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Enhanced anaesthesia strategies for bladder exstrophy patients

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Background: Classic bladder exstrophy (CBE) is a significant congenital defect requiring extensive surgery and a lengthy recovery. There is a paucity of information based on formal studies validating best practices of anaesthesia care in bladder exstrophy patients. Enhanced recovery after surgery (ERAS) and prehabilitation are core principles that can improve surgical outcomes. The available literature suggests that more careful attention could be paid to presurgical optimisation. Perioperative care built on available ERAS and evidence-based practices may improve outcomes.

Methods: We present a summary and review of literature coupled with our experiences in a bladder exstrophy centre of excellence that focuses on the primary closure of CBE. We provide recommendations for ERAS and prehabilitation protocols. We review the potential implications of perioperative anaemia, blood transfusion, and the benefits of using antifibrinolytics intraoperatively. We discuss goal-directed fluid management and the importance of multimodal pain management.

Conclusion: Any team embarking on caring for a bladder exstrophy patient needs a comprehensive team within a bladder exstrophy regional centre of excellence, a multidisciplinary plan for perioperative care, and a multimodal approach to pain management. This perioperative plan should begin before surgery, and all team members should be informed about the evidence-based practices included in the pathway. Perioperative care should be planned, orchestrated, and executed to ensure optimal patient outcomes.

Keywords: bladder exstrophy, enhanced recovery after surgery, ERAS, prehabilitation, anaemia, tranexamic acid

Introduction

Classic bladder exstrophy (CBE) is a rare and complex birth defect with a spectrum of anatomic abnormalities ranging from epispadias alone to the bladder exstrophy-epispadias complex. The prevalence is reported to be approximately 3/100 000 live births.[1,2] CBE is a worldwide problem, with only a few specialised institutions prepared to manage these patients. Primary CBE closures involve pelvic osteotomies to repair the diastasis at the symphysis pubis and bladder and abdominal wall closures. Closure can be performed in the neonatal period; however, these procedures remain highly successful within the first nine months of life, and there is a trend toward repair beyond the neonatal age group.[3-5]

Intraoperative anaesthetic management for these patients includes combining general endotracheal and neuraxial anaesthesia. The cases are lengthy and require attention to providing states of anaesthesia, amnesia, fluid management, and temperature control. The patients are usually infants or young children who may require adjustments in anaesthetic care for age-related respiratory, fluid, or metabolic needs. In addition, preparations for surgery must also consider the patient's psychological and physical readiness for major surgery.

In this paper, we discuss the crucial role of anaesthetic care for the best intraoperative care outcomes and best practices in postoperative management for primary CBE closures (Table I). Recommendations for postoperative management of these patients can be found in the companion paper (in this edition of the journal) titled *Multimodal postoperative pain management including epidural analgesia for primary exstrophy repair*.

ERAS

Enhanced recovery after surgery (ERAS) is a concept of multimodal perioperative care designed to achieve early recovery for patients undergoing major surgery.[6] In this approach, the goal is to reduce the impact of the stress response on patients who are not candidates for minimally invasive surgical techniques.[7] There is limited literature on ERAS protocols in children compared with adults and much less on relevant ERAS protocols in children with bladder exstrophy.[8,9] The goals of enhanced recovery after anaesthesia protocols are to keep patients in an euvolemic state, provide multimodal analgesia, and expedite recovery while minimising readmission rates.[6,7,10]

Outcomes are often improved, as shown in a study comparing 30 historical with 10 ERAS exstrophy patients. The ERAS patients were immediately extubated, 90% began early refeeding, and the group had an overall decrease in length of stay by 1.5 days with no difference in readmission.[11] The primary interventions from the reporting institution, and others in the region, included limiting fasting time, minimising narcotic use, initiating early feeding, and reducing the use of oral antibiotics.[12] If available resources were limited, the critical interventions would start with limiting fasting time, a multimodal approach to analgesic care, and early refeeding. The intraoperative and postoperative antibiotic choice is surgeon-dependent, and the literature is variable.

