massive gastrointestinal bleeding; Post-kasai procedure; Risk factors

OPEN ACCESS

Correspondence:
Shan ZHENG, Department of Pediatric Surgery, Children's Hospital of Fudan University, 399 Wan yuan Road, Shanghai 201102, China, Tel: +86 21 64931212; Fax: +86 21 64931211; E-mail: szheng@163.com
Weili YAN, Department of Clinical Epidemiology, Children's Hospital of Fudan University, 399 Wan yuan Road, Shanghai 201102, China, Tel: +86 21 64931215; Fax: +86 21 64931215; E-mail: yanwl@fudan.edu.cn

Received Date: *01 Jan 2020*
Accepted Date: *11 Feb 2020*
Published Date: *14 Feb 2020*

Citation:
LI K, LIU G, ZHENG S, YAN W, LU X, SHEN Z, et al. Possible Risk Factors for Short-Term Massive Gastrointestinal Bleeding in Patients of Biliary Atresia after Kasai Portoenterostomy. Clin Pediatri Surg. 2020; 1(1): 1002.

Introduction

Compared with Western countries, Biliary Atresia (BA) demonstrates a relatively high incidence in Asian populations. The incidence has been reported to be 1-1.48/10,000 individuals in Asian countries [1,2], while in China, there are 2000 to 3000 new cases per year based on its large population, which makes the research and treatment of BA a key topic in pediatric surgery in China.

In general, considerable progress has been made in BA treatment [3]. The 5-year survival rate with a native liver after the Kasai Procedure (KP) is 50% to 65% reported [4,5]. Our institution is the largest treatment center for BA in China, with 250 to 300 new cases being treated each year with better outcomes. Nevertheless, during the last 7 years, we have observed 13 cases of unexplained postoperative Short-Term Massive Gastrointestinal Bleeding (STMGB) after the KP. Although this number is small, it has become a serious complication, causing rapid postoperative death in children.

Due to the low incidence of BA in Western countries, few studies regarding this issue have been carried out [6,7]. In 2009, a Korean researcher noted that delayed postoperative hemorrhage from caudate lobe artery might be the cause of massive bleeding in the digestive tract, which was

confirmed by Digital Subtraction Angiography (DSA) and CT [8,9]. In our 13 pediatric patients, some cases received enhanced CT but nothing positive was found. Stopping corticosteroids, monitoring coagulation functions and using hemostatic agents has not stopped bleeding from happening. Even if there are a few case reports in literatures, due to the limited number of cases, comprehensive and objective evidence for the reasons of bleeding cannot be obtained, let alone a prospective study.

Therefore, we reviewed the clinical features of 13 BA patients who suffered postoperative STMGB after the KP from 2010 to 2016, in which esophageal variceal bleeding and strangulated intestinal obstruction were excluded. Considering the effect of multiple preoperative factors, Propensity Score Matching (PSM) was used. Each case of bleeding was matched with BA cases who did not suffer bleeding after the KP at the ratio of 1:4. The differences in clinical and laboratory characteristics of the two groups were compared. We aimed to find out the risk factors and related mechanisms of postoperative STMGB and wished to provide a theoretical basis for predicting hemorrhage and preventing such cases from occurring in the future.

Methods

This was a retrospective case-control study.

Case group

From January 2011 to December 2016, patients diagnosed as having BA upon surgery or intraoperative cholangiography at the Children's Hospital of Fudan University (Shanghai, China) who suffered massive gastrointestinal bleeding less than 30 days after the KP were recruited. "Massive gastrointestinal bleeding" was defined as: (1) gross bloody stools with the amount of bleeding estimated to be >10 mL/kg body weight, along with symptoms such as looking pale, increased heart rate, dyspnea, and reduced urine output; (2) hemoglobin level drops to 80 g/L in a short time; (3) hemodynamic instability necessitating infusion of 15 mL/kg erythrocyte suspension. Patients with gastrointestinal bleeding caused by intestinal torsion or intestinal obstruction were excluded.

