Possible Methods to Decrease Blood Loss in Surgical Management of Craniosynostosis

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Abstract

Craniosynostosis represents a relatively common disorder, with an estimated prevalence of one in 2000 births. The cranial deformity is due to the premature fusion of the cranial sutures. The rapid growth of the brain during the first years of life results in compensatory skull deformation, which can lead to intracranial hypertension and subsequent neurobehavioral impairments. Primary operative repair during the first year of life is generally recommended, and most of these procedures are performed in children under 6 months when circulating blood volume is low. Therefore, relatively small blood losses can have a significant impact on hemodynamics and coagulation. The surgical correction of craniofacial malformations will often require blood transfusion during or after surgery. Due to legal and socioeconomic factors and ethical and religious practices, several strategies have has been proposed to reduce or avoid transfusions. Surgical correction of craniosynostosis can involve significant blood loss. Rates of allogenic blood transfusion have been reported to approach 100%. Multiple interventions have been described to reduce blood loss and transfusion requirements. Blood conservation methods Just as in adults, have been used in children to reduce allogeneic transfusion. The most extensively used surgical procedures have been cardiac surgery, liver transplant, scoliosis, and craniosynostosis. Many centers have adopted multiple methods to preoperatively optimize blood volume, decrease intraoperative blood loss, and modifying the transfusion thresholds via intraoperative or postoperative protocols.

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Introduction:

Blood conservation methods Just as in adults, have been used in children to reduce allogeneic transfusion. The most extensively used surgical procedures have been cardiac surgery, liver transplant, scoliosis, and craniosynostosis.

Many centers have adopted multiple methods to preoperatively optimize blood volume, decrease intraoperative blood loss, and modifying the transfusion thresholds via intraoperative or postoperative protocols. **(1)**

1. **Erythropoietin and iron**

During fetal development, Erythropoietin Epo is produced mainly in the liver. However, following birth, the kidney accounts for ~80% of Epo production **(2)**

The hemoglobin concentration decreases over the first 2 to 3 months of life, a condition known as physiological anemia, remains stable over the next several weeks, then slowly rises in the fourth to sixth month of life in response to increased Epo concentrations. Anaemia is a known predictor of higher transfusion needs and in-hospital mortality in paediatric surgery patients ; thus, strategies to improve pre-operative haemoglobin may significantly improve the patient outcome and reduce transfusion requirements **(3).**

Iron deficiency anemia is the most common cause of anemia in both economically developed and underdeveloped countries. Iron supplementation is an effective therapeutic agent to treat iron deficiency (anemia) and to reduce RBC transfusion need. The most effective increments of Hb levels (Hb of 1.9 and 3.9 g/dL) were detected between 2 and 4 weeks after administration. **(4)**

Oral iron can quickly improve pre-operative haemoglobin levels, but the correction may not be rapid . Parental iron supplementation provides a safe and efficient option for rapid correction of anaemia and preventing transfusions in adults, but data on paediatric use is limited. Iron is stored in the body in the form of Ferritin which is influenced by inflammation . Thus, some patients may have a "functional" iron deficiency in which total body stores may be normal or elevated, but iron is not accessible to the developing erythrocytes, a condition called Iron-Restricted Erythropoiesis. Hypoxia induces an increase in Epo hormone production in the kidney, which then circulates in the plasma and binds to receptors abundantly expressed on erythroid progenitor cells, thereby promoting the viability, proliferation, and terminal differentiation of erythroid precursors, and causing an increase in red blood cell mass. The oxygen-carrying capacity of the blood is thereby enhanced, increasing tissue oxygen tension, thus completing the feedback loop and suppressing further expression of Epo. **(5).**

Epo circulates in plasma with a plasma half-life of ~7–8 h and binds to high-affinity (~100 pM) receptors present in relatively small numbers (~1000/cell) on the surface of erythroid progenitor cells in the bone marrow. In man, Epo's hematopoietic role appears to be restricted to the erythron, whereas in rodents, Epo stimulates megakaryocyte proliferation and maturation as well.In a variety of clinical settings, anemia can be caused by underproduction of Epo as in renal failure, chronic inflammation, AIDs and cancer, whereas erythrocytosis can result from overproduction as in chronic obstructive pulmonary disease, renal tumors, hepatic tumors and cerebellar hemangioblastomas. Within a few days after initiation (of rhEpo therapy, the hematocrit approachs normal, necessitating a reduction in dose. The marked increase in red cell mass following treatment is accompanied by enhanced utilization of iron stores, as reflected in a decline in serum iron and serum ferritin. Other patients who have normal or low iron stores before rhEpo therapy need concomitant administration of iron to achieve an optimal erythropoietic response **(6)**

Paediatric patients undergoing elective surgery with a risk of substantial blood loss should have their full blood count and iron stores assessed preoperatively. Where preoperative anaemia is identified, it is important to determine its aetiology, so that appropriate therapy can be given, scheduling of surgery can be coordinated with optimisation of the patient's Hb and iron stores. It is now recommended to screen for anaemia in children with a high risk of bleeding (at least 3– 4 weeks prior to surgery, if possible), consider the use of iron supplementation or EPO to manage anaemia especially if ferritin is <50 and minimize the frequency and volume of sampling to reduce the iatrogenic loss. If anemia is still present despite high ferritin levels >50, it is unlikely to be iron deficiency anemia , consider other causes like thalassaemia, other

haemoglobinopathies, anaemia of chronic disease, haemolytic anaemia, B12 deficiency, folate deficiency or others **(1)**

By far the most common use of recombinant human erythropoietin rhEpo has been in patients with chronic renal failure. **(7)**

Adverse events associated with EPO use include hypertension, thrombosis electrolyte anomalies, hypersensitivity or perioperative mortality, but these effects are typically associated with use over longer time periods and in older patients. It is likely that the prothrombotic effects of rhEpo dose are due to the high doses given rather than to the increase in hemoglobin level. The Effects of Preoperative Administration of Erythropoietin in Pediatric Patients Undergoing Cranial Vault Remodeling for Craniosynostosis

Although usually well tolerated, erythropoietin should be used with careful monitoring in patients with hypertension. **(7)**. rHuEpo Resistance may be due to contamination of water supply by Aluminum or chloramine . It happens also due to inadequate protein intake or deficiency of micronutrients such as B12. If iron saturation is <25% and ferritin <1,200 ng/mL, it is reasonable to try intravenous iron to mitigate rHuEpo resistance. **(8)**.

