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CASE REPORT

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Thoracic epidural analgesia and immediate extubation for less than 10 kg infants undergoing living donor liver transplantation: A report of two successful cases

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Abstract

Background: Perioperative pain management in small infants weighing <10 kg undergoing liver transplantation is challenging. The use of TEA in this setting has not been reported, as well as its potential role to facilitate IE, ie, in the OR.

Methods: We describe here the use of TEA in two small infants who had IE after a LDLT procedure.

Results: TEA was successfully performed and IE was achieved in both cases. Postoperative analgesia assessment in the OR was satisfactory according to the FLACC pain scale, with scores of 2 and 3 for each patient, respectively. There were no major complications in the postoperative period, and the two children were discharged home uneventfully.

Conclusions: The use of TEA and its influence on IE rate and other perioperative outcomes should be more explored in small infants undergoing LDLT.

KEYWORDS
immediate extubation, pediatric liver transplantation, thoracic epidural

1 | INTRODUCTION

Anesthesia for small infants undergoing liver transplantation is challenging in many aspects. Accordingly, many anesthesiologists still routinely send these patients intubated to the pediatric intensive care unit (PICU).[1] Among the factors that possibly make IE—ie, in the OR—a less attractive option in this setting are: lack of cooperation in the early postoperative period due to emotional and cognitive particularities in this population; current severity of illness; graft-recipient size mismatch with the risk of graft failure; neurological status; hemodynamic instability; opioid-induced respiratory depression; preoperative pulmonary abnormalities; and the restrictive ventilatory pattern eventually associated with primary abdominal closure.

Additionally, pain assessment in infants is a difficult task and frequently overlooked,[2] which may also render physicians reluctant to IE. Although most practitioners still rely on intravenous opioids for postoperative pain control, regional and neuraxial techniques have been increasingly used for infants undergoing a variety of surgical

Abbreviations: ETT, Endotracheal tube; FLACC, Face, Legs, Activity, Cry, Consolability; GRWR, Graft-recipient weight relationship; IE, Immediate extubation; INR, International normalized ratio; LDLT, Living donor liver transplantation; LOS, Length of stay; OR, Operating room; PELD, Pediatric end-stage liver disease; PICU, Pediatric intensive care unit; PTT, Partial thromboplastin time; TEA, Thoracic epidural analgesia.

procedures.[3] TEA, for example, has been successfully employed in the setting of cardiothoracic or major abdominal surgery, providing excellent pain relief with improved outcomes.[4–7] Unfortunately, its use for infants undergoing a liver transplant seems to lag behind, probably because of concerns about epidural hematoma. This is clearly justifiable, as preoperative coagulation status is frequently abnormal due to the intrinsic liver disease.

However, there are a definite subset of pediatric liver recipients who may be potential candidates for TEA. Piazza et al[8] successfully described a continuous TEA technique in a 10-year-old child with cystic fibrosis undergoing a liver transplant. Our group described TEA in a 5-year-old child with biliary atresia, who underwent a LDLT.[9] Because of the unique characteristics of the liver diseases in those case reports, it is not uncommon to find a normal preoperative coagulation profile—as assessed by INR, PTT, and platelets count, thereby increasing the safety of epidural catheter placement.

Infants with biliary atresia weighing <10 kg undergoing liver transplantation might benefit from neuraxial regional analgesia as well. TEA for these small infants has not been reported in this setting and could be a valuable technique to support IE, not only by providing excellent analgesia but also by improving pulmonary function and possibly other perioperative outcomes. We report here two cases of small infants who underwent LDLT and successful IE, and discuss the potential beneficial role of TEA in this scenario.

