Published in final edited form as:

Am J Surg. 2010 May ; 199(5): 680–684. doi:10.1016/j.amjsurg.2010.01.014.

STEROID USE AFTER THE KASAI PROCEDURE FOR BILIARY ATRESIA

Oliver B. Lao, MD, MPH,

University of Washington Department of Surgery 1959 NE Pacific Street Box 356410 Seattle, WA 98195 c206.818.6968 p206.559.2566 f206.543.8136 olao@uw.edu

Cindy Larison, MA,

Seattle Children's Hospital Research Institute Seattle, WA

Michelle Garrison, PhD,

Seattle Children's Hospital Research Institute Seattle, WA

Patrick J. Healey, MD, and

General & Thoracic Surgery Seattle Children's Hospital Seattle, WA

Adam B. Goldin, MD, MPH

General & Thoracic Surgery Seattle Children's Hospital Seattle, WA

Abstract

Purpose—To describe patients undergoing the Kasai procedure at children's hospitals, evaluate outcomes, and analyze the association of these outcomes with systemic steroid use.

Methods—We identified biliary atresia patients (ICD-9 751.61) that underwent a Kasai procedure at free-standing children's hospitals in the Pediatric Health Information System database (2003-2008). We examined descriptive characteristics and used regression analyses to determine whether post-operative steroid usage was associated with length of stay, mortality, or cholangitis.

Results—Of the 516 children identified (40% male, 50% <2 months-old), 239 (46%) received peri-operative steroids. The mean total and post-operative length of stay was 14.5 ± 19.7 days and 11.3 ± 16.3 days, respectively. In our analysis, post-operative steroid use was significantly associated with a 3.5 day decrease in post-operative length of stay (95%CI 0.03-6.97).

Conclusions—Peri-operative steroids after the Kasai procedure are associated with shorter post-operative length of stay. Work is needed to ascertain whether this relationship is causal.

Keywords

biliary atresia; Kasai procedure; steroids; outcomes; length of stay

---

© 2010 Excerpta Medica, Inc. All rights reserved.

Correspondence to: Oliver B. Lao.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Biliary atresia is a progressive fibro-obliterative disease of the biliary tract occurring in infancy. Without some form of biliary drainage procedure, less than ten percent of patients with biliary atresia will be alive at two to three years following diagnosis. The etiology may be related to a combination of genetic, immunologic, viral or toxin mediated pathways. The initial surgical treatment most commonly employed to treat these patients is a hepatoportoenterostomy (Kasai procedure) with the goal of providing adequate biliary drainage directly from intrahepatic biliary ductules into the intestinal lumen.

A variety of factors may influence the success of the Kasai procedure including age at procedure (early (<60 days) is better), experience of the surgeon and center, and histology and size of the biliary ductules¹⁻³. The most common complication after the Kasai is cholangitis occurring in 30-60% of patients in the first 1-2 years⁴. Medical management after the Kasai procedure is controversial with respect to the use of medications (such as steroids, choleretic agents and antibiotics) and their effect on outcomes⁴⁻¹¹. As many clinicians believe an inflammatory process is responsible for the underlying disease, steroids are often used with the goal of decreasing inflammation following the procedure. Steroids are not without risk, however, and may affect wound healing as well as the incidence of infections, gastrointestinal perforation, hyperglycemia and hypertension. The relationship between the use of steroids and outcomes is unknown.

The purpose of this study was to describe the population of children with biliary atresia undergoing the Kasai procedure at tertiary-care children's hospitals and to analyze post-operative steroid use and its relationship with cholangitis, length of stay and mortality at children's hospitals.

Materials & Methods

Data Source & Definitions

We studied the Pediatric Health Information System (PHIS) database, created by the Child Health Corporation of America (Kansas City, Missouri), which contains demographic, clinical and charge data for all inpatient discharges from 43 freestanding, non-competing U.S. children's hospitals. We performed a retrospective evaluation of 41 of those 43 hospitals with complete and expanded discharge data for the period January 2003 – June 2008.

Subjects were pediatric patients (≤18 years-old) with an International Classification of Diseases 9th Revision (ICD-9) procedure code for Kasai hepatoportoenterostomy (51.37) and an ICD-9 diagnosis code for biliary atresia (751.61). To reduce misclassification, patients with specific additional discharge diagnoses were excluded from the population [ICD-9 codes: 1550 (primary liver cancer), 1552 (liver cancer NOS), 1561 (extrahepatic duct cancer), 1578 (pancreas cancer NEC), 2118 (benign peritoneum neoplasm), 2390 (digestive neoplasm NOS), 99682 (complete liver transplant)] as were patients whose Kasai procedure was coded either on the same day or after their transplant procedure (ICD-9 procedure code 50.5).