Erythropoietin is available in a lyophilized (freeze-dried form for reconstitution) or in a dilute albumin solution. Doses of 150 to 300 u/kg has been used in open heart surgery. Shimpo, H. recombinant erythropoietin dosages of 1000 and 2500 U/kg achieved neuroprotective serum levels in very low birth weight **(9)**.

Elevated epoetin blood levels after sc injection are much lower than after iv infusion of equivalent doses but more prolonged, and lower doses are required to achieve the same hemoglobin response when administered sc rather than iv. **(10)**.

The use of ESAs may reduce transfusion incidence; however, the studies are underpowered to determine their effect on mortality and thromboembolic events, which are increased in the adult population.a

2. Autologous blood donation

Autologous blood transfusion can avoid serious adverse effects caused by homologous blood transfusion eg hemolytic reactions, transmission of infections, metabolic disturbances, coagulation disorders, immune suppression, alleviate blood shortages and save blood resources. **(11)**.

Autologous blood transfusion includes 3 steps: preoperative autologous blood donation, acute normovolemic hemodilution, and intraoperative or postoperative retransfusion. The units are stored in citrate solution and, at room temperature, can be held for up to 8 h. Units are transfused back to the patient in the reverse order of collection, thus using the more diluted units first, while continued surgical bleeding is expected, and saving the units with the highest hematocrit for last. Since blood lost during the surgical procedure has a lower hematocrit from hemodilution, the net RBC mass loss is reduced **(11)**.

Autologous blood donation before surgery has the following advantages: it stimulates bone marrow cell proliferation, stimulates erythrocyte regeneration.,reduces the concentration of erythrocytes in blood circulation during surgery. In turn, this reduces erythrocyte loss during surgery due to blood dilution with crystalloid or colloidal solution. It provides fresh blood of identical type. Furthermore, autologous blood has low acid content, relatively higher 2,3-diphosphoglycerate levels, and provides better cell vitality by preventing hyperkalemia . **(12)**.

Autologous donation should not be attempted in children with significant cardiac ischemic disease (e.g., hypertrophic cardiomyopathy) or those with an active infection because bacteria can seed the collected unit and overgrow during storage. The amount of blood collected should not exceed 10% of the patient's total blood volume **(13)**.

There have been concerns using this method, however, in very young patients because of poor tolerance of infant myocardium to anemia and an inability to increase stroke volume. Also, because of increased levels of hemoglobin F, there is reduced ability to offload oxygen. Transfusion-Free Cranial Vault Remodeling: A Novel, Multifaceted Approach **(13).**

ANH is optimally reserved for patients with expected blood loss of greater than 1500 m .The patient should have high hemoglobin level before donation at least 11 gm/dl and hematocrit at least 33.It must be remembered that infants may struggle to compensate for this sudden degree of acute blood loss. Of note, concerns over increased bleeding tendency due to lower hematocrit caused by ANH have yet to be resolved. Autologous donation is not widely used in pediatrics as it still lacks evidence on safety and efficacy. **(14)**

3-Hypervolemic hemodilution

involves simply administering colloids or crystalloids to the patient to dilute hematocrit to a predetermined level. Using a mathematical model to compare hypervolemic to normovolemic dilution,. found that for blood loss less than 40 percent total blood volume, there was minimal difference in postoperative hematocrit. **(15)**

With less potential risks and equivocal outcomes, hypervolemic hemodilution appears to be the safer choice.Transfusion-Free Cranial Vault Remodeling: A Novel, Multifaceted Approach **(15)**

3- Avoidance of hypothermia

Prevention of hypothermia in patients undergoing surgery is an important part of good perioperative care. Anaesthesia alters thermoregulatory mechanisms, which can lead to hypothermia if active warming techniques are not used. Even mild hypothermia can cause adverse effects in adult surgical patients, including substantial increases in adverse cardiac outcomes, surgical blood loss, allogeneic transfusion and surgical site infections. Up to 20% of adult surgical patients experience unintended perioperative hypothermia, defined as a core temperature below 36°C. Paediatric patients are more vulnerable to perioperative hypothermia because they have a reduced weight-to-surface-area ratio, lower stores of subcutaneous fat and greater loss of heat from the head compared with adults; hence, they require a vigilant proactive approach to maintenance of normothermia. **(1)**

forced air warmers or warm blankets and intravenous fluid warmers can be used based. and indwelling urinary catheter is one of the measures to monitor the intraoperative temperature **(15)**

3. Intraoperative blood salvage

Recovery of blood from an operative site and reinfusion after some form of processing has been applied to major vascular, cardiac, and multiple trauma situations for many years. Waters, J. H. (2005).Evidence has shown that it decreases the need of allogenic blood transfusion in the first 48 hours postoperative **(1)**

The common techniques used wash the recovered blood in a centrifuge so the product consists of the child's RBCs suspended in saline at a hematocrit of 50% to 60%. Cellular debris, excess citrate or heparin, free hemoglobin, activated clotting factors, and clotted blood are almost completely removed **(16)**

Intraoperative blood recovery is not widely used in infants and children. **(16)** The technique is limited by the minimum cell volume required for adequate washing and preparation The equipment is designed for adults, although some manufacturers have adapted standard devices for pediatric use . but, still not so widely avaialable . **(14)**, this technique can be expensive, and some have cited that it is inefficient in infants and

small children. Enhanced Recovery Protocol after Fronto-orbital Advancement Reduces Transfusions, Narcotic Usage, and Length of Stay