2 | PATIENTS

2.1 | Case 1

A 7-month-old, 6.5 kg female infant with biliary atresia was scheduled to undergo a LDLT. An open cholecystectomy was previously performed, but no Kasai procedure had been attempted. Following this primary surgery, she was referred to our institution, with a PELD score of 11. Her father was chosen as the best living donor, and a left lateral sectionectomy was thus planned. Upon admission in the OR, basic monitors (ECG, SpO_2, and noninvasive blood pressure) were attached, and a modified rapid sequence induction with remifentanil, propofol, and rocuronium was performed through a previous running 22G cannula in the right foot. Endotracheal intubation was successfully performed with a 4.0 mm cuffed ETT. Afterwards, the infant was positioned on the left lateral decubitus. The thoracic epidural space (T7/T8) was identified at the first attempt by a paramedian approach, using an 18G pediatric Tuohy needle with the loss of resistance technique with normal saline (Figure 1). The epidural catheter was then carefully positioned though the needle with 4 cm inside the epidural space. A bolus of 3 ml solution which consisted of bupivacaine 0.25%, morphine 10 mcg/kg, and clonidine 2 mcg/kg was injected through the epidural catheter which was subsequently removed (single-shot technique). The child was repositioned supine, and arterial lines were initiated (left radial and right femoral). A 5.0 Fr triple lumen catheter was inserted in the right internal jugular vein, guided by ultrasound. Maintenance of anesthesia was performed with propofol (50–150 mcg/kg/min) and remifentanil (0.1–0.3 mcg/kg/min) infusions, guided by bispectral index monitoring. Neuromuscular blockade was maintained with rocuronium infusion (2–10 mcg/kg/min), in order to keep a deep level of neuromuscular blockade (post-tetanic count of 1 or 2). Hypothermia was prevented through air-forced underbody warming blankets. Norepinephrine infusion was used to keep the mean arterial pressure above 40 mmHg. Fluid regimen was dictated by trends in cardiac output and dynamic indices of fluid responsiveness, as assessed by transpulmonary thermodilution method (PiCCO® technology, PulsioFlex monitor, Getinge USA, Inc.). Intraoperative coagulopathy was monitored with rotational thromboelastometry (ROTEM®, TEM International GmbH), which guided plasma, cryoprecipitate and blood transfusions according to institutional algorithms. Heparin was not given during surgery. The total volume of crystalloid and colloid solutions was 465 ml (Plasma-Lyte®, Baxter Healthcare Corporation) and 15 ml (Albumin® 5%, CSL Bhering LLC), respectively, and a total of 140 ml (21 ml/kg) of packed red blood cells were transfused. Surgery was uneventful and lasted 340 min. The GRWR was 3.2%. Primary abdominal wall closure was achieved, and neuromuscular blockade was fully reversed with sugammadex. Weaning from ventilation was smooth, and the child was extubated still in the OR. No agitation was noticed, and the FLACC pain score at this time was 2 and remained so until PICU admission. Postoperative analgesia consisted of intravenous tramadol and dipyrone on a regular basis. The first opioid dose was administered 2 h after arrival in the PICU. The FLACC score remained zero over the first postoperative day (POD1). Tramadol was then tapered off and prescribed only as a rescue therapy at POD2. No opioid was needed subsequently along the entire postoperative period. The PICU LOS was 10 days and unremarkable. In the ward, she had mild lower respiratory tract viral infection treated with a short course of supplemental oxygen and continuous positive

FIGURE 1 Thoracic epidural catheterization at the level of T7/T8 using the loss of resistance to saline technique. The infant was intubated and positioned left side down

airway pressure. The patient was discharged home 34 days after the transplant with tacrolimus-based immunosuppression.

2.2 | Case 2

A 9-month-old female infant weighing 8 kg underwent a LDLT. She had biliary atresia with a previous Kasai portoenterostomy procedure, but eventually developed end-stage liver disease over the following 6 months. Her PELD score was 16. Like the previous case, her father was chosen as the best suitable donor, and a left lateral sectionectomy was planned as well. In the OR, as the child had no previous i.v. access, we performed a modified rapid sequence inhalational induction with sevoflurane. Soon after peripheral i.v. line was established, total intravenous anesthesia was initiated (the same dosage regimen as described in case 1). A 4.5 mm cuffed ETT was placed after neuromuscular blockade with rocuronium. The same technique described above was used for thoracic epidural catheter placement at the T7/T8 level. A bolus of 3 mL solution which consisted of bupivacaine 0.25%, morphine 10 mcg/kg, and clonidine 2 mcg/ml was administered through the epidural catheter—single-shot technique. Invasive lines, anesthesia maintenance, and coagulation monitoring were all similar to the previous case, as per institutional protocol. Heparin was not given during surgery. The procedure was uneventful and lasted 335 min. The GRWR was 3.1%. The total volume of crystalloid and colloid solutions was 600 ml (Plasma-Lyte®) and 40 ml (Albumin® 5%), respectively, and a total of 90 ml (11 ml/kg) of packed red blood cells were transfused. Primary abdominal closure was also performed, and neuromuscular blockade was fully reversed with sugammadex. Weaning from ventilation was successful, and the child was immediately extubated. The FLACC pain score evaluated in the OR was 3. Because of our initial experience with the previous case, postoperative analgesia was initially managed with intravenous dipyrone on a regular basis, and tramadol was prescribed as a rescue therapy only. The FLACC score remained zero, and no opioid was needed for the entire postoperative period. The PICU LOS was 12 days, and there was one single episode of catheter-related infection treated by intravenous antibiotics. She was discharged home 23 days after surgery with tacrolimus-based immunosuppression.

