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ORIGINAL ARTICLE

Does pneumoperitoneum adversely affect growth, development and liver function in biliary atresia patients after laparoscopic portoenterostomy?

Hiroki Nakamura · Hiroyuki Koga · Tadaharu Okazaki · Masahiko Urao · Go Miyano · Manabu Okawada · Takashi Doi · Hiroko Watayo · Yuki Ogasawara · Geoffrey J. Lane · Atsuyuki Yamataka

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Abstract
Purpose We assessed the effect of high partial pressure of arterial carbon dioxide ($PaCO_2$) due to pneumoperitoneum (PP) on growth (height/weight) and development (gross/fine motor function, receptive/expressive communication, and social interaction), by comparing outcome after portoenterostomy (PE) for biliary atresia (BA) using laparoscopic PE (LPE: $n = 13$) and open PE (OPE: $n = 13$) cases performed between 2005 and 2014.
Methods Our PE is based on Kasai's original PE. All data were collated prospectively.
Results Differences in duration of follow-up (LPE: 38.8 months; OPE: 38.1 months), jaundice clearance (LPE: 12/13 = 92.3 %; OPE: 9/13 = 69.2 %), survival with the native liver (LPE: 10/13 = 76.9 %; OPE: 9/13 = 69.2 %), incidence of cholangitis, hypersplenism, and incidence of esophageal varices were not significant. Mean intraoperative $PaCO_2$ was significantly higher in LPE (LPE: 50.1 mmHg; OPE: 40.7 mmHg, $p < 0.05$). Liver function impairment was not statistically different, although LPE results were slightly worse. There was no overall delay in growth observed, although height/weight gain was more consistent in LPE. The pattern of developmental delay observed was similar for LPE and OPE suggesting that developmental delay is not PE-related; in other words, PP is not implicated in developmental delay.
Conclusions PP during LPE would appear to have no adverse effects on overall growth/development and liver function in BA patients.

Keywords Biliary atresia · Development · Growth · Liver function · Pneumoperitoneum · Laparoscopic portoenterostomy

H. Nakamura · H. Koga · G. Miyano · M. Okawada · T. Doi · G. J. Lane · A. Yamataka (✉)
Department of Pediatric General and Urogenital Surgery, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
e-mail: yama@juntendo.ac.jp

T. Okazaki · Y. Ogasawara
Department of Pediatric Surgery, Juntendo University Urayasu Hospital, Chiba, Japan

M. Urao · H. Watayo
Department of Pediatric Surgery, Juntendo University Nerima Hospital, Tokyo, Japan

Introduction

Pneumoperitoneum (PP) reportedly decreases hepatocyte proliferation and induces hepatocyte damage in biliary atresia (BA) model mice [1], so it has been suggested that one potential explanation for poorer outcome in BA patients who had laparoscopic portoenterostomy (LPE) could be related to liver damage induced by prolonged, high-pressure carbon dioxide (CO_2) PP used during LPE, a procedure that requires several hours to complete [2]. It has been previously demonstrated that prolonged PP required for laparoscopy has detrimental effects on the liver as evidenced by a transient increase in serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and gamma glutamyl transpeptidase (γGTP) levels [3–7]. The mechanism behind this effect is thought to be transient ischemia produced by PP and subsequent reperfusion injury, with generation of reactive oxygen that promotes inflammation and cell death [8–10]. In an animal model of BA, BA livers are more susceptible than healthy livers to injury by prolonged PP, and injury is caused by both CO_2 and air PP, implying that it is a direct result of pressure [1].

Mogilner et al. [11] showed recently in a rat model that elevated intra-abdominal pressure decreased hepatocyte proliferation and induced liver cell apoptosis. Some authors have shown that CO_2 PP temporarily alters the metabolism and function of various abdominal cells, including hepatic macrophages [12–14], suggesting that these effects might be particularly relevant in children with compromised liver cell function or liver fibrosis.

We examined BA patients treated by LPE, and compared them with patients who had open portoenterostomy (OPE), to determine whether high partial pressure of arterial carbon dioxide ($PaCO_2$) due to PP could hinder growth as reflected by height/weight gain, development (gross/fine motor function, receptive/expressive communication, and social interaction) or adversely affect liver function.

