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ORIGINAL ARTICLE

Evaluation of a standardized protocol in the use of steroids after Kasai operation

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Abstract Although the Kasai operation is still the treatment of choice for infants with biliary atresia, the long-term success rate, as defined by survival without transplantation, is only about 25–40%. It has been proposed that post-operative inflammatory changes affect the bile flow and eventually lead to cholangitis and liver failure. Recent case reports have suggested that the administration of steroids post-operatively can improve outcomes. Since 2004, our unit has adopted a strict protocol for the use of post-operative steroids for patients who undergo Kasai operation. The aim of this study is to access the early outcomes of these patients. A retrospective analysis was carried out for all patients who received Kasai operation between 1996 and 2006. For the treatment group, patients all received prednisolone at 4 mg/kg 1 week after operation as guided by protocol. The demographics and outcomes, including post operative bilirubin level, episodes of cholangitic attack, the need for early liver transplantation (transplant within 1 year of Kasai), and transplantation-free survival, were noted. Statistical analysis was done using Fisher's exact test and unpaired *t*-test when appropriate. A value of $P < 0.05$ was considered to be statistically significant. Kasai operation was performed in 30 patients (11 boys and 19 girls) during the study period. Thirteen patients received post-operative prednisolone according to protocol. The average age at operation and the mean preoperative bilirubin levels for the steroid and non-steroid group were not significantly different. A normal post-operative bilirubin (defined as bilirubin level less than 20 μmol/L) was achieved at 6 months in 7 (53.9%) patients who received steroid and 8 (47.0%) patients who did not ($P = 0.71$). A statistically significant reduction in the post-operative bilirubin level was also seen at 3 and 6 months in the steroid group. Early liver transplantation was required in 5 (38.5%) patients with steroid and 5 (29.4%) patients without it ($P = 0.60$). No significant difference in terms of cholangitic attack was observed. There was also no steroid-associated complication reported. We conclude that lower post-operative bilirubin level can be achieved with the routine use of prednisolone. However, there is no statistical improvement in terms of early liver transplantation and cholangitis. This may be attributed to the small sample size of our study population. Based on this pilot study, a multi-centre randomized trial is needed.

Keywords Biliary atresia · Kasai portoenterostomy · Steroids · Liver transplantation

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Introduction

Biliary atresia is the most common surgical cause for obstructive jaundice in neonates. The pathology mainly consists of inflammatory sclerosing lesion of the bile ducts. Liver biopsy in biliary atresia classically shows bile duct proliferation, canalicular stasis, swelling and vacuolization of bile duct epithelial cells, portal tract edema and fibrosis, and monocytic and lymphocytic cellular infiltration of the portal tracts [1]. While the etiology remains unknown, a number of postulations have been suggested. These include ductal malformation, virus-mediated inflammation, genetic predisposition and auto-immunity [2]. If left untreated, this condition will ultimately lead to liver failure.

Kasai operation remains the treatment of choice for infants with biliary atresia since its description in 1957 [3].

Although the operation alone may restore bile drainage, long term success rate, defined as the preservation of liver function without transplantation, is only about 25–40% [4]. It has been shown in studies that the success rate of the Kasai operation is related to the timing of surgery, the experience of the surgical centre and the type of anatomical defect [5]. Some recent studies have suggested that the administration of steroid after operation improves the outcomes in terms of liver function [6–9]. It has been proposed that steroid suppresses post-operative inflammatory changes that affect bile flow by closing the transected microscopic ducts. This drug may also enhance canalicular electrolyte exchange and stimulates bile flow to prevent cholangitis and liver failure [10]. From these early reports, a variety of post-operative steroid regimes, even among different surgeons within the same center were described. With these variations in the treatment regimen, the clinical evidence to support the efficacy of the drug is not firmly established. It is clear that a standard protocol is needed to ascertain the potential benefits of steroids.

Since 2004, our unit has adopted a strict protocol, with reference to the one suggested by T. Muraji in 2004 [11], for the administration of prednisolone for patients who have undergone Kasai operation. Before that, steroid was mainly given to patients who developed cholangitis or rebound. The aim of this study is to assess the early outcomes of these patients and to compare them with historical patients who did not receive routine steroids according to our protocol. With this pilot study, we hope to review our experience and establish a background for our future prospective randomized trial on this issue.

Methods

A retrospective study was carried out for all patients who received Kasai operation between 1996 and 2006. They were operated by a single chief surgeon within the same centre. The operations were all done with traditional open approach after the diagnosis was confirmed with intra-operative cholangiogram. Portal dissection was carried out up to the level of the portal vein bifurcation and portal duct was joined up to the retrocolic jejunal loop. In this way, the bile can diffuse into the jejunum.