Prehabilitation in children

Prehabilitation is the process of improving the functional capacity of each patient before major surgery. It is a personalised multimodal approach designed to improve a patient's resilience to anticipated stressors of surgery and anaesthesia. Prehabilitation has three main components: physical fitness, nutrition, and psychological preparation.[13,14] All three prehabilitation components may not apply

Table I: Key points regarding anaesthesia for primary bladder exstrophy closure

ERAS
• Multimodal perioperative care designed to achieve a reduced recovery time after surgery
• Limited data in bladder exstrophy surgery
• The overall goals are to maintain euvolemia, provide multimodal analgesia, expedite recovery, and minimise adverse events and readmissions
Prehabilitation in children
• Individualised approach to preparation for surgery, including physical fitness, nutrition, and psychological preparation
• Can be incorporated into ERAS protocols to assist with preoperative optimisation of the patient's condition
Preoperative anaemia and perioperative risk
• Preoperative anaemia increases perioperative morbidity and mortality
• Poor nutritional status may increase the need for transfusion
• Risk factors for transfusion in bladder exstrophy include pelvic osteotomy, neonatal age, delayed closure, larger pubic diastasis, and longer operating time
• Blood transfusions carry their own set of risks and attempts should be made to minimise their need
Fluid management
• The goal of fluid management is to maintain normal physiological fluid balance with normal tissue perfusion, electrolytes, metabolic, and acid-base balance
• Ensure adequate intravenous (IV) access for surgery with peripheral IVs, peripherally inserted central catheters (PICCs) or central lines
• Newborns or infants require blood glucose monitoring and 1–2.5% dextrose added to maintenance fluids with a background continuous infusion rate calculated based on the 4-2-1 rule, which may need alterations based on preoperative fasting even up to 10 ml/kg/hr
Antifibrinolytic therapy
• Antifibrinolytics stabilise fibrin at the site of tissue injury, promoting clot formation and reducing bleeding, which can reduce blood loss and the need for transfusion therapy
Multimodal pain management
• Multimodal analgesia can include neuraxial local anaesthetic infusions, opioids, alpha-2 agonists, benzodiazepines, and other adjuncts
• A combination of medical and physical immobilisation may be needed postoperatively for surgical site protection and to promote wound healing
• Postoperative airway management may affect the choice of analgesics if the patient requires sedation for maintaining intubation
Latex avoidance
• Bladder exstrophy patients are at increased risk for latex allergy, which increases with the number of surgical procedures, so latex should be strictly avoided in their care

to all children; however, it is worth considering which components could be applied. Most of the published studies have been in adults. Consequently, there is minimal literature on paediatric patients and none on exstrophy patients. Some concepts should be applied intuitively, and we can extrapolate information from studies like exercise, nutritional and anaemia studies summarised below. The impact of psychosocial preparation is likely to be an important prehabilitation step, mainly because of the known psychological impact in children with bladder exstrophy.[15] However, evidence for the best approaches in psychological prehabilitation in all surgical patients is insufficient to dictate the best approaches.[16]

One example, though not of patients with CBE, is in malnourished children with congenital heart disease who were randomised to either one or two weeks of presurgical nutritional prehabilitation. The two-week prehabilitation patients had a decreased length of stay in the intensive care unit (ICU) and a shorter duration of hospitalisation.[13] In another study, Noronha et al.[17] performed an electronic database search reviewing patients aged 0–18 years undergoing elective surgeries with a prehabilitation program; 2 219 articles were reviewed. The review demonstrated that exercise-based prehabilitation improves postoperative outcomes and reduces postoperative complications.