Materials and methods

Subjects for this study were 13 consecutive BA patients treated from 2005 to 2014 by LPE and 13 consecutive BA patients who had OPE during the same period. Both OPE and LPE were performed using principles described originally by Kasai, and postoperative management protocols for antibiotics and steroid were identical in both.

Data for age and body weight at portoenterostomy (PE), time taken for jaundice clearance [total bilirubin (T-Bil) $\leq$1.2 mg/dL; JC time], jaundice clearance ratio (JCR: proportion of subjects who achieved JC), total steroid dosage, micro bile duct size, incidence of cholangitis [defined as elevated serum bilirubin (>2.5 mg/dL), leukocytosis with left shift, and normal to acholic stools in a febrile patient (>38.0 °C)], presence of hypersplenism, postoperative liver function, survival with the native liver (SNL), operative time, blood loss, and intraoperative maximum $PaCO_2$ (Op-$PaCO_2$) were collated prospectively from medical records.

Hypersplenism is usually defined as the presence of: (1) any evidence of isolated or concurrent anemia, leukopenia, or thrombocytopenia in peripheral blood films; (2) normocellular or hypercellular bone marrow; (3) splenomegaly; (4) normal erythrocyte, platelet and leukocyte counts following splenectomy. However, (2) and (4) were not applicable in our cases, so hypersplenism was diagnosed based on the presence of both (1) and (3).

Maternal/baby health handbook

The Japanese Department of Health issues each pregnant woman with an official handbook about maternal/baby health that doctors use to record details of the pregnancy, delivery, growth/development, and healthcare such as vaccinations [15]. This maternal/baby health handbook (MBH) is kept by the mother and presented at every clinic attendance to record details of growth/development and also includes a schedule for regular checkups for assessing growth/development milestones at 1, 3, 6, 10 months, 1 year, 18 months, and 2 years, then annually until 5 years old. MBH use in Japan is universal and information may be recorded by medical specialists, public health nurses, midwives and the parents themselves at hospitals, clinics, or health centers [15]. Assessment of gross motor function and receptive communication begins at 1 month of age, fine motor function and expressive communication at 6 months of age, and social interaction at 10 months of age.

Our portoenterostomies

Details of our PE techniques are described elsewhere [16]. We perform OPE and LPE according to the principles described originally by Kasai [17]. During LPE, abdominal CO_2 pressure is maintained at 8 mmHg, and increased to 10 mmHg if required, using CO_2 gas at a flow rate of 0.5–1.0 L/min. PP pressure and gas flow are controlled by an electronic insufflator (Karl Storz, Tuttlingen, Germany). Initially a flow rate of 0.5 L/min is used to insufflate the abdomen slowly, whereupon the rate is increased to 1.0 L/min for PP.

Postoperative management

Postoperative management protocols for antibiotic therapy, steroid dosage, and choice of cholagogues were the same for both groups. Details of our postoperative management including steroid protocol may be found elsewhere [18].

Statistical analyses

The Student's t test and Chi squared test were used for statistical analysis. A p value < 0.05 was considered to be statistically significant.

Ethics

This study was approved by the Ethics Committee of Juntendo University School of Medicine and complies with the Helsinki Declaration of 1975 (revised 1983).

Results

Of the 26 cases of BA we reviewed, all were isolated type III except for one case each of syndromic type III BA (with visceral inversion) [19], type I, and type II in OPE; and one

Table 1 Comparison of data according to type of portoenterostomy

	OPE	LPE	*p* value
Mean duration of follow-up (range)	38.1 (4–99) months	38.8 (4–67) months	NS
Mean weight at PE (range)	4.0 (2.2–5.7) kg	4.2 (3.2–5.0) kg	NS
Mean age at PE (range)	64.7 (29–100) days	65.8 (29–119) days	NS
Mean steroid dosage required for JC (range)	45.3 (0–63) mg/kg	75.0 (0–150) mg/kg	NS
Mean JC time (range)	42.1 (23–64) days	58.6 (26–182) days	NS
Mean micro bile duct size (range)	224 (50–500) μm	243 (absent–1,500) μm	NS
Incidence of cholangitis	69.2 %	46.1 %	NS
Incidence of hypersplenism	46.1 %	46.1 %	NS
Mean operating time (range)	468 (375–576) min	546 (414–662) min	NS
Mean blood loss (range)	12.4 (7–32) g	11.9 (3–21) g	NS
Mean intraoperative max $PaCO_2$ (range)	40.7 (36–43) mmHg	50.1 (33–63) mmHg	<0.05
JCR	69.2 %	92.3 %	NS
SNL	69.2 %	76.9 %	NS
LTx	30.8 %	23.1 %	NS