Indications include any major surgical procedure in which the use of more than 2 units of banked PBCs is likely or in which massive blood loss is occurring; children with rare blood types; and multiple trauma with massive hemorrhage. Collection of blood for potential cell salvage should be considered for surgical procedures where blood loss may exceed 500 ml (or > 10% of calculated total blood volume) in adult patients, or > 8 $ml.kg^{-1}$ (> 10% of calculated total blood volume) in children weighing > 10 kg. **(14)**

Major contraindications to blood-recovery devices include contamination of the operative field by bacteria (e.g., bo3wel trauma, abscess), cancer, and sickle cell disease (e.g., sickling in the device). Recovered blood should not be processed for reinfusion if the surgical field contains topical clotting agents, some topical antibiotics (e.g., polymyxin, neomycin), or other foreign materials (e.g., methyl methacrylate). Surgery for a malignancy is considered to be a relative contraindication because of the theoretical concern that malignant cells may be recovered and reinfused; this can be avoided by discarding blood recovered from the operative field while the tumor is being manipulated. **(1)**
Intraoperative autologous RBC recovery is also effective to reduce the number of patients exposed to allogeneic RBCs by 39% as demonstrated by a recent meta-analysis **(16)**

4. **controlled hypotension**

Controlled hypotension has long been used to reduce intraoperative blood loss or to provide a relatively bloodless operating field **(17)**
Controlled hypotension is reserved for older children and teenagers undergoing major reconstructive (e.g., craniofacial surgery) or orthopedic surgery. The choice of technique and the degree of induced hypotension depend on the surgical procedure. **(17)**
It is suggested that permissive hypotension be allowed while hemorrhage control is ongoing. One exception is in the case of patients with traumatic brain injury, as low blood pressure along with hypoxia can further the damage of injured neuronal tissue. Currently, the maximum time to safely allow permissive hypotension is not known. Even during hypotensive anesthesia, the kidneys should produce 0.5 to 1.0 mL/kg of urine per hour. Make the operative field the highest point of the child's body to take advantage of gravitational forces to help reduce blood pressure and minimize any possible impedance to venous drainage that may contribute to blood loss. **(18)**
Hypotensive anesthesia may be accomplished with many techniques, including continuous infusion of vasodilators, β-adrenergic blockade, deep inhalational anesthesia, and large-dose opioid infusions (e.g., remifentanil). **(18)**

Deep inhalational anesthesia depresses myocardial function and requires time to wash out a rapid offset is difficult to achieve Steffey, **(18)**
If β-blockade is to be used safely, the clinician must understand the differences in half-lives. Esmolol is very short acting, with a half-life in children of approximately 3 minutes. Labetalol and propranolol have longer half-lives, greater time to peak effect, and the effects are less controllable and not recommended. However, β-adrenergic blockade removes a valuable guide to the depth of anesthesia and volume status. Because the cardiac output in children approximately 2 years old or younger depends on heart rate, β-adrenergic blockade is not recommended in this age group. Low-dose, short-acting β-adrenergic blockade may be a reasonable adjunct to hypotensive anesthesia with inhalational anesthetics as a means of reducing the concentration of the anesthetic or as a supplement to reduce the vasodilator requirements Barak, M Sodium nitroprusside has a very rapid onset of action (seconds), brief duration of action (minutes), and minimal

side effects when used in the recommended dose range. Several pediatric anesthetic-related deaths have resulted from cyanide toxicity and its treatment. Cyanide toxicity is characterized by an unexplained metabolic acidosis, increased blood lactate and an increased mixed venous oxygen content. **(19)**

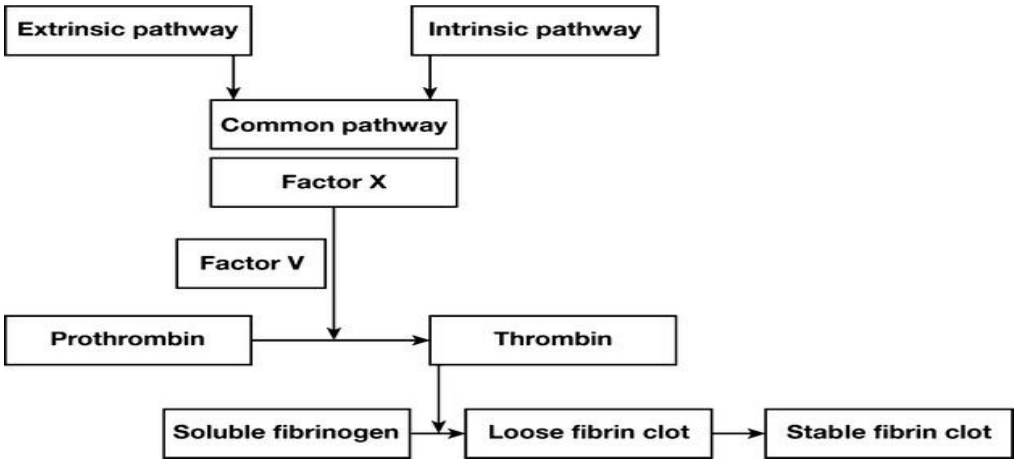
The main advantages of nitroglycerin are its relatively rapid onset of action (minutes), lack of tachyphylaxis and toxicity, and brief duration of action (minutes); the major disadvantage is the limited achievable reduction in blood pressure. Remifentanil-induced hypotension is increasing in popularity because of its relative safety, ease of administration, and titratability. Combination of a low-dose inhalational agent, low-dose propofol, and a remifentanil infusion provides excellent operating conditions **(17)**