Based on the currently available literature, there does not appear to be a downside to integrating prehabilitation into paediatric ERAS protocols; however, there is no direct evidence. The extent of prehabilitation depends on the resources available, but some degree of prehabilitation is better than none. In bladder exstrophy patients, attempts should be made to correct preoperative anaemia, optimise nutritional intake, encourage aerobic exercise, stabilise comorbidities, and prepare patients and families psychologically. More prospective research will be required in the future to determine which measures have the most impact on patient outcomes. It would also be beneficial to explore the monetary impact of prehabilitation.

Infants should be assessed for the presence of other congenital anomalies. CBE is typically not associated with cardiopulmonary or central nervous system anomalies; however, cloacal exstrophy and the omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) complex are. The intricacy of perioperative management of the patient with OEIS complex is beyond the scope of this paper. All patients should have preoperative measurements of haemoglobin and renal function indices.

Preoperative anaemia and perioperative risk

A specific topic of prehabilitation that merits additional attention is preoperative anaemia. Several studies have demonstrated that preoperative anaemia is common and that there are increases in perioperative morbidity and mortality in anaemic patients.[18-20] The association between morbidity and mortality in anaemic paediatric surgical patients has also been shown and further described in neonatal surgical patients.[20-22] Meyer et al.[20] showed a 46.2% prevalence of anaemia in a low- to middle-income country paediatric cohort. In their study, postoperative complications increased 2-fold if preoperative anaemia was present and 3.6-fold if intraoperative transfusion occurred.[20] Other authors have proposed that nutritional status may contribute to intraoperative transfusion risk.[23] Poor nutritional status could result in iron-deficiency anaemia and tissue factors related to bleeding and perturbed clotting. Although studies have shown that preoperative anaemia is common and leads to perioperative risk, few have assessed the presence or impact of iron deficiency.[24]

We do know that there are risk factors leading to blood transfusion in patients having bladder exstrophy repair. Those risks include pelvic osteotomy, neonatal age, delayed closure, larger pubic diastasis, and longer operating time.[25] Clearly, blood transfusion should be avoided when possible because blood products are a limited resource and transfusion comes with potential complications, including transfusion reactions, infectious disease transfer, pulmonary complications, and fluid overload; however, transfusions should not be withheld in situations of haemorrhage or haemoglobin less than 5 g/dl.[26-29] Anaesthesiologists must balance decisions about intraoperative transfusion based on the rate of bleeding, haemoglobin measurement, anticipated ongoing blood loss, and patient haemodynamic response to anaemia and blood loss.

Given the known risks of blood product transfusion, preventing the need to transfuse is arguably a better approach. First, correcting preoperative anaemia due to iron deficiency is minimal risk and inexpensive. Second, intraoperative fluid management practices should prioritise the use of balanced salt solutions targeting maintenance requirements and insensible losses. Patients should be well hydrated the night before surgery to reduce or eliminate fluid deficits at the time of anaesthesia induction. Third, the use of antifibrinolytics can reduce intraoperative blood loss.

Fluid management

Goal-directed fluid management in children

Whereas goal-directed fluid therapy based on haemodynamic changes does reduce adverse perioperative outcomes in adult surgical procedures, evidence is lacking for surgery in children.[30] Contrarily, the impact of goal-directed fluid therapy on alleviating postoperative ileus following gastrointestinal procedures in adults lacks supporting evidence.[31] A major objective of intraoperative fluid management is to maintain normal physiological fluid balance, including normal tissue perfusion, electrolytes, metabolism, and acid-base balance.[32] Patients with bladder exstrophy often arrive at the operating theatre with dehydration from preoperative fasting, bowel clean-out, or insensible losses from the bladder exstrophy defect.