A protocol for post-operative steroids was started in 2004 and since then, all patients would receive oral prednisolone at 4 mg/kg per day (divided into BD dosage per day) on day 7 after operation for 2 weeks. After that, the dosage would then be reduced to 2 mg/kg per day for another 2 weeks. Following that, the dosage will be further reduced to 1 mg/kg per day for the last 2 weeks and then put off (i.e., one patient should have received a cumulative dosage of 98 mg/kg steroid after he finished the protocol). In case, if there was rebound or cholnagitic attack (defined as fever with increased bilirubin level), intravenous antibiotics would be added to the steroid and both would be continued until the episode subsided. In such case, steroid dosage would only be halved until the cholangitic episode subsided. After discharge, the patients were all followed up regularly at 3 to 6-month interval. In this study, the demographics and outcomes of the patients were noted. Outcomes measured include post-operative bilirubin level, episodes of cholangitic attack, the need for liver transplantation as recorded until December 2007 and cumulative transplant-free survival. Statistical analysis was done using Fisher's exact test and unpaired *t*-test when appropriate. Values are expressed as mean ± SEM. A value of $P < 0.05$ was considered to be statistically significant.

Results

Kasai operation was performed in 30 patients (11 boys and 19 girls) with biliary atresia from 1996 to 2006 in our hospital. All patients diagnosed with biliary atresia within this period of time were not associated with splenic malformation. Overall transplant free percentage is 66.7%. Thirteen patients received post-operative prednisolone according to our protocol. The mean age at operation for the steroid and non-steroid groups were 69.7 ± 12.3 and 62.5 ± 16.5 days, respectively ($P = 0.69$). The mean pre-operative bilirubin levels were similar for the treated and untreated (146.2 ± 14.2 and 160.2 ± 18.3 μmol/L, respectively) ($P = 0.01$). Normal post-operative bilirubin level (defined as bilirubin level less than 20 μmol/L) was achieved at 6 months in 7 patients (53.9%) who received steroid and 8 patients (47.0%) who did not ($P = 0.71$) (Table 1). In terms of bilirubin level, there was a statistically significant reduction for all patients in the steroid group with mean levels of 46.4 ± 20.8 μmol/L at 3 months and 17.3 ± 9.2 μmol/L at 6 months. While in the non-steroid group, the mean levels were 142.3 ± 14.3 μmol/L at 3 months and 48.4 ± 10.4 μmol/L at 6 months (Fig 1). Liver transplantation was required in 5 patients (38.5%) with steroid and 5 patients (29.4%) without ($P = 0.60$) (Table 1). All the liver transplantations from both groups were operated within 1 year after Kasai operation. There was no statistically significant difference between the two groups in terms of the frequency of cholangitis (Table 1). Regarding mortality, there was one death at 1 year after liver transplantation in the treated group. This was unrelated to hepatobiliary diseases. In the untreated group, there was one death due to cholangitis before liver transplantation. Overall, the actuarial survival with native liver was similar between the two groups after 15 months (Fig. 2). There was no steroid-associated

Table 1 Comparisons between non-steroid and steroid group

	Non-steroid ($n = 17$)	Steroid ($n = 13$)	P value
Mean age at operation (days)	62.5 ± 16.5	69.7 ± 12.3	0.69
Mean bilirubin level before operation (μmol/L)	160.2 ± 18.3	146.2 ± 14.2	0.01
Mean bilirubin level at 3-month after operation (μmol/L)	142.3 ± 14.3	46.4 ± 20.8	0.03
Mean bilirubin level at 6-month after operation (μmol/L)	48.4 ± 10.4	17.3 ± 9.2	0.02
Normal bilirubin at 6-month post operation(<20 μmol/L)	47.0% ($n = 8$)	53.9% ($n = 7$)	0.71
Liver transplantation	29.4% ($n = 5$)	38.5% ($n = 5$)	0.60
Cholangitic attack	41.2% ($n = 7$)	23.1% ($n = 3$)	0.26
Cumulative dosage of steroid received (mg/kg)			
0–50	5	0	
51–100	2	10	
101–150	1	2	
>150	0	1	

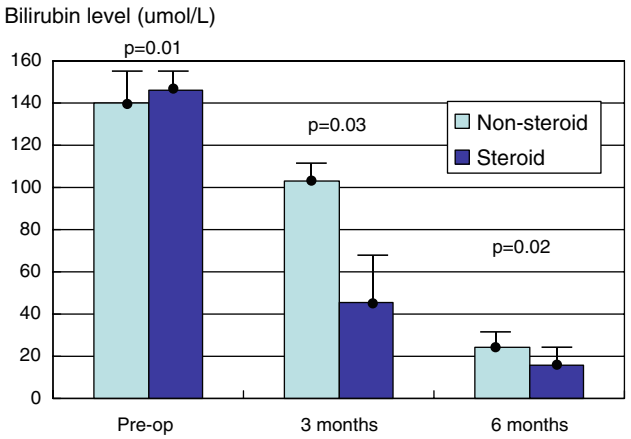

Fig. 1 Comparison of mean bilirubin levels (±SEM) for the two groups of patients taken pre-operatively, 3- and 6-months post-operatively