The risks of hypotensive anesthesia are significant. The risk/benefit ratio must always be considered on an individual basis, particularly with neurosurgical patients and those undergoing spinal instrumentation; any systemic disease compromising the function of a major organ is a relative contraindication. Most reported complications are related to inexperience of the practitioner, inappropriate patient selection, unfamiliarity with the drugs involved, or inattention to details such as blood volume status, pH, Pa co_2 , blood glucose, or not using infusion pumps to carefully titrate medications. If a child is healthy and meticulous attention is paid to all the physiologic variables, the benefits of improved surgical technique, reduced surgical time, and decreased need for blood transfusion may outweigh the potential risk Barak, **(19)**

5. Topical hemostats

Hemostasis is the first stage of wound healing. Upon vessel damage, platelets adhere to the damaged site and aggregate through interactions of platelet receptors with extracellular ligands and soluble proteins. Vascular damage-induced exposure of subendothelial tissue factor generates trace amounts of thrombin with multiple effects on other coagulation factors and platelets. Via multiple enforcement loops in the coagulation system and in platelet activation, large amounts of fibrin are formed stabilizing earlier formed platelet thrombi. **(20)**

Each clotting factor consists of a proenzyme that is converted to an active enzyme by the upstream activated clotting factor . Two different cascades exist that converge in Factor X activation. These are named the intrinsic pathway, so called because all the components are present in the blood, and the extrinsic pathway requiring an external factor from the extravascular tissue. The intrinsic pathway becomes activated in vitro once blood comes into contact with hydrophilic surfaces. **(21)**



Simplified rendition of the coagulation cascade, indicating the critical position of factor V. **(20)**

The utilization of adjuncts to facilitate hemostasis was first recorded in 1886 in the form of beeswax and petroleum jelly. In the 1940s, oxidized cellulose and gelatin changed the landscape of mechanical hemostats

until the introduction of microfibrillar collagen (MFC) in 1970.Commercially available products have since expanded to include topical hemostats, surgical sealants, and adhesives. **(21)**

Resorbable hemostatic agents are routinely used in the management of intraoperative bleeding. The ideal product balances efficacy, with safety practicality and cost-effectiveness. The characteristics of an ideal hemostatic agent are as follows: (1) easily accessible, (2) conforms to a variety of wounds, (3) efficient and effective hemostasis, (4) limited adverse adverse effect profile, (5) self-activating, and (6) removable. **(21)**

Hemostats are broadly separated into five main categories: topical, chemical, physiologic, dressings and synthetic adhesives.

Topical hemostats can be divided into four groups based on functionality:

Mechanical or	Physical such as bone wax and ostene
	Porcine gelatin in the form of powder or sponge
	oxidized regenerated cellulose ORC surgicell
	Bovine collagen
	Microporous Polysaccharide spheres
Active	Bovine Thrombin
	Human pooled plasma thrombin
	Recombinant human thrombin
Flowable	Bovine gelatin
	Human pooled plasma thrombin
	Porcine gelatin ± human thrombin
sealants.	
	Human pooled plasma thrombin + human pooled plasma fibrinogen
	Human fibrinogen + thrombin, ORC
	Human fibrinogen + thrombin, equine collagen
	Autologous fibrinogen and thrombin
	Autologous plasma fibrinogen + bovine thrombin

Bone wax

In 1886, Sir Victor Alexander combined beeswax, salicylic acid and almond oil into “antiseptic wax” to arrest bleeding from canine skulls. Modern formulations maintained a nonabsorbable beeswax base, but differ in the addition of 30% paraffin, 12% isopropyl palmitate, and a wax-softening agent. The mechanism of action involves tamponade, particularly from bleeding channels of bone edges is insoluble and remains at the site of implantation for a prolonged period before being engulfed by phagocytes. Therefore, bone wax is considered a foreign body by the host innate immune system. Adverse events include impeded bacterial clearance, infection, allergic reaction, local tissue reaction and it retards osteogenesis

Ostene

It was introduced in 2001, a water-soluble alkylene oxide block copolymer that contains no beeswax, has similar tactile characteristics to bone wax, but is hydrophilic, watersoluble and excreted in the urine. It has less interference with bone healing and a decreased rate of infection

Gelatin

A nonantigenic and nonreactive, highly hygroscopic material creates a moist three-dimensional meshwork that absorbs blood, leaving slurry of concentrated coagulants. This matrix promotes clot propagation as well as tissue granulation. A neutral pH permits use with topical thrombin and other biologic agents for enhanced hemostasis. Absorption occurs within 4 weeks to 6 weeks. Gelatin provides a nidus for infection.

Other adverse effects include Compression of nearby nerve or vascular structures, Product dislodgment, Interference with bone healing and embolization following intravascular placement.

Oxidized regenerated cellulose surgicell provides a matrix for clot initiation, fostering platelet activation and adherence without directly augmenting coagulation mechanisms. In addition, its acidic pH is caustic, leading to coagulative necrosis, artificial clot formation, and tamponade. local acidosis induces red blood cell lysis, causing brown discoloration of the product. Acidity also inactivates biologically active hemostatic agents, thereby limiting concomitant application. Finally, lowered pH in the local environment is bacteriostatic, offering antimicrobial activity. Oxidized regenerated celluloses are easily adaptable to wound geometry. Absorption begins at 24 hours, with complete dissolution between 2 weeks and 6 weeks depending on product volume, local vascularity, and tissue bed

Adverse effects are secondary to incomplete product absorption and local acidity, leading to inflammation and granuloma formation

Microporous Polysaccharide Hemospheres

Plant starch-based MPHs are ultra-hydrophilic with high osmotic action forming an adhesive, hemostatic polymer gel matrix, accelerating the intrinsic cascade and enhancing clot formation upon contact. It also creates a scaffold for fibrin formation within minutes of application, regardless of the patient's coagulation status. This product is nontoxic, nonimmunogenic, and nonhemolytic. Resorption of the product occurs within 24 hours to 48 hours.

