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REVIEW ARTICLE

Anesthesia for surgery related to craniosynostosis: a review. Part 2

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Summary

The management of children with craniosynostosis is multidisciplinary and has evolved significantly over the past five decades. The treatment is primarily surgical. The anesthetic challenges continue to be the management of massive blood transfusion and prolonged anesthesia in small children, often further complicated by syndrome-specific issues. This two-part review aims to provide an overview of the anesthetic considerations for these children. The first part described the syndromes associated with craniosynostosis, the provision of services in the UK, surgical techniques, preoperative issues and induction and maintenance of anesthesia. This second part will explore hemorrhage control, the use of blood products, metabolic disturbance and postoperative issues.

Bleeding and hemorrhage control

Blood loss and measurement

Massive blood loss during craniofacial surgery is one of the major challenges for anesthetists, with transfusion being unavoidable in the majority of cases. The successful management of potential major hemorrhage requires careful anticipation, knowledge of the surgical procedure and perioperative vigilance. The percentage blood volume lost increases with small children, by both young age (1) and weight (2). This is because of the relatively large head creating an increased surface area for blood loss and the fact that the head has a proportionally greater percentage blood volume.

Prolonged surgery (duration from the start of anesthesia to departure from theatre of more than 5 h) is associated with increased blood volume loss (BVL). This increased BVL can result in further donor exposure and transfusion of other blood products (3). The presence of a known craniofacial syndrome is not an independent risk factor for increased BVL; however, syndromic synostosis is often complex (Figure 1) and therefore prolonged surgery is required (2). While hypothermia is known to contribute to the development of coagulopathy (and therefore increased BVL) and is often present at some stage during craniofacial surgery, the early and active interventions to maintain normothermia mean that hypothermia is not found to be a causative factor in BVL (2).

There are surgical stages where sudden and extensive blood loss occurs. Knowledge of these stages enables the anesthetist to predict and prepare for hemorrhage. This occurs during initial scalp dissection and raising the periosteum. Significant hemorrhage can therefore occur relatively early on in the surgical procedure, and if attention is not paid to ensuring the maintenance of intravascular volume from this early stage, decompensation may occur. In addition to the key stages associated with acute blood loss, the capacity for gradual but significant blood loss exists throughout the whole surgical procedure and extends into the postoperative period. Communication between the surgeon and anesthetist is vital and a verbal warning as the key stages are approached ensures prompt management and close proximity of packed red blood cells.

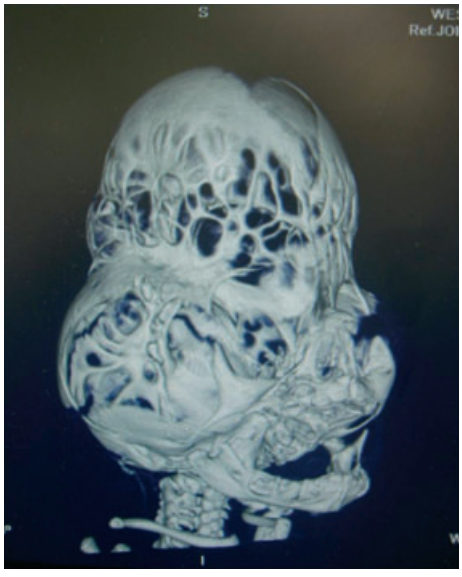

Figure 1 3D CT Scan of neonate with Pfeiffer syndrome demonstrating craniolacunae in a cloverleaf skull.

During the intraoperative period, direct assessment of BVL is difficult. The amount of blood collected in the suction is often minimal, with the majority of blood lost to surgical drapes and the surrounding area. Therefore, calculating BVL is often dependent upon assessing the required volume of fluid resuscitation and blood products transfused. Postoperatively, blood loss can be quantified more accurately by collection in the surgical drains.

Transfusion triggers vary in different centres and circumstances. During periods of rapid blood loss, hemodynamic parameters, such as arterial blood pressure and central venous pressure, are more likely to guide transfusion. During hemodynamic stability, absolute transfusion triggers may be employed, such as a hemoglobin level of 7–8 $g \cdot dl^{-1}$ or hematocrit (Hct) of 0.27–0.3. Another approach is an early transfusion strategy, where after the surgical stage of the coronal opening, a transfusion of 20% of the estimated red cell volume combined with a third of this volume of fresh frozen plasma (FFP) and a crystalloid infusion of 8 $ml \cdot kg^{-1} \cdot h^{-1}$ (4) is given. This pre-emptive approach has been criticized, as this may result in unnecessary or over-transfusion, exposing children to the risks of allogenic blood (5).