3 | DISCUSSION

We described two successful cases of TEA and IE for infants weighing <10 kg undergoing LDLT. The use of TEA for such small liver recipients has not been described so far, and its potential role as an adjuvant to support IE should be explored. Although IE in the setting of pediatric liver transplantation has increasingly been reported,[9–13] it is still not a standard practice in many institutions. Also, it is noteworthy that most of the case series did not focus on the IE rate of small infants, particularly in children <10 kg.

TABLE 1 Preoperative coagulation profiles of the two pediatric recipients

Variables	Patient 1	Patient 2
INR (s)	1.16	1
PTT (relation to control)	1.02	1.3
Fibrinogen (mg/dl)	368	392
Platelets (×1000/mm^3)	232	231
ROTEM-Extem		
CT (s) [38–79]	70	59
CFT (s) [34–159]	82	61
MCF (mm) [50–72]	68	72
ROTEM-Intem		
CT (s) [100–240]	233	217
CFT (s) [20–110]	34	40
MCF (mm) [50–72]	66	72
ROTEM-Fibtem		
MCF (mm) [9–25]	14	18

Note: Preoperative coagulation status of both patients was normal.
Abbreviations: CFT, clot formation time; CT, clotting time; INR, international normalized ratio; MCF, maximum clot firmness; number in brackets refer to the normal range; PTT, partial thromboplastin time; ROTEM-Extem, thromboelastometry parameters evaluating the extrinsic pathway; ROTEM-Fibtem, qualitative fibrinogen evaluation; ROTEM-Intem, thromboelastometry parameters evaluating the intrinsic pathway.

There has been a renewed interest on neuraxial techniques for infants undergoing major abdominal surgery.[6,7] This may be related to the increased awareness among pediatric anesthesiologists about the importance of providing optimal postoperative analgesia. Inadequate pain control in this population is associated with serious complications, including altered pain perception in the long term.[2] Unfortunately, neuraxial blocks have not been widely used for pediatric liver recipients, mainly because of concerns about epidural hematoma in this setting. We chose to use this technique because both of our patients did not have alterations on preoperative coagulation status, as revealed by a normal preoperative ROTEM and INR, PTT, fibrinogen, and platelets count (Table 1), and TEA was thus chosen as an attractive option for postoperative analgesia. Also, the anesthesiologist's expertise was undoubtedly a major factor that has been considered: the first author (RD), who performed the TEA in both cases has more than 20 years of experience in pediatric anesthesia, including neuraxis blocks for major abdominal surgeries.

In the current report, we used TEA for two infants weighing <10 kg using the landmark palpation technique. Although we did not use ultrasound, it may be of valuable help in finding the epidural space, since anatomical features at this age are more remarkable and easier to identify with ultrasound when compared to adults.[8,14] Visualization of epidural vessels would increase the safety of this procedure as well. Some clinicians use the caudal approach for positioning thoracic epidural catheters, particularly in children under 2 years old.[15] On one hand, this technique avoids the risk of spinal

cord injury from the needle. This may be relevant, since epidural catheterization is essentially performed in the anesthetized children, though this approach has not been shown to be associated with a greater risk of spinal cord damage.[16] On the other hand, it is more labor intensive as it requires additional equipment for neuroestimulation. Also, caudal catheters are associated with a greater risk of colonization when compared to lumbar or thoracic placement,[17] which may be an important factor to consider when a continuous infusion of local anesthetics has been planned.