A priori defined outcomes were post-operative length of stay, in-hospital mortality, and readmission for episodes of cholangitis. Length of stay was calculated using the admission, operative and discharge dates in the database. Cholangitis was defined by ICD-9 diagnosis code for cholangitis (576.1). All mortality data reflects in-hospital events. Descriptive characteristics such as age at operation, sex, race, ethnicity, and year of hospitalization were evaluated.

We defined steroid use as dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone administered via any route (enteral, parenteral, or intra-muscular). A cut-off of four days post-operatively defined 'peri-operative' steroid administration. Descriptive information on post-operative steroid administration over time was studied. We analyzed steroid administration on the day of discharge as a surrogate for continued steroid use as an out-patient.

Statistical Analysis

Descriptive characteristics such as age, sex, race/ethnicity, and year of discharge are presented as means with standard deviations. We used regression analyses to examine the relationship between peri-operative steroid usage and outcomes, each modeling hospital as a fixed effect to control for unmeasured confounding at the hospital level. Hospitals with only one patient or in which only one type of outcome was observed were omitted from the regression model (0 hospitals for length of stay, 23 hospitals for mortality). The relationship between peri-operative steroids and outcomes are presented as odds ratios and their 95% confidence intervals. A p value of .05 (two sided) was considered significant. The analyses were conducted using STATA SE version 10 (College Station, TX) statistical software package.

This study was approved by the institutional review board at the Seattle Children's Hospital in Seattle, Washington (IRB # 12769).

Results

We identified 516 children that had a Kasai procedure for biliary atresia (40% male). Almost half (49%) were less than two months old and 99% were less than one year old (Table 1). Sixty-two percent of the population was identified as white while 17% was black with the remainder being Asian (5%), American Indian (1%), other (11%) or missing (4%). The frequency of this discharge diagnosis over time has been relatively stable (Table 2); although it should be noted that this data is not population-based.

Two of our three outcomes (mortality and cholangitis) were found to have a small number of children experiencing these outcomes, 16 and 10, respectively. We were unable to perform an adequate regression analysis on these outcomes as a result of insufficient data. We chose to focus on post-operative length of stay following Kasai, and this was the main outcome in our analysis.

Of the 509 children still hospitalized on post-operative day 4, steroids were prescribed in 239 (46%) within 4 days of their Kasai and their demographics mirror the entire group (Table 1). More than one type of steroid may have been prescribed to a patient on a given day. The two most common steroid types given peri-operatively were methylprednisolone (45%) and prednisolone (30%) (Table 3). Of those 239 patients, 26% (135) had steroids on the day of their operation and an additional 10% (52) received steroids on post-operative days 1-4. On the day of discharge, 36% (186) of children that underwent the Kasai procedure were still receiving steroids (Table 1). The most common steroids prescribed on the day of discharge were prednisolone (18%) and methylprednisolone (10%, Table 3).

The mean total length of stay for the entire cohort was 14.5 days $\pm$ 19.7 (Median 9, IQR 7-15). The post-operative length of stay was 11.3 $\pm$ 16.3, 7 (IQR 5-11) (Table 1). In the regression analysis those patients receiving peri-operative steroids appeared to stay 3.5 days less (95% CI 0.03-6.97) than those that did not receive any peri-operative steroids, within the same hospital. Hospitals in the study were highly variable in their use of steroids following the Kasai procedure; on average, steroids were given to 46% of patients (Table 1), but this varied between zero and 96%.

Discussion

We observed an association between the use of systemic steroids in the post-operative period and post-operative length of stay. Children receiving systemic steroids within four days following their Kasai had a statistically significant reduction in their post-operative length of stay. We also observed a slight female predominance of this condition as well as a high proportion of cases among whites compared to other races such as blacks and Asians. The incidence of these cases evaluated at children's hospitals participating in the PHIS database does not appear to be changing over time. The use of post-operative steroids and steroids at discharge (46% & 36%) in our study population agrees with a retrospective review of 9 centers and 104 children in 2006⁴.

It is still unclear whether steroids mediate their effects on children after the Kasai procedure through an anti-inflammatory, immunosuppressive or choleretic route⁶. Davenport et al. have suggested that the use of steroids may have a beneficial effect on the rate of reduction of serum bilirubin levels following the Kasai procedure¹². These results have led other investigators to study the dosage and duration of treatment of steroids in this population. Karrer et al. studied sixteen patients with biliary atresia undergoing the Kasai procedure and found that a 'blast' type (high dose/short duration) steroid administration had effects on bile flow, serum bilirubin and alkaline phosphatase¹³. Further use of the 'blast' type steroids amongst fourteen Japanese patients provided varying results, but the authors still urge use of aggressive corticosteroid therapy despite the varying initial response⁷. Duration of therapy (longer-term) was studied retrospectively at three institutions for the outcomes of jaundice-free status and survival without liver transplantation. Their use of steroids for a minimum of 6 weeks appeared to be safe and well tolerated without any significant incidences of adverse effects⁸. Unfortunately, decreased bilirubin levels have not had an impact on the clinical outcomes of subsequent liver transplantation¹² or overall survival¹⁴. None of these studies has evaluated post-operative length of stay as an outcome.

