Pediatric Surgery International (2019) 35:1059–1063
https://doi.org/10.1007/s00383-019-04537-7

ORIGINAL ARTICLE

Efficacy of and prognosis after steroid pulse therapy in patients with poor reduction of jaundice after laparoscopic Kasai portoenterostomy

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Accepted: 1 August 2019 / Published online: 8 August 2019

Abstract

Purpose High-dose postoperative steroid therapy after Kasai portoenterostomy is reported to improve jaundice clearance and a strong anti-inflammatory activity might prevent fibrous tissue formation which is often observed at the porta hepatis in revision surgery. We started steroid pulse therapy for the patients with cessation of decrease in jaundice and aimed to evaluate the efficacy in this study.

Methods The demographics and outcomes of patients who underwent laparoscopic Kasai portoenterostomy and received steroid pulse therapy within 2 months postoperatively between September 2014 and December 2018 were retrospectively reviewed; the therapy was determined successful when the serum total bilirubin level decreased to or below two-thirds of the pre-therapy level after 2 weeks. Patient data in the successful group were compared with those in the unsuccessful group.

Results Steroid pulse therapy was successful in seven of 16 patients (43.8%). The percentage of patients whose serum total bilirubin level decreased to normal was significantly higher in the successful group at 3 months (85.7% vs. 11.1%, $P=0.0028$) and after all (100% vs. 33.3%, $P=0.011$).

Conclusions Steroid pulse therapy was effective for some patients. Unsuccessful cases may have little chances of jaundice clearance; revision Kasai portoenterostomy would be a good option.

Keywords Biliary atresia · Steroid pulse therapy · Kasai portoenterostomy · Revision surgery · Endoscopic surgery

Introduction

Postoperative steroid therapy after Kasai portoenterostomy has been widely used to provide anti-inflammatory effects in the periductal regions to improve bile flow. Some reports showed that high-dose steroids would improve jaundice clearance [1–4]. However, we often encounter newly developed fibrous tissue covering the porta hepatis in revision surgery with Kasai portoenterostomy [5]. Therefore, a much stronger anti-inflammatory activity might be necessary to prevent fibrous tissue formation in these patients. Considering the increased risk of side effects, long-term higher dose administration of steroids should be avoided, and steroid pulse therapy was started only in patients, whose decrease in jaundice level stopped in the postoperative period. In this report, we aimed to evaluate the efficacy of steroid pulse therapy for patients with poor jaundice reduction after a laparoscopic Kasai portoenterostomy. To our knowledge, only one report has evaluated postoperative steroid pulse therapy after Kasai portoenterostomy in 1985 [6].

Patients and methods

This study was approved by the ethics committee of our hospital (#2015-0094) and conforms to the provisions of the Declaration of Helsinki. Since December 2013, laparoscopic Kasai portoenterostomy has been established as the standard surgery for biliary atresia, and all operations were performed by or under the supervision of one qualified surgeon (H.U.) without open conversion, and our operative technique and

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postoperative management had been well established by the latter half of 2014. We retrospectively reviewed the demographics and outcomes of patients who underwent laparoscopic Kasai portoenterostomy for biliary atresia and underwent steroid pulse therapy within 2 months postoperatively between September 2014 and December 2018.