Fibrin sealants

In general, fibrin hemostats are made according to a common recipe: fibrinogen, thrombin (human or bovine), and FXIII or an antifibrinolytic agent, such as aprotinin, or tranexamic acid (TXA). Together, these ingredients utilize the common final pathway to yield a crosslinked insoluble fibrin matrix wherein the antifibrinolytic agent stabilizes the clot and decreases clot breakdown by limiting plasmin generation.Fibrin sealants are biodegradable, do not provoke inflammation, and are not associated with foreign body reactions, tissue necrosis, or extensive fibrosis as the fibrin clot is reabsorbed within 14 days through intrinsic thrombolysis. An advantage of these agents is that they do not require active bleeding and can function independent of the patient's own fibrinogen. Topical fibrin sealants are often used in procedures such as skin grafting, dural sealing, bone repair . **(23)**

Safety concerns include: transmission of blood borne pathogens, anaphylaxis or hypersensitivity **(20)**

PEG Polymers Synthetic sealants are nonfibrin sealant, made from PEG polymer, used for vascular, visceral pleural and dural sealing **(20).** DuraSeal is approved as an adjunct to sutured dural repair during cranial surgery to provide watertight closure **(23)**

Cyanoacrylate

Cyanoacrylate is synthetic sealant liquid interface that binds tissues creating a physical barrier to further bleeding or leakage of fluids. they are used to seal adjacent skin surfaces together. These agents are only approved for topical dermal use and often used instead of sutures. **(24)**

Chemical hemostasis

Zinc paste, ferric subsulfate, silver nitrate and aluminum chloride share a common mechanism of action: tissue destruction leading to protein precipitation, occlusion of small vessels, and coagulation. Zinc paste causes Pain and local irritation at application site. Ferric subsulfate causes dyspigmentation, increased erythema, infection, delayed wound reepithelialization and dermal fibrosis. Silver nitrate decreases healing, causes silver particle deposition and stinging sensation. Side effects of aluminum chloride include paresthesia, tissue Irritation and larger scars.

Physiological hemostasis

Physiologic hemostats augment hemostasis by mimicking latter steps of the coagulation cascade8 and causing vasoconstriction of small vessels. It includes epinephrine, cocaine, hydrogen peroxide, tranexamic acid, aminocaproic acid and aprotinin.

Cocaine

An alkaloid solution concentrated from Erythroxylon coca. It is indicated for analgesia in procedures involving the naso-oropharynx. Intense local vasoconstriction confers hemostatic activit. Side effects include myocardial infarction, syncope, central nervous stimulation including seizures, stroke and death.

Hydrogen peroxide

Although the exact mechanism of action is unknown, a dose-dependent effect on phospholipase A2 and cyclooxgenase is hypothesized to lead to platelet aggregation.but, it causes delayed wound healing.

Tranexamic acid

Tranexamic acid was first discovered in 1957 in Japan and utilized in the management of postpartum hemorrhage, it is a synthetic analogue of lysine. It competitively inhibits plasminogen activation but becomes a noncompetitive inhibitor at higher concentrations and noncompetitively inhibits plasmin activity. **(25)**

Plasminogen has 4 to 5 binding sites with low affinity for tranexamic acid and 1 high-affinity binding site. The high-affinity binding site is involved with the binding of plasminogen to fibrin. Saturation of this high-affinity binding site by tranexamic acid displaces plasminogen from the surface of fibrin. This prevents the binding of fibrin to plasmin and preserves and stabilizes the matrix structure of fibrin and diminishes the ability of plasmin to lyse fibrin. The end result is inhibition of fibrinolysis. A secondary benefit of this plasmin inhibition is the reduced plasmin-induced platelet activation resulting in a higher circulating platelet count to aid clotting as the surgical procedure progresses. Tranexamic acid is minimally bound to plasma proteins (3%) and binds exclusively to plasminogen. It distributes into various tissues. It diffuses rapidly into joint fluid and the synovial membrane. It is also distributed in both the cerebrospinal fluid and the aqueous humor of the eye at one-tenth the plasma concentration. Concentrations will, however, remain high for a longer period in tissue than in plasma, possibly because of strong binding to plasminogen and time to peak concentration and retention time may vary among tissues. **(25)**

It can be used either orally, intravenous, local infiltration or topical application. No single superior means of administration or dosage is supported in the literature, and lowest effective dose is unknown. There may not be one single ideal dosing regimen, but rather many possibilities adaptable for different surgical situations. An alternative to systemic use of tranexamic acid is local administration, which may provide sufficient drug concentrations at the wound surface with negligible risk of systemic adverse effects. Three meta-analyses on the use of topical tranexamic acid in surgery all demonstrate a significant reduction of blood loss and transfusion needs without any increase in adverse events. **(24)**

The lowest effective concentration for local use is unknown.It is also unclear whether topical effect is determined by drug concentration, total drug dose, and/or a combination of concentration and contact time. In a meta-analysis by Montroy et al. **(25)** on topical use of tranexamic acid, the effect on transfusion needs was not affected by dose; drug concentrations ranged from 1 to 100 mg/ml. Even the lowest concentration of 1 mg/ml solution will expose the wound surface to a concentration 100-fold stronger than what is considered the lowest inhibitory concentration in plasma. The effect of tranexamic acid may possibly be achieved through both prolonged exposure to low concentrations and short exposure to high concentrations. Transfusion-Free Cranial Vault Remodeling: A Novel, Multifaceted Approach **(25)**

Tissue concentration after intravenous administration quickly matches that of plasma and local administration resulting in a peak plasma concentration above 10 µg/ml can thus theoretically provide an antifibrinolytic concentration in other tissues. Plasma concentrations after topical administrations have

mostly been investigated using single measurements at single timepoints, and peak plasma concentrations have therefore been largely unknown. Systemic concentration may be proportional to topical drug concentration and dose and may also be influenced by tissue vascularity and contact time.