Anaesthetic volatile gases, intravenous anaesthetics, analgesics, and central neuraxial blocks can cause further vasodilation and decrease functional intravascular volume. Central line placement is frequently used for intraoperative monitoring and sustained IV access postoperatively. However, more commonly, PICCs are placed for adequate access that can be maintained after surgery. Extended dwell peripheral IV lines (also known as midlines), which are long IV catheters not placed into central veins, have been used at other institutions.[11]

Restoring the fluid balance before anaesthetic induction can be helpful to avoid intraoperative hypotension, especially for those children who had a bowel cleanse before surgery. Several authors have published studies examining the effects of fasting time on intraoperative hypotension. Although small and observational, these studies show more hypotension associated with longer fasting times.[33-35] Other factors, including the choice of anaesthetic, affect blood pressure. Young children and infants receiving combined general and regional anaesthesia experience less hypotension than those with general anaesthesia.[36,37] This evidence, though limited, provides additional support for the ERAS concepts of preoperative hydration and multimodal anaesthesia and analgesia.

Many first-stage exstrophy closure patients are newborns or infants and require meticulous fluid management. One way to achieve this is to run a continuous infusion based on the patient's fluid deficits and maintenance needs, which includes dextrose and balanced isotonic solutions mirroring extracellular fluid composition.[32] For infants under three months of age or patients that are small for age or with other metabolic disorders, adequate maintenance and monitoring of blood glucose levels are required to avoid hypoglycaemia, and 1–2.5% dextrose can be added to maintenance fluids.[32,38] The background continuous infusion rate can be calculated based on the 4-2-1 rule and may need to be increased based on preoperative fasting, even up to 10 ml/kg/hr.[32,39] Solutions with 5% dextrose or more have been found to induce hyperglycaemia, especially with the addition of physiological stress response to surgery.[38]

Intermittent intraoperative blood glucose measurements should be completed so adjustments can be made to maintain children in normoglycaemia, thus avoiding metabolic distress. Central line and PICC access facilitate ease of haemoglobin, electrolyte, blood gas, and blood glucose testing, but these may not be possible in low-resource settings. Another possibility to facilitate laboratory test monitoring during these prolonged surgeries in small children is to conduct point-of-care testing from the peripheral IV access or intermittent peripheral or capillary blood sampling.

Assessing fluid management adequacy

While goal-directed fluid therapy has not been widely studied in children, blood pressure monitoring is one indicator that can be used to measure the adequacy of fluid management. Another measure to assess the patient's fluid status is the urine output, which is unavailable to the anaesthesiologist due to the inherent nature of the bladder exstrophy defect. Normal intraoperative blood pressure range definitions, and therefore definitions of hypotension, have been undefined. Blood pressure measurements under anaesthesia are often lower than pressures compared to existing sepsis management and resuscitation guidelines.[37] However, in 2016, the Multicenter Perioperative Outcomes Group (MPOG) published blood pressure reference tables in children based on

Table II: Blood pressure reference tables for children

Weight (kg)	Female			Male		
	Mean non-invasive blood pressure (mmHg)			Mean non-invasive blood pressure (mmHg)		
	-2SD	0SD	+2SD	-2SD	0SD	+2SD
2	22	35	58	23	36	60
3	25	39	63	25	38	63
4	27	42	66	27	40	65
5	29	44	69	29	42	66
7	32	47	73	31	45	69
10	35	51	77	34	49	73
15	38	54	80	37	53	78
20	40	57	83	40	56	82
30	42	59	86	42	59	86
40	44	61	88	43	61	89
50	45	62	90	44	63	90
80	47	66	95	46	66	93
100	–	–	–	47	67	95

100 000 American Society of Anesthesiologists (ASA) 1 and 2 anaesthetic records.[40] An abbreviated version of the information can be found in Table II.[37]

Additionally, the effects of intraoperative hypotension in children are not well studied. The context of hypotension in relation to the outcomes of children is a variable that needs to be fully understood to know when low blood pressure should be treated. De Graaff recommends considering the individual patient's normal pre-anaesthesia blood pressure when determining acceptable blood pressure ranges during anaesthesia; however, obtaining accurate pre-induction blood pressure in young children can be challenging.[37]

Fundamentally, the extent to which intraoperative hypotension contributes to poor outcomes in children is unknown. Moreover, a comprehensive understanding of how hypotension affects patient outcomes requires the integration of multiple modalities, such as blood pressure plus cerebral oxygenation monitoring.[41] Since definitive data is unavailable, it is sensible to individualise treatments and know population-based norms.