Albumin administration has been shown to increase the incidence of postoperative coagulation disturbance and the need for blood products (2).

During periods of hemodynamic instability, it is important to remain vigilant to other causes of significant intraoperative hypotension such as venous air embolism (VAE) and anaphylaxis.

Reducing homologous blood transfusion and cell salvage

Homologous blood transfusion (HBT) is associated with significant and well-known risks (SHOT) (6,7). These include acute hemolytic reactions, transfusion-related acute lung injury, infection, and the complications of massive transfusions, such as coagulopathy and electrolyte and acid–base disturbance. For these reasons, a number of strategies have been developed to decrease or eliminate the requirement for HBT (Table 1).

A preoperative low Hct is predictive of an increased requirement for HBT (8). The optimization of Hct preoperatively includes the diagnosis and treatment for pre-existing anemia, iron supplementation, and erythropoietin. Recombinant human erythropoietin (EPO) given subcutaneously weekly for 3–4 weeks prior to the surgery can markedly increase the preoperative Hct by 28–56% and decrease transfusion requirements (8,9).

Autologous transfusion is difficult to achieve for the majority of pediatric craniosynostosis patients because of their young age and insufficient blood volume and will not be discussed further.

During the intraoperative period, meticulous surgical technique, the pre-emptive infiltration of adrenaline-containing solution (with or without local anesthesia) and diathermy have contributed to reducing BVL.

Cell salvage

Interest in the use of cell salvage for craniofacial surgery has increased in recent years due to concern over the safety of homologous blood and the development of pediatric cell salvage reservoirs. Studies evaluating the use of cell salvage in pediatric craniofacial surgery have shown variable results. Some studies have

Table 1 Blood conservation strategies

Preoperative	Intraoperative
Iron supplement	Meticulous surgical technique
Erythropoietin	Adrenaline infiltration
(autologous blood donation)	Intraoperative cell salvage
	Acute normovolemic hemodilution
	Hypervolemic hemodilution
	Controlled hypotension
	Antifibrinolytics
	Transfusion strategy

suggested little benefit in terms of reducing homologous blood exposure owing to the necessity of transfusing homologous blood before autologous blood has been processed, or inadequate volumes are salvaged (10). However, in some cases, the use of cell salvage decreased the incidence and volume of homologous blood transfusion (11), in particular, those which used cell salvage in combination with other blood conservation techniques such as EPO (8,12). A decrease in the average donor exposure from two units of packed red cells to one unit after the introduction of cell salvage has been shown by Dahmani *et al.* and supported by Carver *et al.* (13,14).

Blood dilution techniques have been used in an effort to reduce allogenic blood transfusion. Acute normovolemic hemodilution involves removing whole blood from the patient and replacing this volume with crystalloid or colloid, thereby reducing the Hct of blood lost during surgery. The removed blood is then re-infused at the end of the surgery. A study by Hans *et al.* (15) showed no benefit in terms of reduction in allogenic blood transfusion using this technique. Hypervolemic hemodilution has also been used.

Controlled hypotension is a method employed in a range of surgical situations involving anesthesia to decrease blood loss; however, its role in craniosynostosis surgery is limited because of the concerns regarding cerebral perfusion pressure (16).

Coagulation

The majority of pediatric craniofacial patients have normal coagulation preoperatively (17). Accordingly, our institution does not routinely check coagulation profiles preoperatively, unless clinically indicated. The development of deranged coagulation occurs intraoperatively because of significant blood loss and resultant transfusion of packed red cells. The decline in the use of whole blood in recent years is likely to be a contributory factor in the development of coagulopathy in cases of massive transfusion.

Williams *et al.* (17) found that only five of 27 pediatric patients undergoing major craniofacial surgery lost >100 ml·kg^{-1} blood during the perioperative period. Those who lost >100 ml·kg^{-1} had a significantly prolonged prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time, thrombin time and thromboelastogram (TEG) reaction time (r time). Coagulation factor analysis did not reveal an isolated severe factor deficiency. Fibrinolysis was not associated with increased bleeding and platelet function as illustrated by the fact that the TEG maximum amplitude was within normal limits. Hence, Williams *et al.* postulate that the dilution of clotting factors is the cause of the abnormal clotting profile. This group required administration of blood products to correct the derangement. By contrast, the 22 patients losing <100 ml·kg^{-1} blood did not display abnormal coagulation results requiring correction with blood products. Blood loss in the postoperative period was approximately equal to the intraoperative loss for both groups. For the majority of patients, the normal coagulation tests at this point suggests that postoperative blood loss is not generally a result of deranged coagulation. This view is supported by Carver *et al.* who suggest that the potential for significant postoperative blood loss is a consequence of the large areas of exposed bone surfaces that ooze blood (14). However, three patients did develop clinically significant coagulopathies in the postoperative period, these were variable and of mixed origin.