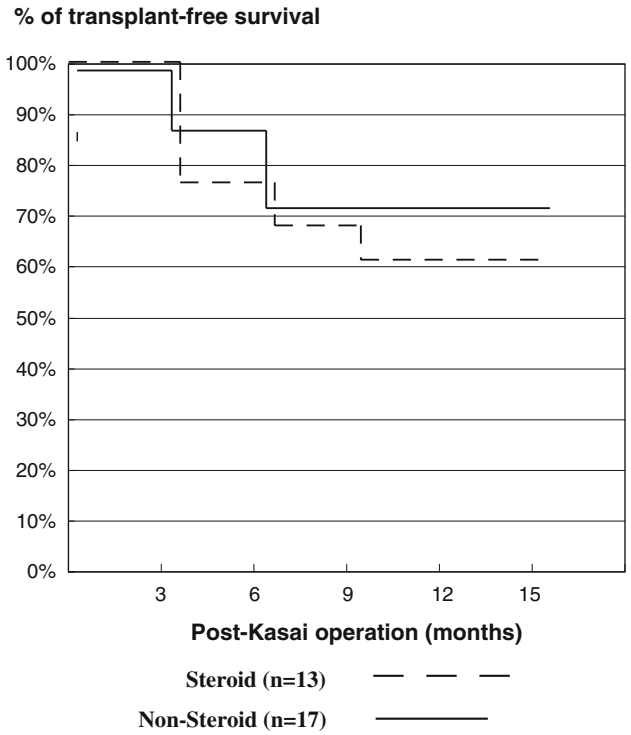

Fig. 2 Post-Kasai operation liver transplant-free survival curve

complication such as sepsis, wound infection, gastrointestinal bleeding and fluid retention reported.

Discussion

The management of biliary atresia remains challenging over the decades. Kasai operation has been the recommended treatment since 1957 [3]. Despite the macroscopic relief of extra-hepatic biliary obstruction, Kasai operation does not produce a consistently satisfactory long term outcome. Given this, new technique or adjuvant therapies that may help to improve the outcome have been sought. Examples include the extent of debridement at the biliary plate and the approach to construct the Roux-en-Y jejunal limb [12]. However, the additional benefit is not clinically significant with these measures. With a better understanding of the pathophysiology that leads to a failure, the focus has been switched to alter post-operative inflammatory changes, which have been shown to be the main factor affecting the outcomes.

Since inflammatory changes are believed to affect the patency of the transected microscopic ducts, steroid is being investigated to be the adjuvant therapy due to its anti-inflammatory function [6, 7, 11, 13]. It helps to reduce ductal inflammation and edema, making subsequent fibrosis and sclerosis less prominent. The effect of steroid is believed to be mediated through the expression of glucocorticoid receptors, namely GcRα and GcRβ [14]. Steroid

is believed to have choleretic effect which can increase canalicular electrolyte exchange by the induction of Na–K ATPase and stimulate bile flow [15]. The effectiveness of steroid has been suggested by various studies. Karrer and Lilly [10] reported their successful experience of using blast type (high dose with short duration) steroid for treatment of poor bile flow after Kasai operation. A reduction of periductal inflammation and depletion in lymphocytes were demonstrated in their studies. Extending to their work, Dillon et al. [16] were the first to advocate long-term high dose steroid to achieve a higher jaundice free period after the operation. Recently, Escobar et al. [6] also concluded that the use of steroid after Kasai operation improved the clearance of jaundice. However, the dosage of steroid administered was not standardized and was subjected to surgeon's preference. Obviously, the clinical evidence of steroid usage after Kasai operation is not firmly established and there is still no standard protocol regarding the optimal dosage. This also explains the reason for the observed difference in various studies.

Before 2004, steroid was mainly given on a cholangitis-triggered basis without standard dosage in our centre. In 2004, Muraji [11] has conducted a national survey on the practice of post-Kasai steroid usage. The recommended initial dosage was $\geq$4 mg/kg per day. With reference to this, we established our own protocol and since then routine steroid was given to all patients after the Kasai operation regardless of the post-operative progress. We believed an initial high dose steroid with gradual reduction would benefit our patients given the successful experience from our nearby country. Furthermore, all patients were operated by the same chief surgeon within the same centre, thus eliminating surgeon variability. As seen in Table 1, the demographics of our patients were similar in both groups. As a result, we felt confident that we had minimized most variables and could, therefore assess the effect of steroids on the post-operative outcome. From the data we gathered, we can conclude that a lower post-operative bilirubin level can be achieved with the use of prednisolone according to our protocol. This result is comparable to a recently published prospective randomized trial by M. Davenport et al. [9]. In their series, the administration of steroid after Kasai operation was found to have effect on the improvement of liver function but not overall liver transplantation rate. However, we believe that the reduction in post-operative bilirubin level signifies a positive impact regarding the prognosis. The lack of obvious improvement in liver transplantation rate and cholangitic attacks in our study may be attributed to the small sample size in the compared groups. Besides, some of the patients in the "non-steroid" group also received non-standardized dose of steroids for variable durations, which could make the difference between the two groups less statistically significant. Other variables, such as patient selection and the change in peri-operative care may also contribute potential bias. Furthermore, the long-term outcome for our patients is still unknown. Nonetheless, being a pilot study, our protocol shows encouraging results in terms of improving bile drainage and we recommend the use of post-operative steroids for biliary atresia patients. A prospective study with larger sample size and longer period of follow-up is required.

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