PE portoenterostomy, *OPE* open portoenterostomy, *LPE* laparoscopic portoenterostomy, *JC* jaundice clearance, *$PaCO_2$* partial pressure of arterial carbon dioxide, *JCR* jaundice clearance ratio, *SNL* survival with native liver, *LTx* liver transplantation ratio, *NS* not significant

case each of syndromic type III (with absent subhepatic inferior vena cava) and type II in LPE. All subjects were of similar severity based on preoperative clinical and biochemical assessments. Our results are summarized in Table 1.

Mean weight at PE was 4.0 kg (range 2.2–5.7 kg) for OPE and 4.2 kg (range 3.2–5.0 kg) for LPE (p = NS). Mean age at PE was 64.7 days (range 29–100 days) for OPE and 65.8 days (range 29–119 days) for LPE (p = NS). Mean duration of follow-up was 38.1 months for OPE (range 4–99 months) and 38.8 months for LPE (range 4–67 months) (p = NS). Mean micro bile duct size was 224 μm (range 50–500 μm) for OPE and 243 μm (range absent to 1,500 μm) for LPE (p = NS). Mean operative time was 468 min (range 375–576 min) for OPE and 546 min (range 414–662 min) for LPE (p = NS). Mean Op-$PaCO_2$ was significantly higher in LPE [50.1 mmHg (range 33–63 mmHg) in LPE; 40.7 mmHg (range 36–43 mmHg) in OPE, $p < 0.05$]. Mean blood loss was 12.4 g (range 7–32 g) for OPE and 11.9 g (range 3–21 g) for LPE (p = NS).

Mean steroid dosage required for JC was 45.3 mg/kg (range 0–63 mg/kg) for OPE and 75.0 mg/kg (range 0–150 mg/kg) for LPE (p = NS). Mean time to achieve JC was 42.1 days (range 23–64 days) for OPE and 58.6 days (range 26–182 days) for LPE. (p = NS). JCR was 9/13 (69.2 %) for OPE and 12/13 (92.3 %) for LPE. (p = NS) Liver transplantation (LTx) was required for 1/9 of the OPE cases who achieved JC, and 3/12 of the LPE cases who achieved JC. Of the 4/13 OPE cases who did not achieve JC, 3/4 required LTx, and the remaining case is awaiting LTx, and the 1 LPE case who did not achieve JC is also awaiting LTx. Thus, SNL in our series is 9/13 (69.2 %) for OPE (8 cases with JC and 1 case awaiting LTx) and 10/13 (76.9 %) for LPE (9 cases with JC and 1 case awaiting LTx) (p = NS). Rate of LTx for OPE was 4/13 (30.8 %) and for LPE was 3/13 (23.1 %).

Differences in postoperative biochemistry such as T-Bil, ALT, AST and γGTP were not statistically significant between the two groups for cases who achieved JC (Fig. 1), although ALT, AST and γGTP levels were slightly higher for LPE. Preoperative levels of ALT and AST were slightly lower in LPE, but higher postoperatively; while γGTP was slightly higher in LPE both pre-and postoperatively. Overall, ALT, AST, and γGTP levels were not statistically different between LPE and OPE. Data for cases who did not achieve JC were not included in Figs. 1 and 2. For cases who achieved JC but later required LTx, only data up to registration for LTx were included in Figs. 1 and 2.

Incidence of cholangitis was 9/13 (69.2 %) for OPE and 6/13 (46.1 %) for LPE (p = NS). Incidence of hypersplenism was 6/13 (46.1 %) for OPE and 6/13 (46.1 %) for LPE (p = NS).

Results for growth/development parameters at 1, 3, 6, 10 months, 1 year, 18 months, and 2 years of age are shown in Fig. 2. All recorded results for growth (i.e., both height and weight) were within ±1 SD of normal, which we classified as normal, but increase in height was more consistent in LPE although not statistically significant and growth in OPE caught up to LPE between 25 and 30 months of age. There was no delay in fine motor function and social interaction identified in both groups. However, delay evidenced in gross motor function was of the same pattern for LPE and OPE. Delays in receptive and expressive communication were transient in both groups and of similar pattern. In summary, both growth and development for LPE were not significantly different from OPE.