The primary limitation of this study is its reliance upon an administrative database that is dependent upon accurate data entry. Specific dosages, lengths of administration and underlying motivation behind prescribing certain steroids are unknown. Similarly, the concomitant use of other medications such as antibiotics or choleretics was not measured or analyzed and the retrospective nature of this study precludes an independent analysis of their effect on outcomes. These data represent an entire hospitalization so migration to care at another facility in addition to out of hospital events cannot be adequately quantified. Laboratory values, such as bilirubin, are not provided by the database. Similarly, progression to liver transplant is not quantified in this database. Finally, the PHIS database represents large free-standing children's hospitals that serve as tertiary referral centers. Thus, this may represent a skewed population and we cannot make any population-based inferences. Biliary atresia is a complex disease, and it would stand to reason that most neonates with biliary atresia would be seen and cared for at hospitals with a children's focus, such as those in the PHIS database.

Our analysis of 516 children with biliary atresia that have undergone a Kasai procedure at children's hospitals has revealed an association between peri-operative steroid usage and post-operative length of stay. This relationship merits further research into the pathophysiology and mechanism behind these findings. Future study into the individual and additive effect of these medications and their effect on outcomes in children with biliary atresia is needed.

Clearly, there is a significant degree of controversy that surrounds the use of steroids in patients with biliary atresia. In order to identify if a benefit truly exists, a properly designed prospective trial, powered to study the impact of timing, dose, duration and type of steroids and the independent impact of these factors is sorely needed. The Biliary Atresia Clinical Research

Consortium (BARC) randomized, double-blinded, placebo-controlled trial of steroid therapy following Kasai in children with biliary atresia may assist us in further understanding this relationship and what the underlying mechanism is.

2 Sentence Summary

The use of steroids and their relationship with outcomes following the Kasai procedure are unknown. We describe patients undergoing the Kasai procedure for biliary atresia at children's hospitals and analyze the association of these outcomes with systemic steroid use.

Discussion

Marvin Harrison, M.D., Portland, Oregon

The authors of this study have compiled a large multi center group of patients with biliary atresia. I for one am grateful for this effort. As they have mentioned, the efficacy of steroid administration to these infants following portoenterostomy is difficult to study and has occasioned multiple communications from many groups over the past 40 years.

Portoenterostomy (first described by Kasai in 1957) has been done for most patients with biliary atresia. Many factors complicate the evaluation of the operation and the analysis of any single intervention to attempt to improve the success of the operation is difficult.

The thought that the anti inflammatory, immunosuppressive, and/or choleretic effect of corticosteroids may positively impact on the course of biliary atresia following portoenterostomy derives from the observation of inflammatory changes as a prominent part of the histopathology of the biliary tract that is excised in this procedure.

Unfortunately, despite many papers addressing this issue, there is still not a significant study suggesting that exogenous steroids substantially benefit the infant with biliary atresia. This study of 516 infants treated in 41 children's hospitals over four and one half years might seem to be that study. It should be noted, however, that this represents only 112 patients per year or about three patients per year per hospital undergoing portoenterostomy for biliary atresia. In order to cope with the wide range of experience, the authors have assumed that there are no differences in practice between one hospital and another, lumping for simplicity of analysis all hospitals into one, as well as all criteria for continued hospitalization. They have also not accounted for the considerable variation in the pharmacology of the steroids used, and there is no stratification given for description of the dose, timing, or reason for starting, continuing, or discontinuing the steroid regimen used in any given infant. It is unwarranted to assume that all steroids are the same. Further, there is an assumption that portoenterostomy is the same in the hands of all the surgeons. It is also implied that length of stay is a surrogate for efficacy of both surgery and the use of steroids. Bile flow is not addressed directly by any measurement of the study. We are left agreeing with the authors' closing statement – the prospective data addressing this issue is needed.