Thirteen cases met the criteria stated above and were termed the Bleeding Group (BG).

Control Group (CG)

A total of 189 pediatric cases with a definitive diagnosis of BA through surgical exploration in our center from January 2015 to September 2015 who did not demonstrate postoperative bleeding after the KP formed the control group.

Due to multiple confounding factors and the small sample size of the BG, the number of confounding factors that could be controlled by a multivariate regression model was limited. Therefore, PSM was employed to match control cases for BG to control preoperative confounding factors [8].

Collection of possible risk factors

The clinical data of BG and CG were obtained by retrospective review. Three main parameters between the two groups were assessed: Surgical method (regular hepatic dissection, size of the fibrous block, length of the Y arm); postoperative treatment (hormone usage, antibiotic usage, feeding pattern), postoperative clinical status (fever, exclusion of surgery-related fever occurring <24 h after surgery, stool color 12 days after surgery, routine blood tests, blood coagulation and liver function 12 days after surgery). Among them, patients with normal portal hepatic anatomy who had received corticosteroids, antibiotics or had suffered fever were designated as "1", otherwise "0". The length of the Y-arm, the size of the fibrous block, routine blood tests, blood coagulation function and liver function were recorded numerically. The levels of WBC, RBC, hemoglobin and platelets were evaluated through routine blood tests. Coagulation function was evaluated by the Prothrombin Activity (PTA), the most responsive indicator of blood coagulation). Liver function was evaluated by measuring levels of total bilirubin and direct bilirubin. "Exclusive breastfeeding" was designated as "1" and other feeding patterns as "0". "Dark-green" or "golden" stools were designated as "2", "light-yellow" as 1, "white" as 0, and "red" as "3".

PSM was carried out using STATA v11.2 SE (Stata, TX, USA) [9]. The specific approach was: (1) preoperative confounding factors were considered for PSM program that included sex; gestational age at childbirth; history of pregnancy; age at surgery; body weight at surgery; platelet counts; levels of Alanine Transaminase (ALT), Aspartate Transaminase (AST), the total bilirubin and direct bilirubin at onset, level of Gamma Glutamyl Transferase (GGT) and preoperative Cytomegalovirus (CMV) load. These were obtained from the medical records; (2) nearest neighbor matching was according to a ratio of 1:4. Finally, 41 cases were selected (11 control cases were shared among the cases who suffered bleeding) as the CG. Stepwise logistic regression models were performed to identify possible predictive factors of bleeding. Candidate predictors included fever (1 for yes, 0 for no), the length and width of fibrotic block, serum direct bilirubin before operation, pre- to post-surgery changes of serum direct bilirubin (Ch_ddbil), as well as serum album, hemoglobin, RBC counts, WBC counts and platelet counts at day 12 after surgery were included as independent variables to fit best models with largest determinant coefficient. $P<0.15$ was considered significant for entry model. Receiver operation curve analysis was performed and point estimation and 95% CI of area under curve were reported as evaluation of the accuracy of the fitted predictive model.

Results

Bleeding in children in the BG

Hematochezia occurred at an average of 13.70 ± 4.12 (range, 7-21) days postoperatively in the BG. The hemorrhagic manifestations were blood in the stool without hematemesis, which was dark-red to red. A bloody stool occurred at an average of 2-5 times, and the total amount of bleeding in <24 h was 35 mL to 500 mL. Patients also demonstrated symptoms such as increased heart rate, shallow breathing, and reduced urine output. Eight cases were transferred to the intensive care unit. In these eight cases, the lowest hemoglobin level was 29.2 g/L. In addition to an increase in blood volume by administration of saline, the median volume of erythrocyte suspension infused was 50.6 mL/kg (75 mL to 900 mL). Ten children were treated conservatively, and the remaining three patients underwent surgical exploration. Two of the children (20%) treated conservatively died, and one patient died after surgery. Only one patient received an abdominal puncture which demonstrated light-yellow (not bloody) puncture fluid. One patient was subjected to emergency enhanced CT, but a significant abnormality was not found. Clinical evidence and abdominal radiography of all children ruled out gastrointestinal bleeding caused by intestinal torsion.