A tissue concentration of at least 10 µg/ml tranexamic acid is needed to significantly inhibit fibrinolysis.A single intravenous dose of 10 to 15 mg/kg will keep plasma concentration above 10 µg/ml for 1 to 3 hours and may have little risk of adverse effects, such as venous thromboembolism or seizures **(26)**

Although much higher dosing has been practiced, particularly in cardiac

but also craniomaxillofacial surgery there is little clinical support for increased effect with high dosing and the reports of a dose-dependent increase in seizures is changing dosing practice. **(27)**

Topical use of tranexamic acid is mostly applied at the end of a surgical procedure and, thus, cannot influence perioperative bleeding. Systemic administration of tranexamic acid before the initiation of surgery may be preferred when there is a risk of significant intraoperative hemorrhage

Although local infiltration may provide higher and longer-lasting levels of tranexamic acid in the tissue, infiltrated tranexamic acid may not reach the raw wound surface to the same extent as free-flowing, topically applied tranexamic acid. **(28)**

Although topical (i.e., intraarticular) application of tranexamic acid has been proven noninferior to intravenous administration in orthopedic surgery, studies assessing infiltration are few and find less effect. **(29)**

Studies on the local toxicity of tranexamic acid have mainly been conducted on cartilage, tendon, synovial tissue, keratinocytes and fibroblasts in vitro. Short exposures even to high doses seem well-tolerated, as do prolonged exposures to concentrations below 10 mg/ml. The threshold value for toxicity may lie around 25 mg/ml given several hours of exposure, such as after intraarticular administration.. In soft tissue, a physiological dilution of the drug may ensue faster that prolonged exposure to high concentrations of topical tranexamic acid caused lack of re-epithelialization and even nontoxic epithelial detachment in an ex vivo human skin wound model.The possible effect by tranexamic acid on cell adherence and migration caused by mechanisms linked to plasminogen/ plasmin outside of the fibrinolytic system may explain these observations **(30)**

The elimination half-life of tranexamic acid is approximately 2 hours, and the mean terminal half-life is approximately 11 hours. Actually, it remains in tissues for about 17 hours and in the serum for 7 to 8 hours. Only a small amount of tranexamic acid is metabolized. It is eliminated by urinary excretion primarily via glomerular filtration. More than 95% of the dose is excreted unchanged. After an intravenous dose of 10 mg/kg, excretion of tranexamic acid is approximately 90% at 24 hours, with most elimination occurring during the first 10 hours. Tranexamic acid is approximately ten times more potent than aminocaproic acid. Orally administered tranexamic acid can cause gastrointestinal upset, headache, abdominal pain, muscle pain, and thrombosis. Visual defects may occur; thus, patients should undergo routine ophthalmologist examinations. Intravenous tranexamic acid can also cause hypotension with rapid administration.

Seizures have been reported in patients who have been administered tranexamic acid which is dose-dependent. Lysine analogues act as competitive antagonists to inhibitory neurotransmitters acting on glycine and GABAA 41 receptors in the central nervous system and thus cause hyperexcitability. Direct application of tranexamic acid onto the central nervous system after accidental intrathecal injection has led to generalized seizures and even death. Transfusion-Free Cranial Vault Remodeling: A Novel, Multifaceted Approach **(30)**

The dose and frequency of tranexamic acid should be adjusted in patients with renal dysfunction. Importantly, tranexamic acid should not be used when there is evidence of active intravascular thrombosis Caution should be exercised if tranexamic acid is used concomitantly with prothrombin complex

concentrates (PCC) or activated prothrombin complex concentrates (APCC) due to risk of thrombosis. If treatment with both agents is deemed necessary, it is recommended to wait 4–6 hours after the last dose of PCC or APCC before administering tranexamic acid **(31)**

Dose in craniostenosis

Safety and efficacy have not been established in neonates, infants and children up to 11 years.

Although prolonged exposure to high concentrations is discouraged, no single superior means of administration or dosage is supported in the literature, and lowest effective dose is unknown. There is little consensus on the optimum dose of TXA; however, 10 mg/kg has been shown to inhibit 80% of plasminogen conversion to active plasmin, the TXA remaining active for more than 17 hours. Administer at a rate not to exceed 100 mg/minute to avoid hypotension, a loading dose of 10 mg up to 100 per kg usually infused over 15 minutes before skin incision followed by an of infusion 3 ; 10mg kg_h till closure of skin **(31)**

An alternative to systemic use of tranexamic acid is local administration, which may provide sufficient drug concentrations at the wound surface with negligible risk of systemic adverse effects.

The concentration of topically administered TXA ranges from 1 to 5 mg/mL.

Concentration remains high for a longer period in tissue than in plasma, possibly because of strong binding to plasminogen.The lowest effective concentration for local use is unknown.It is also unclear whether topical effect is determined by drug concentration, total drug dose, and/or a combination of concentration and contact time. In a meta-analysis by Montroy et al.**(25)** on topical use of tranexamic acid, the effect on transfusion needs was not affected by dose; drug concentrations ranged from 1 to 100 mg/ml. Even the lowest concentration of 1 mg/ml solution will expose the wound surface to a concentration 100-fold stronger than what is considered the lowest inhibitory concentration in plasma. The effect of tranexamic acid may possibly be achieved through both prolonged exposure to low concentrations and short exposure to high concentrations.

Aminocaproic acid

Aminocaproic acid is an antifbrinolytic that reduces the conversion of plasminogen to plasmin by binding competitively to plasminogen which results in the inhibition of fbrin degradation. Aminocaproic acid is 10 times less potent than tranexamic. **(32).**

The most common adverse effect of enteral aminocaproic acid is gastrointestinal upset. Other adverse effects include thrombosis and an increase in blood urea nitrogen (BUN) and skeletal muscle weakness. Aminocaproic acid can also cause skeletal muscle weakness; therefore, creatinine phosphokinase (CPK) should be monitored in patients with symptoms and treatment should be discontinued with a signifcant rise in CPK. Other monitoring parameters include fbrinogen, BUN, and creatinine. Importantly, aminocaproic acid should not be used when there is evidence of active intravascular thrombosis.