References

1. McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet* 2000;355(9197):25–9. [PubMed: 10615887]
2. Mieli-Vergani G, Howard ER, Portman B, et al. Late referral for biliary atresia--missed opportunities for effective surgery. *Lancet* 1989;1(8635):421–3. [PubMed: 2563796]
3. Serinet MO, Broue P, Jacquemin E, et al. Management of patients with biliary atresia in France: results of a decentralized policy 1986-2002. *Hepatology* 2006;44(1):75–84. [PubMed: 16799986]

4. Shneider BL, Brown MB, Haber B, et al. A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000. *J Pediatr* 2006;148(4):467–474. [PubMed: 16647406]
5. Davenport M, Ure BM, Petersen C, et al. Surgery for biliary atresia--is there a European consensus? *Eur J Pediatr Surg* 2007;17(3):180–3. [PubMed: 17638156]
6. Meyers RL, Book LS, O'Gorman MA, et al. High-dose steroids, ursodeoxycholic acid, and chronic intravenous antibiotics improve bile flow after Kasai procedure in infants with biliary atresia. *J Pediatr Surg* 2003;38(3):406–11. [PubMed: 12632357]
7. Muraji T, Higashimoto Y. The improved outlook for biliary atresia with corticosteroid therapy. *J Pediatr Surg* 1997;32(7):1103–6. discussion 1106–7. [PubMed: 9247243]
8. Dillon PW, Owings E, Cilley R, et al. Immunosuppression as adjuvant therapy for biliary atresia. *J Pediatr Surg* 2001;36(1):80–5. [PubMed: 11150442]
9. Escobar MA, Jay CL, Brooks RM, et al. Effect of corticosteroid therapy on outcomes in biliary atresia after Kasai portoenterostomy. *J Pediatr Surg* 2006;41(1):99–103. discussion 99–103. [PubMed: 16410116]
10. Bu LN, Chen HL, Chang CJ, et al. Prophylactic oral antibiotics in prevention of recurrent cholangitis after the Kasai portoenterostomy. *J Pediatr Surg* 2003;38(4):590–3. [PubMed: 12677572]
11. Wong KK, Fan AH, Lan LC, et al. Effective antibiotic regime for postoperative acute cholangitis in biliary atresia--an evolving scene. *J Pediatr Surg* 2004;39(12):1800–2. [PubMed: 15616934]
12. Davenport M, Stringer MD, Tizzard SA, et al. Randomized, double-blind, placebo-controlled trial of corticosteroids after Kasai portoenterostomy for biliary atresia. *Hepatology* 2007;46(6):1821–7. [PubMed: 17935230]
13. Karrer FM, Lilly JR. Corticosteroid therapy in biliary atresia. *J Pediatr Surg* 1985;20(6):693–5. [PubMed: 4087100]
14. Petersen C, Harder D, Melter M, et al. Postoperative high-dose steroids do not improve mid-term survival with native liver in biliary atresia. *Am J Gastroenterol* 2008;103(3):712–9. [PubMed: 18177447]

Table 1
Demographics for all children with Biliary Atresia undergoing Kasai hepatportoenterostomy.

	All (516)	Steroids within post-operative day 4 (239, 46%)		Steroids on day of discharge (186, 36%)	
		Yes	No	Yes	No
M:F	208 (40%):308 (60%)	99 (41%):140 (59%)	109 (39%):168 (60%)	74 (40%):112 (60%)	134 (41%):196 (59%)
Age					
<2mos	255 (49%)	120 (50%)	135 (49%)	98 (53%)	157 (48%)
2-11mos	256 (50%)	117 (49%)	139 (50%)	85 (46%)	171 (52%)
≥1yr	5 (1%)	2 (1%)	3 (1%)	3 (2%)	2 (1%)
LOS [days]					
Median (IQR)	9 (7-15),				
Mean ±SD	14.5±19.7				
Post-Op LOS [days]					
Median (IQR)	7 (5-11)	9.7±9.1	12.8±20.5	10.7±11.5	11.7±18.5
Mean ±SD	11.3±16.3				
Death		1 (<1%)	7 (3%)	4 (<1%)	4 (1%)
Cholangitis		22 (9%)	27 (10%)	18 (10%)	31 (10%)
Readmit Cholangitis		4	1	5	0

Table 2

Distribution of biliary atresia patients and use of post-operative steroids over time at PHIS hospitals

Year	Total Patients # (%)	Post-operative Steroids # (%)	No Post-operative Steroids # (%)
2003	91 (18%)	35 (38%)	56 (62%)
2004	90 (17%)	46 (51%)	44 (49%)
2005	100 (19%)	51 (51%)	49 (49%)
2006	90 (17%)	44 (49%)	50 (51%)
2007	98 (19%)	48 (49%)	50 (51%)
2008*	47 (9%)	15 (32%)	32 (68%)

* 2008 only includes information from January - June

Table 3

Steroid administration: within four days of Kasai procedure and on last hospital day; by type^{*}

Steroid N (%)	Within 4 days postoperatively	On last hospital day
Methylprednisolone	233 (45.2)	53 (10)
Prednisolone	156 (30.2)	94 (18)
Prednisone	89 (17.2)	46 (9)
Dexamethasone	45 (8.7)	4 (1)
Hydrocortisone	28 (5.4)	5 (1)

^{*} More than one type of steroid may have been prescribed to a patient on a given day.