Indications for the administration of haemostatic blood products depend upon the unit protocol. For example, PT or activated partial thromboplastin time (APTT) values $>1.5\times$ normal, fibrinogen <0.8–1 g·l^{-1}, platelet count <50–$80\,000$ μl^{-1} or clinical evidence of coagulopathy (2,14,17). When BVL approaches $1.5\times$ blood volumes, hemostatic blood products may be used empirically (such as FFP and platelets) in the absence of supporting laboratory results in an attempt to correct the anticipated dilutional coagulopathy. Despite median BVL being similar between different centres, the percentage of patients receiving FFP is markedly variable (2,17). In one centre, 78% of pediatric patients undergoing craniofacial surgery receive FFP. This centre advocates early use of FFP, adopting a 1 : 1 ratio for transfusion of packed red cells and FFP to avoid dilutional coagulopathy (2). A criticism of this practice is the potential for unnecessary administration and multiple donor exposures. However, in defence of this practice, Stricker *et al.* describe the use of FFP and packed cells from a single donor, so avoiding the risks of multiple donors.

The antifibrinolytic aprotinin had been used and shown to reduce transfusion requirements prior to the drug's withdrawal from clinical practice (18). Vitamin K, activated factor VII, desmopressin (DDAVP) and fibrinogen concentrates have also been used to enhance coagulation (9,19). Tranexamic acid is used in some centres around the world, although there is a significant variability in dosing regimens. Goobie *et al.* and Dandure *et al.* demonstrated significantly lower perioperative blood loss and mean blood transfusion with tranexamic acid (20,21). Both of these studies included around 40 patients, with various surgical conditions, ranging from simple to complex craniofacial

procedures. There has been debate in the literature regarding the exact mechanism by which tranexamic acid helps to reduce blood loss (22,23).

Metabolic disturbance

The metabolic disturbance that occurs during the perioperative period for pediatric craniofacial surgery in terms of acid–base and electrolyte derangement is primarily related to significant blood loss and resultant transfusion of crystalloid and colloid (including blood products).

The incidence of hypocalcaemia in one study of blood loss and blood replacement in children undergoing craniofacial surgery was 10% (hypocalcemia was defined as calcium < 0.9 mM). This is primarily caused by the transfusion of citrated blood. During the perioperative period, an increase in plasma potassium often occurs in patients in whom blood is transfused. The incidence of hyperkalemia (potassium > 5.5 mM) in one study was 45% (24). Packed cells stored for longer than 2 weeks contain > 40 mM potassium, in contrast to packed cells stored for < 1 week, which have < 20 mM. For this reason, in our unit, packed cells transfused during pediatric craniofacial surgery are < 1 week old.

In a recent study by Choi *et al.* looking at the degree and duration of perioperative metabolic disturbance during major craniofacial surgery in children, the median base excess (BE) was −9 (range, −3 to −20). The median time taken for the base deficit to normalize (defined as BE as > -6) was 9.25 h (range, 0–18) (25). Thirty-nine percent of patients had a BE of < -10 recorded. For the majority of patients, the maximum base deficit occurred at the end of surgery. There was a statistically significant relationship between maximum base deficit and total volume of blood and colloid given intraoperatively. Stricker *et al.* found that there was a statistically significant relationship between the volume of crystalloid administered and the development of intraoperative metabolic acidosis (pH < 7.3 and BE < -5) (2).

Choi *et al.* did not investigate the etiology of metabolic acidosis, but it is likely to be multifactorial. An interesting finding was that in 25% of patients, the initial base deficit, taken at the time of insertion of the arterial line, was < -4. This could be explained by ketoacidosis developing as a consequence of preoperative starvation.

Analgesia

There is a paucity of published data about analgesia for pediatric craniofacial surgery. Intraoperative analgesia is opiate based, such as high dose fentanyl or remifentanil, and morphine. For the postoperative period, the prescribed analgesia varies with different unit protocols. Regular paracetamol, increasingly via the intravenous route, and opiates are the primary agents used. In pediatric intensive care analgesia has been achieved using an infusion of remifentanil (26). A recent prospective audit of our postoperative analgesia regime revealed that the majority of patients were successfully managed on a morphine nurse controlled analgesia (NCA) regime with a background of 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and bolus doses of 20 $\mu g \cdot kg^{-1}$ with a 20-min lockout (unpublished data). We collected data from 26 patients over a 9-month period. The average number of morphine bolus doses in the initial 24 h postoperatively was 15. Pain scores were assessed using a behavioral scoring system. The modal pain score was zero in 92% of patients (i.e. no pain), and 29% patients had an episode(s) of pain that was classed as severe/excruciating. There were no complications associated with the use of morphine NCA in this patient group. The sedation scores of these children (0 – awake; 1 – asleep, responds to verbal/physical stimuli; 2 – asleep, poor response to verbal/physical stimuli; 3 – no response to verbal/physical stimuli) were recorded as modal scores of 0 for 46% and 1 for 50% of patients. A sedation score of 1 was the highest (worst) sedation score for 92% of patients.