We recalculated all statistics using only data for isolated type III BA patients (i.e., by excluding the five cases who were not isolated type III BA) and found there were no differences in statistical significance.

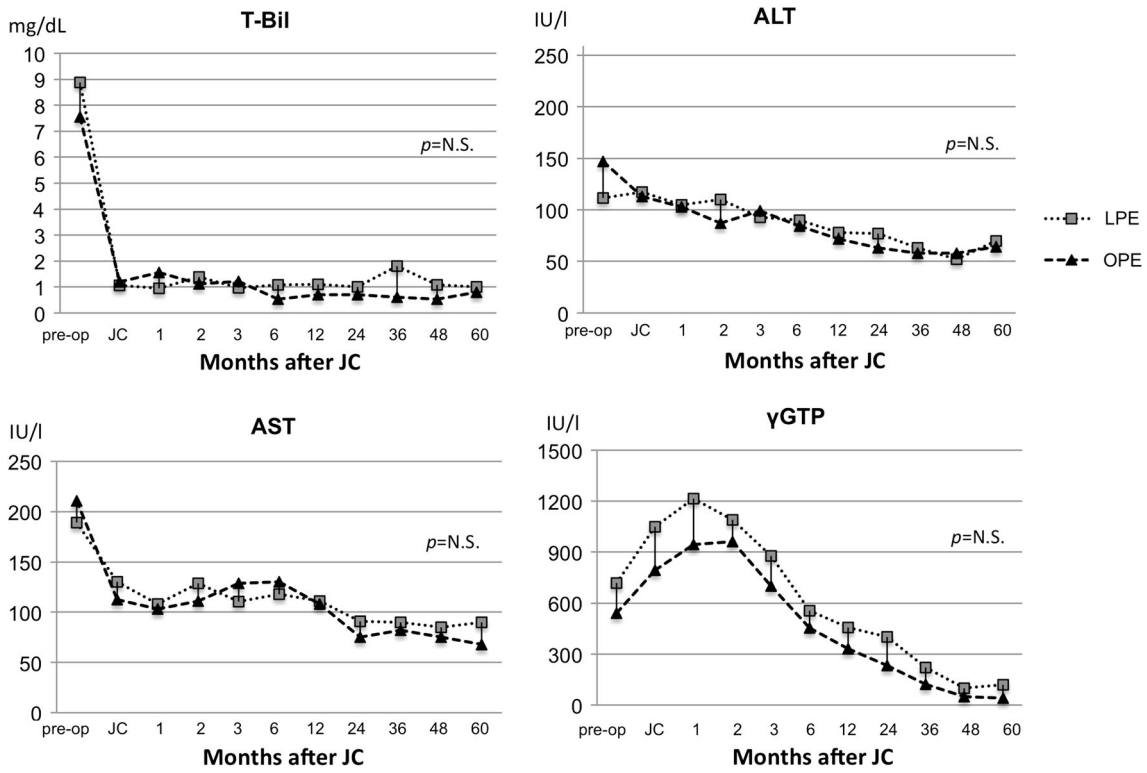

Fig. 1 Changes in liver function in BA patients who had jaundice clearance (JC) after portoenterostomy (PE). Comparison of T-Bil, ALT, AST and γGTP. *T-Bil* total bilirubin; *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *γGTP* gamma glutamyl transpeptidase, *LPE* laparoscopic PE, *OPE* open PE, *NS* not statistically significant

Discussion

Initially considered to be a feasible treatment for BA [20–26], LPE was actually abandoned as a viable treatment option because of poor results [2, 27]. It is not just OPE performed using laparoscopy; rather, LPE involves different stresses on the body due to PP that must be considered as additional to the impact of OPE. One would assume that PP would affect acid base balance and produce some degree of physiological stress on the body [3–6, 28–33], for example, delayed growth/development or compromised liver function which has not been documented specifically after LPE to the best of our knowledge. Thus, we are the first to investigate the effect of PE on growth/development and liver function to determine if there is any difference between LPE and OPE.