Recent pharmacokinetic models suggest regimen (50;100 mg/kg load and20; 40 mg/kg/h infusion) may be indicated in pediatric patients. **(33).**

Aprotinin

Aprotinin is a serine protease inhibitor that inactivates free plasmin by preventing the binding of plasminogen to fibrin so inhibits clot breakdown while also possessing some anti-inflammatory properties. It had been extensively used in adults and children, but was removed from the North American market in 2008 after a large study in high-risk adult cardiac surgery showed increased mortality. It is still used in Europe, and has recently been reestablished in Canada for pediatric indications, but remains unavailable in the United States. Royston D, 2015: loading dose of 171.5 mL/m2 intravenously over period of 30 minutes, followed by maintenance infusion of 40 mg/m2 per hour **(33).**

Fibrinogen Concentrate

Fibrinogen concentrate (coagulation factor I) is generated from pooled human plasma and is a physiological substrate of thrombin, factor XIIIa, and plasmin. Cross-linked fbrin, the end result of the coagulation

cascade, is stabilized by factor XIIIa. Human fbrinogen concentration has a fairly long elimination half-life of 61–97 hours; however, this half-life may be decreased in children and adolescents. Fibrinogen concentrate is available as intravenous powder, for reconstitution **(34)**

Fibrinogen concentrate can be used in children for the treatment of congenital fbrinogen defciency , pediatric cardiac surgery , reduction of blood loss after surgical craniosynostosis repair , pediatric blunt trauma and leukemia. Fibrinogen concentrate may cause hypersensitivity reactions, thrombosis, and headache. Similarly to all plasma-derived factor products, fbrinogen concentrate may also transmit disease, since the product is derived from human plasma. Monitoring parameters include fbrinogen levels and signs/ symptoms of thrombosis and hypersensitivity. In general, a target fbrinogen level of 100 mg/dL is a goal concentration for hemostasis and wound healing. The reference range for normal fbrinogen is 200–450 mg/dL Dose 30 mg/kg IV.

Factor VIIa (Recombinant)

literature shows that there are lots of questions about the safety and efficacy of factor VII in children with off-label indications. The Network for Advancement of Patient Blood Management (NATA) task force recommended against activated factor VIIa being administered during cardiac surgery in infants and children unless it is part of a clinical trial or to treat extreme bleeding despite the use of standard blood product.

Desmopressin

Stimulates the release of VWF from endothelial storage and increases the factor VIII.

Thrombin Powder

Protamine Sulfate

Prothrombin complex

The prothrombin complex (PCC) contains factors II, VII, IX, and X, as well as anticoagulant factors such as Protein S, Protein C and heparin traces. It is used in management of perioperative bleeding refractive to the use of fresh frozen plasma, platelets and cryoprecipitate.

A recent review showed that Prothrombin complex concentrates (PCC) administered to control postoperative bleeding due to coagulation disturbances in traumatic injuries and vitamin K antagonists following Cardiopulmonary bypass (CPB) and surgeries for congenital heart disease are safe and effective in reducing bleeding and minimizing transfusions without adverse events in infants and children.

Resuscitative Products and Blood transfusion

During the early years of MT, use of crystalloid to sustain normal blood pressure was encouraged. Practice began to change as evidence revealed that large volume crystalloid resuscitation increases the risk of edema, compartment syndrome, and acute lung injury . Additionally, hemodilution exacerbates anemia, thrombocytopenia, and coagulopathy resulting in further bleeding. After the bleeding has crossed 20% of blood volume preferred ratio of crystalloid to colloid is 1:1 **(35)**

Holiday and Segar published their paper "*The maintenance need for water in parentral fluid therapy*" and came up with the widely used 4/2/1 principle of fluid Holliday, All the guidelines still follow the Holiday Segar Formula for maintenance therapy and they recommend infusion of isotonic solutions. …. **(36)**

Replacement of intraoperative blood losses with isotonic solution or blood will depend upon the hematocrit of the patient.[3] The 3rd space loss (its existence is a matter of debate) because of leaking of fluid from vascular space into tissues around the surgical site is difficult to account for and is roughly estimated as 2 ml/kg/h for superficial surgery 5–10 ml/kg/h for extensive surgery **(37).**

It has been not that in children undergoing major pediatric and neurosurgeries have shown better acid-base status with balanced crystalloids like plasmalyte and ringer lactate. **(37).**

After administration of a total of 30–50 ml/kg of crystalloid solution, the administration of a colloid solution (albumin or synthetic colloid) to maintain intravascular osmotic pressure is indicated **(36)**

Albumin remains the main colloid used in the neonatal period and early infancy for volume expansion. However, its use is restricted in view of high cost and possibility of it carrying other sources of infection. 5% albumin remains the preferred colloid in young infants as it is iso-oncotic to plasma and very effective to maintain blood pressure and plasma colloid perfusion pressure **(38)**

In an actively hemorrhaging patient, it is important to monitor physiological processes at the time of resuscitation in order to guide care. This may be done using both invasive and noninvasive tools such as a pulse oximeter, capnometer, blood pressure cuff, arterial line, and urine catheter, to name a few.

It is important to note lag time associated with laboratory testing and that treatment should not be delayed while waiting results . In the hemorrhaging patient, development of coagulopathy is a well-documented phenomenon . There is an array of laboratory tests that may be performed to identify alterations in the coagulation cascade including traditional assays such as activated partial thromboplastin time, PT, and INR and, the more modern, viscoelastic hemostatic assay (VHA) which includes thromboelastography and thromboelastometry . Use of a VHA in goal-directed resuscitation has been shown to reduce blood product administration volumes and improve mortality, suggesting overall benefit

The use of allogeneic blood products and its potential side effects has been the focus of many discussions and whether a liberal transfusion strategy is superior to a restrictive one is still under debate.