Table 1: Comparison of exposure factors between the BG and matched CG after PSM program.

Possible confounding Variables	Matched	Treated	Control	%Bias	Bias	t	P value	V(C)
Gestational age, week	U	38.615	39.154		-38.3	-1.43	0.155	1.32
	M	38.615	38.596	1.4	96.4	0.03	0.974	1
Parity	U	1.3846	1.4521		-13	-0.45	0.657	0.91
	M	1.3846	1.5192		-125	-0.62	0.54	0.72
Age at surgery, day	U	67.538	64.83		14.8	0.53	0.6	1.07
	M	67.538	70.404		-21.5	-0.37	0.713	0.81
pre_surgery steroid treatment	U	0.15385	0.11702		10.5	0.39	0.694	1.36
	M	0.15385	0.07692	22	-109	0.59	0.558	1.83
Body weight at surgery, kg	U	5.0385	4.9388		12.8	0.49	0.625	1.49
	M	5.0385	5.0885	-6.4	49.8	-0.17	0.869	1.62
plt at admission (*10^{12}/L)	U	251.85	304.77		-50.5	-1.5	0.136	0.39
	M	251.85	238.4	12.8	74.6	0.41	0.688	0.76
alt at admission (IU/L)	U	94.923	99.809		-8.3	-0.26	0.798	0.51
	M	94.923	113.42		-310	-0.79	0.439	0.48
ast at admission (IU/L)	U	153.31	162.98		-11.4	-0.38	0.707	0.76
	M	153.31	167.54		-63.9	-0.46	0.649	1
ggt at admission (IU/L)	U	777.15	811.13		-6.8	-0.19	0.853	0.17*
	M	777.15	908.48		-313	-0.61	0.551	0.14*
direct bil at admission (umol/L)	U	115.97	106.58		27.2	1.06	0.292	1.57
	M	115.97	119.82	-11.1	59	-0.26	0.797	1.06

Note: *If variance ratio outside [0.31; 3.28] for U and [0.31; 3.28] for M
PSM: Propensity Score Matching

Table 2: Possible predictors to bleeding based on stepwise multiple regressions.

Predictors	Odds Ratio	Std. Err.	z	P>z	95% Conf.	Interval
Ch_ddil	2.42	0.86	2.49	0.013	1.21	4.87
Fever	5.1	5.19	1.6	0.11	0.69	37.55
WBC	1.42	0.21	2.31	0.021	1.05	1.9
Platelets	0.99	0.01	-2.05	0.041	0.98	1

Comparison of the general clinical data between the BG and CG after PSM

After PSM program, differences in considered possible confounders were not significant between the BG and CG group (Table 1). Hence, the two groups were well balanced with respect to these characteristics with good control of confounding effects.

Stepwise logistic regression analysis identified four significant predictors to bleeding, including change of direct bilirubin (OR=2.42, 95% CI: 1.21-4.87), as well as fever after surgery (OR=5.10, 95% CI: 0.69-37.5), WBC counts (OR=1.42 95% CI: 1.05-1.90), and platelet counts (OR=0.99, 95% CI: 0.98-1.00). The model determined by the four significant factors explained 42.8% of the variation of the event risk (P<0.0001) and achieved a statistical power of over 0.9 (Table 2). The ROC analysis showed that this model obtained good accuracy to predict bleeding (AUC=0.91, 95% CI: 0.82-0.99) (Figure 1).