Due to the long duration of CBE repairs and continued insensible losses, patients might require substantial amounts of fluid replacement during surgery. Consequently, anaesthetic and surgical considerations should be made for whether a patient is suitable for postoperative extubation. When deciding on the viability of postoperative extubation, consideration should also be made for the level of sedation required post-repair and whether spontaneous respirations can be maintained with the required sedation.[42]

Ensuring normothermia is another important concern for patients undergoing bladder exstrophy repair. Neonates and infants are particularly susceptible to hypothermia due to their limited thermoregulatory capabilities, increased surface area relative to body weight, and the prolonged surgical procedures associated with bladder exstrophy repairs.[43]

Antifibrinolytic therapy

The use of intraoperative antifibrinolytics is now a well-established practice. Antifibrinolytics stabilise fibrin at the site of tissue injury, promoting clot formation and reducing bleeding. Tranexamic acid (TXA) and ε-aminocaproic acid (EACA) specifically act by preventing plasminogen from binding to and breaking down fibrin (Figure 1).[44]

In addition to TXA and EACA, aprotinin has also been used to inhibit fibrin degradation and reduce bleeding. The use of antifibrinolytics has been studied extensively in adults, particularly for orthopaedic surgeries with high blood loss potential, as well as paediatric orthopaedic, cardiac, and craniofacial surgeries. Evidence shows significant benefits for reduced blood loss and reduced blood transfusion.[45] TXA and EACA have good safety profiles, while numerous complications have been reported with aprotinin, leading to its declining use.[45] There are known cases of seizures associated with the use of TXA; however, a baseline seizure disorder is not a contraindication to the use of TXA.

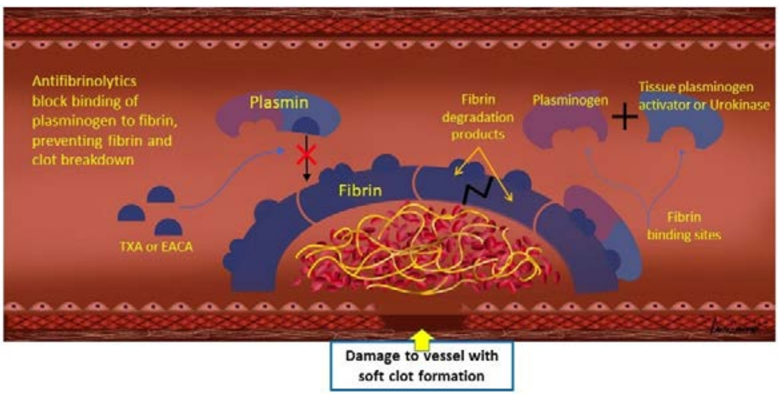

Figure 1: Depiction of the action of antifibrinolytics to prevent fibrin breakdown
TXA – tranexamic acid
EACA – ε-aminocaproic acid

Recommendations for TXA use were published by Patel et al.,[44] who report on its efficacy in children. This group noted a reduction of blood loss in the range of 25–50% and a reduction of perioperative adverse events in craniofacial surgery, and it is now included in the expert consensus guidelines in paediatric blood management protocols.[44] They further clarify that the seizure risk is related to high doses during cardiac surgery and report that there should be a dose adjustment in renal insufficiency.[44] Contraindications include hypersensitivity, active thromboembolic disease, and fibrinolytic conditions.[44]