Laparoscopic Kasai portoenterostomy techniques were described in our previous report [5]. All manipulations were performed using 3-mm forceps and 5-mm microbipolar forceps with five ports. The fibrous tissue in the hilar plate was almost resected, leaving it very thin so as to not expose the liver parenchyma. After creating a Roux-en-Y limb, end-to-side portoenterostomy was performed laparoscopically. From the fifth day postoperatively, prednisolone at 4 mg/kg/day was routinely administered orally to all patients together with ursodeoxycholic acid and fat-soluble vitamins, with dose tapered to 2, 1, and 0.5 mg/kg/day every 5 days (37.5 mg/kg in total). When the steady decrease in the jaundice level stopped for a week or the jaundice level increased, the steroid pulse therapy was initiated. The protocol for steroid pulse therapy was as follows. Methylprednisolone was injected intravenously at a dose of 20 mg/kg/day for 2 days, followed by 10 mg/kg/day for 2 days and 5 mg/kg/day for 2 days, lasting for a total of 6 days. Then, the original protocol of oral prednisolone intake was resumed. The steroid pulse therapy was determined successful when the serum total bilirubin (T.bil) level decreased to or below two-thirds of the pre-therapy level after 2 weeks. When the steroid pulse therapy was unsuccessful, revision of laparoscopic Kasai portoenterostomy was an option of treatment for the patients who had bile lakes or once had yellowish stool after surgery [5]. Revision surgery was also an option of treatment for all the patients who had sudden elevation of jaundice level more than 2 months after the initial Kasai portoenterostomy, even though they had achieved or nearly achieved jaundice clearance. Another steroid pulse therapy was an option of treatment for the patients who had some decrease in jaundice level after steroid pulse therapy, or for the patients whose serum jaundice levels were not decreased for more than a week, but need not undertake a liver transplantation at once.

Patient data in the successful steroid pulse therapy group were compared with those in the unsuccessful steroid pulse therapy group. The patients who had comorbid disorders, such as portosystemic shunt and right heart failure that might influence jaundice clearance, were excluded from this study.

Fisher's exact test, Mann–Whitney *U* test, and log-rank test were used to compare clinical data. *P* values < 0.05 were considered statistically significant.

Results

In total, 30 patients underwent laparoscopic Kasai portoenterostomy during the period and 18 patients underwent steroid pulse therapy within 2 months postoperatively. Among them, one patient had portosystemic shunt (congenital extrahepatic portosystemic shunt type 1) and another patient had right heart failure due to a double outlet right ventricle; both were excluded from this study. The demographic characteristics of the remaining 16 patients are shown in Table 1. All patients had type III biliary atresia, and no complication due to steroid pulse therapy was observed.

The overview of the clinical course of the patients who underwent steroid pulse therapy is shown in Fig. 1. Steroid pulse therapy was successful in seven patients

Table 1 Demographic data and operative outcomes of patients who underwent steroid pulse therapy within 2 months after laparoscopic Kasai portoenterostomy

	Successful steroid pulse therapy ($n=7$)	Unsuccessful steroid pulse therapy ($n=9$)	*P* value
Age at operation (days)	Median 61 (range 29–89)	Median 68 (range 28–80)	0.84
Body weight at operation (kg)	4.21 (range 2.86–5.47)	4.72 (range 2.24–5.12)	1
Male/female	3/4	5/4	1
Serum T.bil level just before surgery (mg/dl)	Median 7.1 (range 2.9–14.3)	Median 9.0 (range 5.5–10.0)	1
Operative time (min)	Median 310 (range 291–483)	Median 350 (range 249–497)	0.76
Intraoperative bleeding amount (mL)	Median 14 (range 14–100)	Median 24 (range 6–80)	1
Age at first steroid pulse therapy (days)	Median 78 (range 49–110)	Median 93 (range 51–117)	0.92
Serum T.bil level just before first steroid pulse therapy (mg/dl)	Median 5.2 (range 1.8–7.7)	Median 5.6 (range 2.4–10.2)	0.96
Serum AST level just before first steroid pulse therapy (IU/dl)	Median 134 (range 86–345)	Median 141 (range 77–198)	0.79
Serum ALT level just before first steroid pulse therapy (IU/dl)	Median 156 (range 35–267)	Median 102 (range 56–396)	0.27
Performed revision laparoscopic Kasai portoenterostomy	14.3% (1/7)	44.4% (4/9)	0.31

T. bil total bilirubin, *AST* aspartate transaminase, *ALT* alanine transaminase

The *P* value was calculated using the Mann–Whitney *U* test and Fisher's exact test