We used a single-shot technique, instead of leaving the catheter *in situ* to provide extended postoperative pain control. This was mainly due to the unpredictable pattern of coagulation profile that follows a liver transplant, and the timing of catheter withdrawal could be potentially difficult to achieve. Most of the reports of epidural hematoma occur after catheter removal,[18] showing that this is a critical event in some vulnerable patients. However, epidural hematoma may go unnoticed intraoperatively after an initial bloody tap, as coagulopathy may develop during liver transplantation, even in patients with a normal preoperative coagulation profile.[19,20] Indeed, the best management of a bloody tap in this setting is currently unknown. Ideally, the larger the time lag between a bloody tap and the surgical incision the better, as long as it is feasible, since liver ischemia time is a major factor that has to be accounted for. According to recent guidelines, when a bloody tap happens right before a cardiac surgery with bypass, the surgical procedure should be postponed for at least 24 h.[21] This recommendation is based on the fact that the patient will be fully anticoagulated with heparin. However, this waiting time is clearly impractical for liver transplant cases. Surely, the risk of a bloody tap cannot be overlooked, reinforcing that the risk-benefit ratio of TEA must always be carefully considered before its use in this setting. Fortunately, in our patients, the epidural catheter placement was uneventful and no signficant coagulopathy, ie, significant bleeding in the surgical field, developed intraoperatively as assessed clinically and with thromboelastometry. In theory, the use of ultrasound could increase the safety of TEA in pediatric liver recipients, potentially reducing the incidence of traumatic bloody punctures. However, there is no study addressing this issue in this population. For all these reasons, we therefore believe that TEA should only be considered in very selected pediatric liver recipients and performed by a highly skilled anesthesiologist.

Another reason for using a sinlge-shot tecnique is that continuous infusion of local anesthetics over a period of 48 h increases the risk of local anesthetic systemic toxicity.[22] It has been shown that infants have a premature hepatic microsomal system, which may compromise the metabolism of amide local anesthetics.[23] Thus, a renewal interest on the use of a preservative-free 2-chloroprocaine infusion has been reported.[24] Initial experience with this drug has been shown an excellent safety profile in infants, and future studies may also prove it to be useful in the setting of pediatric liver transplantation.

Instead of a continuous infusion, we injected a mixture of bupivacaine, morphine, and clonidine through the epidural catheter. Total volume of solution was calculated as approximately 0.5 ml/kg. Hemodynamic parameters were virtually unaffected after the epidural bolus, probably because of the relatively low volume of local anesthetic. Clonidine and morphine were added because of their alfa-2 agonistic properties in the spinal cord receptors and prolonged neuraxial opioid analgesia, respectively. In addition, clonidine has sedation effects which might be useful for preventing emergence agitation and postoperative delirium. In fact, both children remained calm in the postoperative period, and no respiratory depression was noticed as well.

Thong et al[4] in a large retrospective series of children undergoing major abdominal procedures (but not transplants) have shown that TEA is safe and effective, with a very small number of complications. Indeed, many centers routinely perform TEA in this setting, reporting successful IE rate in up to 80% of children.[4,7] Similarly, IE after pediatric liver transplantation has been considered a primary goal by many anesthesiologists, and a satisfactory IE rate has been achieved in some specialized pediatric liver centers,[10–12,25,26] ranging from 40% to more than 70%. Ulukaya et al[13] were the first to report IE in this setting. In their retrospective series, 12 of 40 (30%) children had undergone IE, without any reintubation. Postoperative pain management was not described, however. Fullington et al[11] reported a historical cohort of pediatric liver recipients who underwent IE, with the ratio steadily increasing over the years (from 2005 to 2011) in their center, reaching up to 67% of patients. The authors used i.v. opioids for postoperative pain control, rather than neuraxial blockade. Interestingly, Alper et al[25] showed in their series that pediatric patients undergoing LDLT had more successful IE (74%) than those who received deceased donor liver grafts (49%). Since LDLT is essentially an elective procedure, it is possible that an enhanced and timely preoperative optimization of the pediatric recipient could have been a factor explaining this difference.