There was an interesting trend observed that LPE cases gained height/weight more consistently than OPE cases although the difference was not statistically significant, and overall, height and weight were actually within normal limits for both LPE and OPE. We observed deterioration in gross motor function following PE, but the most striking finding was that the pattern of delay was similar for LPE and OPE which would suggest that gross motor deficits detected in postoperative BA patients are not PE-related. Similarly, there were some receptive/expressive deficits in communication observed but they were transient and of the same pattern for both LPE and OPE, indicating that deficits in communication were also not PE-related. There were no deficits in fine motor function and social interaction observed. Thus, our data strongly suggest that deficits detected following PE would appear to have no specific relation to PP or other features of minimally invasive surgery.

Similarly, we are also the first to show conventional parameters of liver function such as ALT, AST, and γGTP after PE shows more deterioration in LPE than OPE, although differences were not significant indicating that PP appears to have no adverse effect on BA patients. Nevertheless, close follow-up of liver function is indicated because of the deterioration observed.

Ure et al. [2] suggested that potential adverse effects of PP during laparoscopy could be related to a temporary pressure-related compromisation of liver perfusion with subsequent liver cell damage, and did not recommend LPE in a prospective trial comparing LPE with OPE. However, while they used an insufflation pressure of 8 mmHg which is similar to ours, the flow of CO_2 they used for PP was 5 L/min which establishes PP quickly but at an unacceptably high flow rate. We believe that such an exceedingly