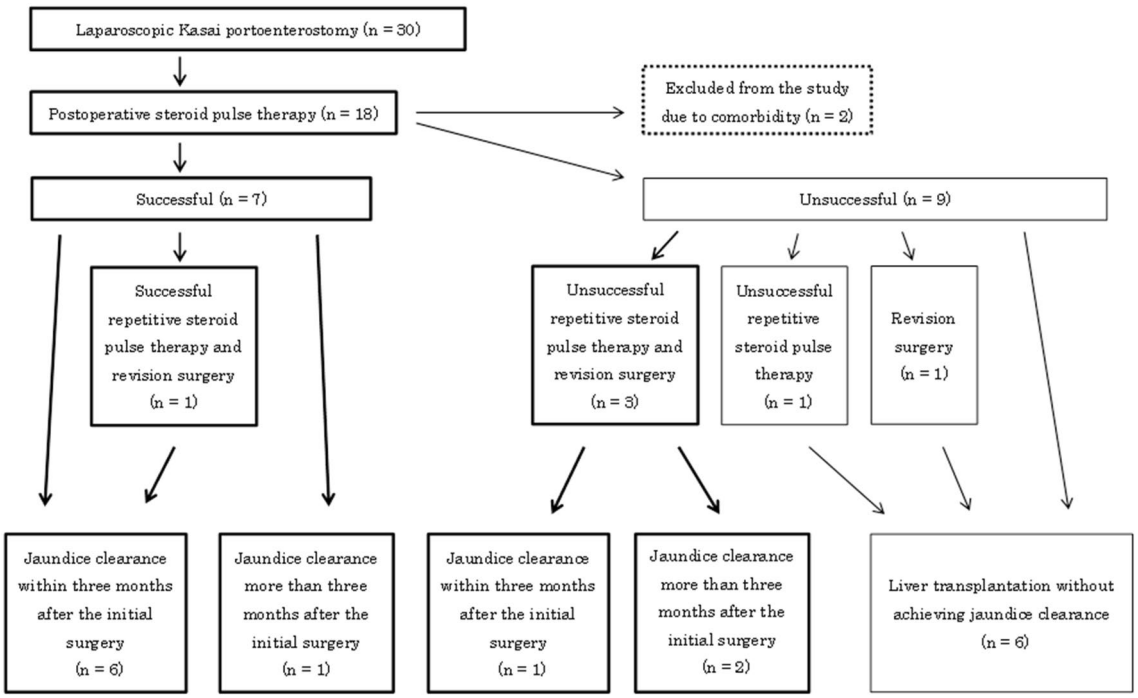

Fig. 1 Overview of the clinical course of the patients who underwent steroid pulse therapy after laparoscopic Kasai portoenterostomy

(43.8%). There was no statistical difference concerning demographic data, operative outcomes, age at first steroid pulse therapy, and serum total bilirubin, aspartate transaminase, and alanine transaminase level just before first steroid pulse therapy between the successful group and unsuccessful group. Five patients underwent steroid pulse therapy twice with more than 2 week interval. The treatment was successful both times in one patient and unsuccessful both times in the other four patients. Notably, in none of the patients, the treatment was successful one time and unsuccessful the other time. The percentage of patients with serum total bilirubin level that decreased to the normal level according to our hospital criteria (jaundice clearance) at 3 months postoperatively in the successful steroid pulse therapy group was significantly higher than that in the unsuccessful group [85.7% (6/7) vs. 11.1% (1/9), $P = 0.0028$] (Table 2). The proportion of patients who eventually achieved jaundice clearance was also significantly higher in the successful steroid pulse therapy group than in the unsuccessful group [100% (7/7) vs. 33.3% (3/9), $P = 0.011$]. Remarkably, all three patients who eventually achieved jaundice clearance in the unsuccessful steroid pulse therapy group underwent revision Kasai portoenterostomy. Among the patients who underwent laparoscopic Kasai portoenterostomy more than a year ago, the native liver survival rate at 1 year was 83.3% (5/6) and 25% (2/8) in the successful and unsuccessful steroid pulse therapy groups, respectively ($P = 0.10$). The only patient who needed liver transplantation within a year in the successful steroid pulse therapy group underwent steroid pulse therapy twice and revision laparoscopic Kasai portoenterostomy before achieving jaundice clearance. The Kaplan–Meier curve for native liver survival is shown in Fig. 2. The period of native liver survival after the initial Kasai portoenterostomy was longer in the successful steroid pulse therapy group than in the unsuccessful group although without significance in the log-rank test ($P = 0.066$).