Based on the best fitted model, we developed a formula to predict individual patient risk of post-surgery bleeding, which is expected to validate in future clinical study.

r = -5.41+1.63*(fever) +0.35*(WBC-d12) +0.89(ch_ddbi) -0.01(platelet-d12)

Risk of bleeding= exp(r)/(1+exp(r))

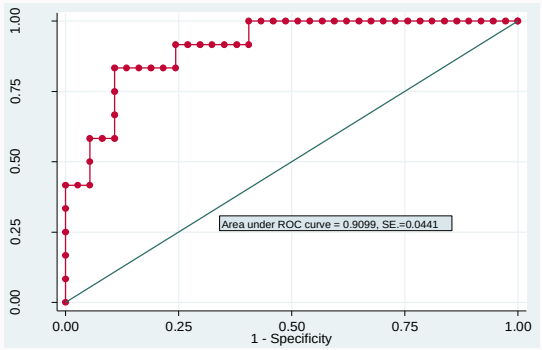

Figure 1: The ROC analysis showed that this model obtained good accuracy to predict bleeding (AUC=0.91, 95% CI: 0.82-0.99).

Discussion

Severe short-term postoperative hemorrhage and even death is rare. Indeed, the 13 cases summarized here were collected in 7 years, whereas >1500 cases of BA were treated in our center over the same time, showing a very low prevalence of 0.8%.

The common characteristics of children in BG can help us to find the reasons underlying hemorrhage. First, hemorrhage usually

occurred 13.7 days after surgery. Second, hemorrhage was urgent, children suddenly turned pale with considerable hematochezia without any forewarning, even some of them were planning to discharge from hospital. The difference of hemoglobin level in BG and CG at 12 days after surgery was not a risk factor by stepwise regression analysis, suggesting that the massive bleeding would happen urgently in 1-2 days. Third, the amount of bleeding was large and the prognosis was poor. In the severest case, the hemoglobin level fell to 29.2 g/L dramatically in a short time. Eight of the 13 patients had been transferred to the intensive care unit and received blood transfusion of 50.6 mL/kg in median. Three patients (23%) died, and one of them could not be saved even with surgical hemostasis. Fourth, as shown by results of stepwise logistic regression analysis, comparing with those in CG, children in BG recovered from jaundice faster, tended to have higher fever, higher WBC counts and lower platelets counts.

Laparotomy conducted in the three patients who could not tolerate conservative treatment demonstrated that dark-red blood clots had been observed at the hilar region. When the anterior wall of the Y-arm was opened and explored, a sustained small flow rather than large amount of bleeding from hilar region was found. After hemostasis using hemostatic powder and gelatin sponges in hilum, bleeding stopped and vital signs returned to normal in two children's, however the third one succumbed to persistent and massive hemorrhage. These findings suggest the hilar region is supposed to be the most possible place of hemorrhage, but which anatomic site will be the exact one? And why does hemorrhage tend to occur in patients with faster recovery from jaundice? Obviously, intestinal mucosal bleeding from Y arm was excluded. The Y arm is 15 cm under the flexion ligament and it is physiologically alkali-resistant. Postoperative massive hemorrhage had never happened on children of choledochal cyst whose Y arm were as same anatomic site as biliary atresia. Therefore, if the hemorrhage was happened at Y arm, the probability should be higher in choledochal cysts patients because they had larger bile drainage amount. However, in our decades' experience of treating choledochal cysts, not even one case had suffered STMGB. Then the hilum is highly suspicious. The hilum contains the hepatic artery, hepatic vein, and the trunk of portal vein and its branches. In Kasai procedure, hilum is dissected and exposed to bile flow directly. We take it for granted that thrombus of the blood vessels stump closed by electrocoagulation is washed up by bile flow and re-opens 13-14 days after surgery (vulnerable day). But why is there no hemorrhage at the hilum in patients with choledochal cysts? That is because the hilum part of choledochal cyst is intact, and the ductus hepaticus communis where the bile flows into his native resistance to bile corrosion. If a BA patient with more bile drainage has fever, inflammation and low platelet at the same time, the probability of bleeding will increase. This seems reasonable to explain why hemorrhage tends to occur in BA children who have a rapid recovery of jaundice, higher fever, higher WBC counts and lower platelet counts postoperatively which were supposed to be risk factors. By the formula constructed based on the best fitted predictive model, BA patients who are vulnerable to postoperative massive bleeding are possible to be identified in advance. To make the prediction more accurate, validation and optimization to the predictive model is expected in future clinical studies in larger sample size.