Nausea and vomiting

There are no published data on the incidence of nausea and vomiting in pediatric craniofacial surgery. As part of the audit mentioned earlier, we looked at data for postoperative vomiting. Sixty percent of children had vomiting episodes within the first 24 h; 40% of those children who vomited did so only once. All children received perioperative dexamethasone, and ondansetron was administered to a subset. Of the children who vomited in the first 24 h, only 26% had received intraoperative ondansetron. Our audit found that 73% of vomiting episodes occurred in the first 8 h postoperatively, of which only 18% had received an intraoperative dose of ondansetron. Although not statistically significant, this was clinically significant and so produced a change in the management of these patients. The episodes of vomiting did not appear to be related to the timing of bolus doses of morphine. The implications of vomiting in children undergoing craniofacial surgery, apart from the general issues of delayed recovery and dehydration, relate to the increase in intracranial pressure that occurs during vomiting. This elevation in intracranial pressure could result in a cerebrospinal fluid leak, and possibly fistula

formation. Ondansetron is effective at reducing the incidence of postoperative vomiting in children undergoing craniofacial surgery (27). In our unit, dexamethasone is started in the preoperative period as part of the surgical plan to minimize/delay edema and is continued into the postoperative period. Dexamethasone has a proven antiemetic effect in children, and in conjunction with ondansetron is recommended for the prevention of nausea and vomiting in at-risk groups (28).

Postoperative management

The majority of patients are extubated either at the end of surgery or in the immediate postoperative period. Perioperative factors that make the requirement for continued intubation and mechanical ventilation in the postoperative period more likely are prolonged anesthesia and surgery, increased volume of crystalloids and packed red cells (29). Patient factors include preoperative respiratory compromise and obstructive sleep apnea. The majority of patients will be cared for in a pediatric high dependency or pediatric intensive care unit, depending upon patient factors and individual unit protocols.

A postoperative protocol detailing the management of pediatric craniofacial patients is utilized in some centres (e.g. management of drain losses, intravenous fluid therapy, and transfusion triggers). Drain losses are closely monitored and blood gas measurements are performed to help guide therapy. Urine output helps to guide fluid management. The analgesic regime for the initial 24 h is likely to include intravenous opiates, and this will be discontinued generally within the first 24 h and an oral analgesic regime introduced. Debate still exists around the association between nonsteroidal anti-inflammatory drugs and bleeding. Some centres choose to commence these 24 h after surgery.

During the initial postoperative period, close attention to serum biochemistry and hematology is imperative. Of particular importance is the risk of hyponatremia; this is present after any major pediatric surgery, but may be increased after craniofacial surgery. The cause of hyponatremia is likely to be related to anti-diuretic syndrome secretion or administration of hypotonic intravenous fluids. The risks of hyponatremia include cerebral edema, seizures and death. An avoidance of low sodium containing intravenous fluids is used both intraoperatively and postoperatively. In spite of this, a degree of hyponatremia frequently develops (30).

Cadis *et al.* found a 30.6% incidence of postoperative hyponatremia occurring after cranial vault remodeling. Factors associated with an increased risk of development of hyponatremia include syndromic craniosynostosis, greater BVL and raised intracranial pressure preoperatively. Hyponatremia was not related to postoperative complications but was related to prolonged ICU stay (31).

Conclusion

Providing anesthesia for children undergoing craniofacial surgery is challenging. A comprehensive multidisciplinary approach is vital to ensuring good outcomes. Careful preoperative planning is essential, with a particular focus on airway management and management of blood loss. Close liaison with the hematology department is essential to ensure the successful management of hemorrhage, including the availability of blood and blood products and the existence of protocols for cross-matching blood and blood products. The complex nature of the management of pediatric craniofacial synostosis has led to a centralized service for the provision of care for these children in the UK. With much of the recently published data available focusing on issues surrounding bleeding and the associated management, we have highlighted a paucity of data about other areas such as acute pain management and postoperative nausea and vomiting. Regular review and audit of perioperative outcomes are key to ensuring best practice in anesthesia for craniofacial surgery at local, national, and international levels.

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Conflicts of interest

No conflicts of interest declared.

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