Table 2 Jaundice clearance in patients who underwent steroid pulse therapy within 2 months after laparoscopic Kasai portoenterostomy

	Successful steroid pulse therapy ($n = 7$)	Unsuccessful steroid pulse therapy ($n = 9$)	*P* value
Patients with jaundice clearance at 3 months after initial surgery (%)	85.7% (6/7)	11.1% (1/9)	0.0028
Patients with eventual jaundice clearance (%)	100% (7/7)	33.3% (3/9)	0.011

The *P* value was calculated using the Fisher's exact test

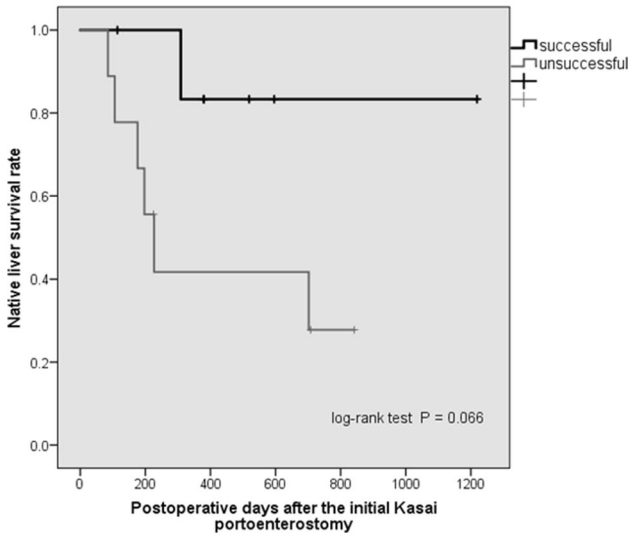

Fig. 2 Kaplan–Meier curves for survival with a native liver. Patients with successful steroid pulse therapy ($n=7$) and unsuccessful steroid pulse therapy ($n=9$) were compared

Discussion

Postoperative steroid pulse therapy after Kasai portoenterostomy remains controversial, and some authors report that it improves short-term jaundice clearance only and does not improve native liver survival [7, 8]. However, a prospective study also showed that high-dosage starting from 5 mg/kg/day (75 mg/kg in total) of oral prednisolone would improve the estimated native liver survival compared to that with low dose (37 mg/kg in total) or placebo [1]. Thus, we speculate that most previously published studies that did not recommend postoperative steroid therapy might have used low-dose therapy.

Several mechanisms have been suggested for the efficacy of steroid therapy after portoenterostomy, including the choleretic [9, 10] and anti-inflammatory effects [6, 11]. Concerning the anti-inflammatory effects, steroids are expected to play three different roles, namely, anti-edema effect around the thin bile duct regions to improve bile flow, ameliorating the inflammatory surge after surgery, and immunosuppression. First, some clinicians even use intravenous administration of steroids right after the surgery due to its anti-edema effect [12], although this practice is not common because of the possibility of anastomotic leakage. We also expect the effects of steroids in terms of reducing the tissue collagen content useful after the dilatation of esophageal stricture [13]. Similarly, steroids might prevent fibrous tissue formation on the porta hepatis. Second, it was reported that a marked inflammatory surge in serum cytokines and adhesion molecules after Kasai portoenterostomy was observed [14] and steroids are expected to ameliorate the detrimental effect. Third, autoimmune liver disease-related autoantibodies, especially anti-neutrophil cytoplasmic antibody (ANCA), have been reported to be higher in patients with biliary atresia, which might cause cholangitis postoperatively [15].