Many different dosing regimens have been proposed for the use of TXA. In 2019, Goobie et al.[46] published their recommendations based on a combination of efficacy data and acceptable side effects. Although future research to study ideal TXA plasma concentrations is needed, they recommend a loading dose of 10–30 mg/kg followed by an infusion of 5–10 mg/kg/hr for the duration of the surgical procedure.[46]

Studies on the efficacy of EACA in children having spinal fusion or cranial vault surgeries suggest that it is effective in reducing operative blood loss. However, there are no studies on its use in bladder exstrophy repair surgeries. Furthermore, few studies compare TXA and EACA, and pharmacokinetic studies of EACA are lacking. Doses of EACA profiled in a craniofacial pharmacokinetic study by Stricker et al.[47] resulted in a 100 mg/kg bolus recommendation followed by an infusion of 40 mg/kg/hr. However, there is no evidence in bladder exstrophy patients. Many existing studies on the effectiveness of antifibrinolytics are small, single-centre studies. Prospective comparison studies are needed.[48]

Multimodal pain management

In patients undergoing CBE repair, a multimodal approach to pain management and postoperative sedation for postoperative immobilisation is essential to promote proper healing. Depending on the patient's age, the surgical approach, and the desired postoperative sedation regimen, the patient could remain intubated postoperatively for 1–3 days. The patient's airway management will impact the sedation regimen. Multimodal pain management not only includes the use of neuraxial local anaesthetic infusions but also opioids, alpha-2 agonists, and benzodiazepines, as well as other adjuncts.

Postoperatively, the goal is to provide medical and physical immobilisation techniques, including external fixator devices, casting, and traction. Additionally, acute postoperative pain and sedation treatments are needed to promote incisional wound healing and reduce emotional distress in the postoperative period. For more details on the multimodal pain management options available, please refer to Schwengel's complementary article in this journal edition.

Latex avoidance

Bladder exstrophy patients must be treated with latex avoidance. We have known for many years that complex urology patients, hydrocephalus patients, and patients with neural tube defects (with or without hydrocephalus) are at increased risk of latex allergy. Natural rubber latex sensitisation is related to the number of surgical exposures to latex. A study of the sensitisation of bladder exstrophy patients to natural rubber latex showed that environmental exposure to latex is foundational to developing latex allergy.[49] The number of surgical procedures and early surgeries are significant risk factors for latex allergy, resulting in the policy for strict avoidance of latex during all surgical procedures in bladder exstrophy patients.[50] It is known that the first evidence of allergic reaction to latex may be intraoperative anaphylaxis.[50]

Conclusion

We recommend optimising patients requiring primary bladder exstrophy repair following several principles. Care for bladder exstrophy should be provided by a well-prepared and comprehensive care team at a regional bladder exstrophy centre of excellence. Prehabilitation and a strict focus on ERAS protocols are foundational to the care of these patients. Anaemia should be corrected. Although blood transfusion might be required, attempts should be made to avoid or minimise transfusion with careful attention to fluid management, including preoperative hydration and the use of TXA to reduce blood loss related to pelvic osteotomies. Goal-directed fluid management should include maintaining organ perfusion, avoiding tissue oedema, and maintaining optimal glucose levels. Blood pressure management should be individualised to provide tissue oxygenation. This is based on blood pressure trends and values related to patient baseline numbers. Because intraoperative anaesthetic care also includes a transition plan to postoperative care, bladder exstrophy patients should have a multimodal pain management plan that includes neuraxial analgesia with a tunnelled epidural catheter (see Schwengel et al. *Multimodal postoperative pain management including epidural analgesia for primary exstrophy repair.*) Neuraxial anaesthesia may result in better blood pressure maintenance with the added benefit of decreased dependence on opioids. Reducing the use of opioids results in the improved function of many body systems, including respiratory and bowel functions. Additional important care considerations for bladder exstrophy patients include strict latex avoidance, age-appropriate support of body temperature, and glucose management.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This work is exempt from Institutional Review Board approval because it did not involve human subjects.

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