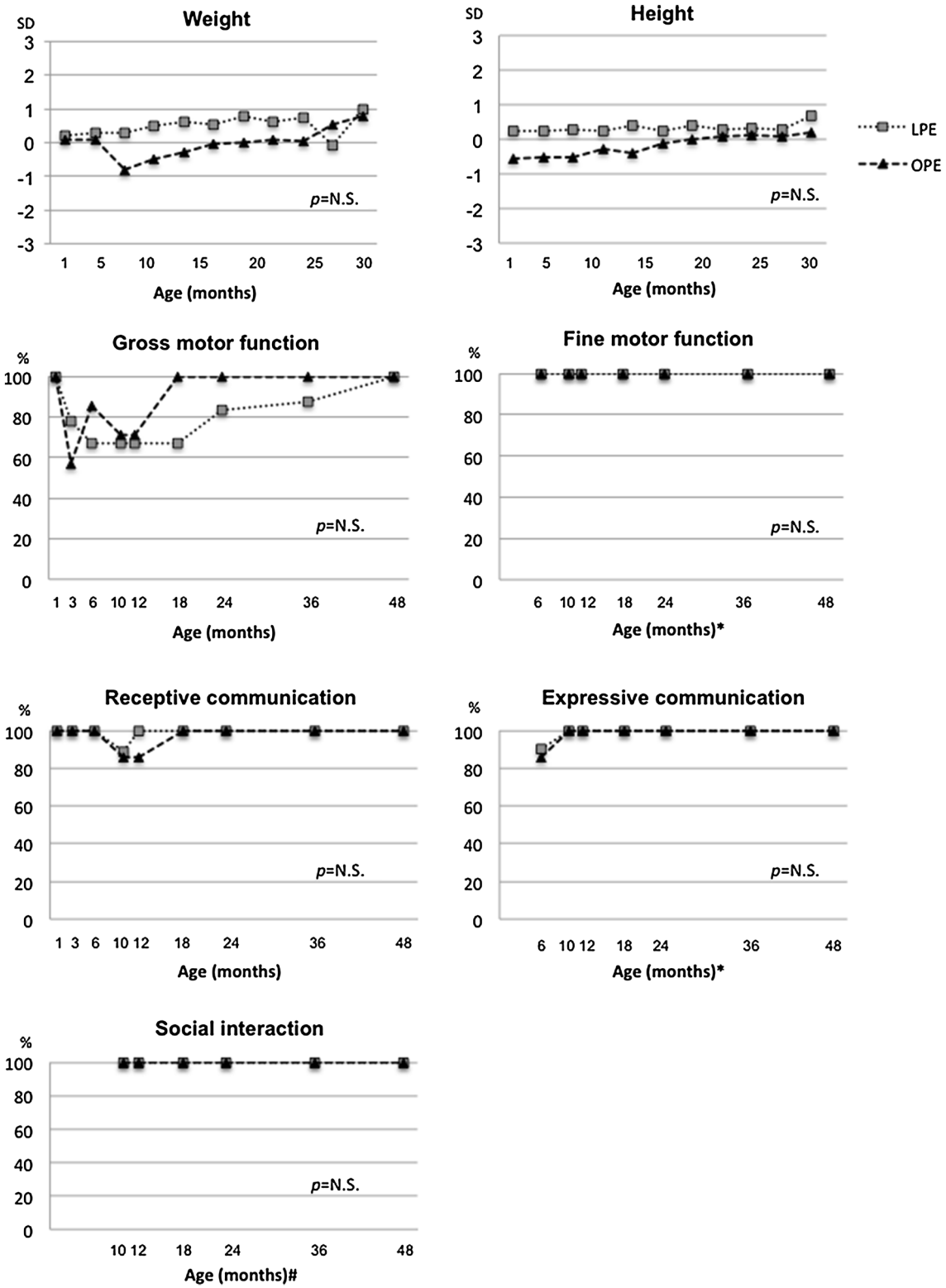

Fig. 2 Changes in growth and development in BA patients who had jaundice clearance (JC) after portoenterostomy (PE) Comparison of weight, height, gross motor function, *asterisk* fine motor function, receptive communication, *asterisk* expressive communication, *hash* social interaction *asterisk* assessed from 6 months of age *hash* assessed from 10 months of age. *LPE* laparoscopic PE, *OPE* open PE, *NS* not statistically significant

high flow rate is inappropriate for patients with compromised liver function.

Researchers have also used animal models to investigate the effects of insufflation. Sahin et al. [8] used a rat model to show that a stepwise increase in CO_2 insufflation reduced oxidative stress as reflected by malondialdehyde, the antioxidant, superoxide dismutase, and inflammatory cytokine (tumor necrosis factor-alpha, interleukin-6) levels. In our LPE, we initiate PP using a lower insufflation pressure at a flow rate of 0.5 L/min to distend the abdomen, and then maintain PP at an insufflation pressure of 8 mmHg at a low flow rate (0.5–1.0 L/min). Laje et al. [1] looked at the effects of PP on BA mice using either CO_2 or air for insufflation and found that BA livers did not respond well to PP, with no major difference related to the gas used for insufflation. In other words, the concept of exposing livers with advanced degeneration and fibrosis to prolonged, high-pressure PP might be more harmful than was generally appreciated [1]. However, their study involved comparing 18-day-old naive Balb/c mice and BA mice exposed to 60 min of continuous, uninterrupted air or CO_2 PP at an insufflation pressure of 8 mmHg and flow rate of 2.5 L/min, which are unacceptably severe conditions, especially for BA mice because they are only approximately 1/3 the size of naive Balb/c mice and the conventional settings for insufflation pressure and CO_2 flow infants and small children with BA are usually 8–10 mmHg and less than 1.5 L/min, respectively. We strongly feel the conditions they used for PP are inappropriate for assessing the response of the human body to laparoscopic surgery; in other words, their model mice cannot be used to represent the response of children with BA during LPE. Although they did not present data for $PaCO_2$ and serum pH, their levels would most probably have been much worse than those generally experienced during laparoscopic surgery in children because of the conditions of their study; thus, liver cell damage as they reported would be to be expected, especially in their BA mice.

One feature of our LPE that we believe improves outcome is minimizing the effects of lateral thermal energy on tissues. Most pediatric surgeons use monopolar hook diathermy to coagulate and divide vessels around the fibrotic biliary remnant in patients with BA during LPE. However, monopolar diathermy emits thermal energy laterally that could also damage any micro bile ductules that may still be present in the biliary remnant when used during LPE. Because of this, we use a Ligasure device (Valley Lab, Boulder, CO) for dividing vessels around the biliary remnant at the porta hepatis because there is less heat emitted laterally and less risk for injuring surrounding tissues [24].

Chan et al. [26] reported very recently that because their LPE cases had JC ratio (JCR) of 50 % and SNL of 50 % after follow-up of 4 years, they reintroduced OPE because their results for OPE were better; i.e., JCR and 2-year SNL for LPE were 50 and 50 %, respectively, but for OPE were 81 and 74 %, respectively [27]. In our series, JCR was 92.3 % and SNL was 76.9 % for LPE which were both better than OPE, but our duration of follow-up for both groups (mean follow-up was 38.8 months for LPE; and 38.1 months for OPE) was shorter than Chan KW's. Longer follow-up may change our results but we believe our LPE is a viable procedure for treating BA.

Based on our results, we conclude that LPE does not appear to be a detrimental procedure when performed according to the techniques described.

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