As reported by Karrer and Lilly, the anti-inflammatory response of steroids is accelerated by a sudden high dose of steroids, an effect that persists beyond the period of elevated plasma steroid levels [6, 16]. They used intravenous administration of 10 mg/kg methylprednisolone initially, reducing the daily dose by half, and discontinued by the fourth to seventh day, which was similar to our steroid pulse therapy protocol.

In this report, we showed that steroid pulse therapy is effective for some patients in whom the steady decrease in jaundice level stopped for a week or in those with increased jaundice level. Remarkably, all patients in whom the therapy was effective eventually achieved jaundice clearance, and the proportion of such patients was significantly higher than that of patients with unsuccessful steroid pulse therapy. Therefore, patients who underwent unsuccessful steroid therapy might have minimal chances of jaundice clearance with conservative treatment, and revision of Kasai portoenterostomy should be considered in such cases [17]. Thus, the efficacy of the steroid pulse therapy could anticipate to some extent the prognosis of patients who experienced cessation of jaundice-level decrease during the postoperative course. Although we did not notice any side effects of steroid pulse therapy in this series, some reports have shown gastrointestinal bleeding, infection, and poor growth [7, 18]. Therefore, this therapy should be limited to patients with cessation of jaundice-level decrease.

Our study had some limitations, including a short follow-up period, small number of patients, and the fact that it was a non-randomized study. A randomized controlled trial with longer follow-up is necessary to demonstrate the effects of steroid pulse therapy on patients with poor reduction of jaundice after laparoscopic Kasai portoenterostomy.

Conclusion

Steroid pulse therapy was effective for some patients who had cessation of jaundice-level decrease during the postoperative course. Moreover, patients who underwent an unsuccessful steroid therapy might have little chance of jaundice clearance with conservative treatment; therefore, revision Kasai portoenterostomy should be considered.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in this study.