In recent years, early postoperative tracheal extubation following liver transplantation has been proposed as a quality indicator of care and as a fast-track strategy with the aim of reducing intensive care unit resource utilization and overall costs.[27] Reduction of postoperative ventilation time may result in decreases in intrapleural pressure, thereby improving venous return and liver graft blood flow. Importantly, PICU and total LOS have been reduced in patients who had IE,[10–13,25,26] reinforcing that this should be strongly considered for all pediatric recipients as long as they meet clinical criteria for IE. These are not well defined in the literature, but it is mostly based on clinical judgement and include: hemodynamic stability, good graft function, minimal or no vasopressor infusion, and preserved pulmonary gas exchange. Equally important are the risk factors for IE failure, as suggested by current evidence[10,12]: growth failure, length of surgery, large amount of i.v. fluids, volume of packed red blood cell and/or fresh frozen plasma transfused, and peak intraoperative serum lactate. Preoperative encephalopathy and high AST levels have also been associated with prolonged mechanical ventilation.[26] In a large retrospective database analysis of 108.392 children undergoing major abdominal surgery, Partain et al[28] showed that neonatal age, preoperative inotropic support, duration of operation >150 min and ASA >3 were major predictors of prolonged postoperative ventilation.

All those factors aforementioned should be taken into consideration when IE is planned in advance. In addition, anesthesiologists should keep in mind that a relatively large graft has the potential to markedly increase intra-abdominal pressure upon closure, thus making IE very unlikely. In a large series of children weighing <10 kg undergoing liver transplantation, Neto et al[29] reported that primary abdominal closure was not possible in only two children (1.6%). Both had GRWR greater than 4%. This value is usually considered a cut-off risk for developing the large for size syndrome. In our two cases, the GRWR was <4% (3.2% and 3.1%), and primary abdominal closure was easily achieved. Interestingly, in a meta-analysis of pediatric liver recipients receiving monosegmental grafts, Enne et al[30] have shown that a second closure was still necessary in up to 70% of patients, despite the reduced-sized grafts. These data suggest that the choice of surgical technique may have an influence on the IE rate.

The role of anesthetic technique—including postoperative analgesia—on the IE rate is far less clear, however. Most of the series cases in the literature does not focus on anesthetic management or postoperative analgesia. Drugs with no liver metabolism (remifentanil and cisatracurium) have been successfully used by some,[27] while others have used fentanyl and isoflurane with similar IE rates.[11] Postoperative analgesia was not emphasized on most of the case series, and it seems that many centers still rely on i.v. opioids for these children.

To the best of our knowledge, we are not aware of any report of TEA for small infants (<10 kg) undergoing LDLT. Usually considered as the gold standard of postoperative analgesia for major abdominal surgeries, TEA has a beneficial role on pulmonary function as well.[31] We believe that this might have been a factor helping us to extubate these two infants immediately. The FLACC pain score was 2 and 3, suggesting that immediate postoperative analgesia was satisfactory. Furthermore, the postoperative need for opioids was overall decreased and even absent in the second case we reported. Other potential benefits of TEA include better splanchnic perfusion and reduced dose of inhalational agents.[3,31] Although we used total intravenous anesthesia, this is relevant since most practitioners still rely on inhalational anesthesia, and there is evidence suggesting an association between this anesthetic technique—which seems to be dose dependent—and late neurocognitive impairment in pediatric patients.[7,32]

4 | CONCLUSION

In summary, we described two successful cases of TEA and IE in infants weighing <10 kg who underwent LDLT. It seems that TEA may be safe when performed by a skilled anesthesiologist and in highly selected pediatric liver recipients without coagulopathy, and it was likely helpful to achieve the goal of IE for our patients. This initial impression, however, must be ideally confirmed with randomized trials comparing TEA with other non-neuraxial technique, with end-points such as postoperative analgesia and IE rates in this very specific population. Although the widespread use of TEA in small infants undergoing LDLT cannot be recommended, it is our belief that this technique should be more explored for selected patients in this setting.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

GG idealized and performed the writing; RD was the head of the anesthesiology team taking care of both children and fully reviewed the case report. CSS, DC, FCC, AA, and ALP are all members of the anesthesia liver team and participated on the recipient and donors procedures as well. All of them read the manuscript and contributed to the final version. RF, KS, and DBN are transplant surgeons and fully participated in both procedures. The last author (ME) is the head of the liver transplantation unit and was the main surgeon in both pediatric transplants. All of them revised the final version of this manuscript.

DATA AVAILABILITY STATEMENT

All paper's data were retrieved from electronic medical records from both patients.

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