The length of Y arm, the width of the fibrous block, corticosteroid therapy [10,11], antibiotics [12], breast feeding, etc., are not supposed to be the risk factors of postoperative massive hemorrhage in our study, although high-dose corticosteroids has hemorrhagic side effect and breastfeeding is likely to cause Vitamin-K deficiency. The standard operative procedure done by same surgeon and the same antibiotics was used in all cases of the two groups, both of them were not supposed to be risk factors either in this study.

In summary, this study shows that rapid recovery from jaundice, correlated with fever; higher WBC counts and lower platelet counts are the most likely risk factors affecting massive short-term postoperative hemorrhage in pediatric patients with BA. Reasons supposed to be greater flow of bile washes up and corrodes the dissected/non-intact hilar hepatis. In future studies, formula constructed in this study need to be verified in large samples, and approaches such as reduction of electrocoagulation, reliable ligation, or postoperative application of drugs to increase the anti-alkali ability of hilar hepatis and decrease fever and WBC, could be evaluated in decreasing the incidence of postoperative STMGB in BA patients.

References

1. Chen SY, Lin CC, Tsan YT, Chan WC, Wang JD, Chou YJ, et al. Number of cholangitis episodes as a prognostic marker to predict timing of liver transplantation in biliary atresia patients after Kasai portoenterostomy. BMC Pediatr. 2018;18(1):119.
2. Nio M. Japanese biliary atresia registry. Pediatr Surg Int. 2017;33(12):1319-25.
3. Pang WB, Zhang TC, Chen YJ, Peng CH, Wang ZM, Wu DY, et al. Ten-year experience in the prevention of post-Kasai cholangitis. Surg Infect (Larchmt). 2019;20(3):231-5.
4. Wang Z, Chen Y, Peng C, Pang W, Zhang T, Wu D, et al. Five-Year native liver survival analysis in biliary atresia from a single large Chinese Center: The death/liver transplantation hazard change and the importance of rapid early clearance of jaundice. J Pediatr Surg. 2019;54(8):1680-5.
5. Ihn K, Na Y, Ho IG, Lee D, Koh H, Han SJ. A periodic comparison of the survival and prognostic factors of biliary atresia after Kasai Portoenterostomy: A single-center study in Korea. Pediatr Surg Int. 2019;35(3):285-92.
6. Moon SB, Park KW, Jae HJ, Jung SE. Caudate arterial branch bleeding: a rare complication after a Kasai portoenterostomy. J Pediatr Surg. 2009;44(7):e27-30.
7. Takazawa S, Uchida H, Kawashima H, Tanaka Y, Sato K, Jimbo T, et al. Massive hemorrhage after Kasai portoenterostomy in a patient with a congenital extrahepatic portosystemic shunt, malrotation and a double aortic arch: report of a case. Surg Today. 2014;44(8):1561-4.
8. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41-55.
9. Pearl J. Causality: Models, Reasoning, and Inference. New York: Cambridge University Press. 2000. ISBN 0-521-77362-8.
10. Chen Y, Nah SA, Chiang L, Krishnaswamy G, Low Y. Postoperative steroid therapy for biliary atresia: Systematic review and meta-analysis. J Pediatr Surg. 2015;50(9):1590-4.
11. Sarkhy A, Schreiber RA, Milner RA, Barker CC. Does adjuvant steroid therapy post-Kasai portoenterostomy improve outcome of biliary atresia? Systematic review and meta-analysis. Can J Gastroenterol. 2011;25(8):440-4.
12. Decharun K, Leys CM, West KW, Finnell SM. Prophylactic antibiotics for prevention of cholangitis in patients with biliary atresia status Post-Kasai portoenterostomy: A systematic review. Clin Pediatr (Phila). 2016;55(1):66-72.