References

1. Davenport M, Parsons C, Tizzard S, Hadzic N (2013) Steroids in biliary atresia: single surgeon, single centre, prospective study. J Hepatol 59:1054–1058. https://doi.org/10.1016/j.jhep.2013.06.012
2. Chen Y, Nah SA, Chiang L, Krishnaswamy G, Low Y (2015) Postoperative steroid therapy for biliary atresia: systematic review and meta-analysis. J Pediatr Surg 50:1590–1594. https://doi.org/10.1016/j.jpedsurg.2015.05.016
3. Kobayashi H, Yamataka A, Koga H, Okazaki T, Tamura T, Urao M, Yanai T, Lane GJ, Miyano T (2005) Optimum prednisolone usage in patients with biliary atresia postportoenterostomy. J Pediatr Surg 40:327–330. https://doi.org/10.1016/j.jpedsurg.2004.10.017
4. Japanese Biliary Atresia S, Nio M, Muraji T (2013) Multicenter randomized trial of postoperative corticosteroid therapy for biliary atresia. Pediatr Surg Int 29:1091–1095. https://doi.org/10.1007/s00383-013-3377-6
5. Murase N, Uchida H, Ono Y, Tainaka T, Yokota K, Tanano A, Shirota C, Shirotsuki R (2015) A new era of laparoscopic revision of Kasai portoenterostomy for the treatment of biliary atresia. Biomed Res Int 2015:173014. https://doi.org/10.1155/2015/173014
6. Karrer FM, Lilly JR (1985) Corticosteroid therapy in biliary atresia. J Pediatr Surg 20:693–695
7. Bezerra JA, Spino C, Magee JC, Shneider BL, Rosenthal P, Wang KS, Erlichman J, Haber B, Hertel PM, Karpen SJ, Kerkar N, Loomes KM, Molleston JP, Murray KF, Romero R, Schwarz KB, Shepherd R, Suchy FJ, Turmelle YP, Whitington PF, Moore J, Sherker AH, Robuck PR, Sokol RJ, Childhood Liver Disease R, Education N (2014) Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia: the START randomized clinical trial. JAMA 311:1750–1759. https://doi.org/10.1001/jama.2014.2623
8. Zhang MZ, Xun PC, He K, Cai W (2017) Adjuvant steroid treatment following Kasai portoenterostomy and clinical outcomes of biliary atresia patients: an updated meta-analysis. World J Pediatr 13:20–26. https://doi.org/10.1007/s12519-016-0052-8
9. Miner PB Jr, Gaito JM (1979) Bile flow in response to pharmacologic agents. Hepatic DNA as a reference standard. Biochem Pharmacol 28:1063–1066
10. Alvaro D, Gigliozzi A, Marucci L, Alpini G, Barbaro B, Monterubbianesi R, Minetola L, Mancino MG, Medina JF, Attili AF, Benedetti A (2002) Corticosteroids modulate the secretory processes of the rat intrahepatic biliary epithelium. Gastroenterology 122:1058–1069
11. Dillon PW, Owings E, Cilley R, Field D, Curnow A, Georgeson K (2001) Immunosuppression as adjuvant therapy for biliary atresia. J Pediatr Surg 36:80–85. https://doi.org/10.1053/jpsu.2001.20013
12. Suzuki T, Hashimoto T, Kondo S, Sato Y, Hussein MH (2010) Evaluating patients' outcome post-Kasai operation: a 19-year experience with modification of the hepatic portoenterostomy and applying a novel steroid therapy regimen. Pediatr Surg Int 26:825–830. https://doi.org/10.1007/s00383-010-2637-y
13. Yokota K, Uchida H, Tanano A, Shirota C, Tainaka T, Hinoki A, Murase N, Oshima K, Shirotsuki R, Chiba K (2016) Steroid pulse therapy prevents restenosis following balloon dilatation for esophageal stricture. Pediatr Surg Int 32:875–879. https://doi.org/10.1007/s00383-016-3939-5
14. Narayanaswamy B, Gonde C, Tredger JM, Hussain M, Vergani D, Davenport M (2007) Serial circulating markers of inflammation in biliary atresia—evolution of the post-operative inflammatory process. Hepatology 46:180–187. https://doi.org/10.1002/hep.21701
15. Pang SY, Dai YM, Zhang RZ, Chen YH, Peng XF, Fu J, Chen ZR, Liu YF, Yang LY, Wen Z, Yu JK, Liu HY (2018) Autoimmune liver disease-related autoantibodies in patients with biliary atresia. World J Gastroenterol 24:387–396. https://doi.org/10.3748/wjg.v24.i3.387
16. Coburg AJ, Gray SH, Katz FH, Penn I, Halgrimson C, Starzl TE (1970) Disappearance rates and immunosuppression of intermittent intravenously administered prednisolone in rabbits and human beings. Surg Gynecol Obstet 131:933–942
17. Shirota C, Uchida H, Ono Y, Murase N, Tainaka T, Yokota K, Oshima K, Shirotsuki R, Hinoki A, Ando H (2016) Long-term outcomes after revision of Kasai portoenterostomy for biliary atresia. J Hepatobiliary Pancreat Sci 23:715–720. https://doi.org/10.1002/jhbp.395
18. Alonso EM, Ye W, Hawthorne K, Venkat V, Loomes KM, Mack CL, Hertel PM, Karpen SJ, Kerkar N, Molleston JP, Murray KF, Romero R, Rosenthal P, Schwarz KB, Shneider BL, Suchy FJ, Turmelle YP, Wang KS, Sherker AH, Sokol RJ, Bezerra JA, Magee JC, Chi LN (2018) Impact of steroid therapy on early growth in infants with biliary atresia: the multicenter steroids in biliary atresia randomized trial. J Pediatr 202(179–185):e174. https://doi.org/10.1016/j.jpeds.2018.07.002