Blood transfusion in pediatrics is not about the transfusion of smaller volumes to smaller humans because children are not simply smaller adults due to the physiologically higher average haemoglobin concentrations and oxygen requirements compared to adults. PBM in pediatric practice remains far from ideal due to the limited amount of data and the substantial variation in practice. Further studies are needed to close the gap with clinically significant endpoints beyond transfusion thresholds to address the best oxygenation requirements and transfusion strategy for patients with different medical and surgical conditions.

Acute blood loss of greater than 20% of circulating volume is an indication for immediate red cell transfusion

There are several defnitions used to describe MT including replacement of the entire blood volume in 24 hours, replacement of 50% blood volume in 3 hours, transfusion of more than 10 or 20 units of red blood cells (RBC) in 24 hours, and transfusion of more than 3 or 4 units of RBC in 1 hour . Defnitions used in pediatric transfusion vary even further with weight playing a larger role . In children, 40 mL/kg of total blood products administered over 24 hours has evolved as a well accepted definition.

Another definition is super massive blood transfusion in which the pediatric patient receives 80 ml /kg blood in 24 hours and this has a significant lower rate of survival compared to massive transfusion 78% vs 86%. MTPs are a component of damage control resuscitation, a systematic approach to reducing hypothermia, acidosis, and coagulopathy in order to prevent death by exsanguination. Several societies with recommendations on massive transfusion suggest a minimum transfusion ratio of 1:1:2 (plasma/platelets/PRBC). In children, the impact of component ratios on outcome is unclear. The volume of a single unit of RBCs is 250–350 mL, depending on the storage media used. This includes 200–250 mL of RBCs, 20–100 mL of plasma and 63–70 mL of anticoagulant. The hematocrit of each unit is between 55 and 80% according to which additive solutions are used .

In the pediatric and neonatal populations, dosing is 10–15 mL/kg. This dose is expected to increase the hemoglobin by 2–3 g/dL. Transfusion of up to 20 mL/kg in pediatric patients without adverse events has also been described. In adults who are not actively bleeding, one unit of RBCs is expected to increase the hematocrit by 3% or 1 g/dL increase in hemoglobin. The use of a blood warmer is encouraged, especially in those patients receiving rapid transfusions. Once the unit has been spiked, the transfusion must be completed within 4 h due to the increasing risk of bacterial contamination.

Estimated circulating blood volume (volemia) in accordance with the age of the patient. So, in Preterm newborn 90ml/kg, in term newborn to 3 months 80–90ml/kg , in infants 3 months to 2 years 70–80ml/kg, while in children over 2 years old 70 ml/kg. **(37).**

The decision when to transfuse blood to children depends on the maximum allowable blood loss (MABL) calculated as: MABL = EBV × (H0 – H1)/H0 (EBV = estimated blood volume; H0 = starting Hct; H1 = lowest acceptable Hct). Volume to transfuse (VTT): Estimated blood volume × (ideal hematocrit – actual hematocrit)/Hematocrit of packed red blood cells to be transfused (60–70). Example: 1-year-old child and 12 kg of weight. Actual hematocrit: 21 Ideal hematocrit: 35. Hematocrit of 1 Unit of packed red blood cells: 60–70. - VTT: (12 × 75) × (35 – 21)/70 900 × 14/70 180ml of red blood cells to transfuse. **(37).**

The volume of blood to be transfused must be calculated for achieving the desired hematocrit. Calculating a suboptimal volume places the child at risk of a repeated blood transfusion from a different donor.

1 unit of red cells administered to an infant may represent replacing the total circulating blood volume, while 1 unit of red blood cells administered to an adult only represents replacing 10% of their volume. **(37).**

Complications

In the setting of a mild allergic reaction such as hives or itching that resolves immediately with the administration of diphenhydramine, the transfusion may continue. Finally, RBCs should only be transfused in the same IV line with 0.9% normal saline, ABO-compatible plasma, 5% albumin, or other FDA-approved product. Transfusion with solutions containing dextrose can be associated with hemolysis, while the calcium in Ringer's lactate may lead to clotting. If a transfusion reaction is suspected, the current transfusion should be immediately suspended, and all transfusions should be discontinued until the blood bank has confirmed the reaction is not a hemolytic transfusion reaction. **(37).**

The infective risks of blood transfusion are more closely related to the number of donors to whom the patient is exposed than the volume transfused from each unit. Although allogeneic transfusions are considered safe, hemolytic reactions, transfusion-associated cardiac overload, transfusion related lung injuries, the transmission of pathogens, and other minor reactions like fevers, chills, and tachycardia. The literature also shows less explicable findings, such as increased mortality, increased risk of surgical site infection and increased length of hospital stay. …. Enhanced Recovery Protocol after Fronto-orbital Advancement Reduces Transfusions, Narcotic Usage, and Length of Stay**(38).**

The most serious risks include acute transfusion reactions, transfusion-related acute lung injury, transfusion-related circulatory overload and ABO incompatible blood transfusion due to administrative error . Red blood cell transfusions are also associated with an increase in resource utilization. **(39).**

Hypocalcemia: The citrate present in blood products chelates the calcium and produces hypocalcemia; this is more frequent with frozen fresh plasma that exhibits a higher concentration of citrate per unit of volume. myocardial dysfunction secondary to citrate-induced hypocalcemia and this is worsened by the myocardial depressant effect of halogenated anesthetics. Hypocalcemia can be treated by calcium chloride 5–10mg/kg or calcium gluconate 15–30mg/kg IV. **(39).**

Hypomagnesemia: it presents by arrhythmia (ventricular tachycardia or ventricular fibrillation) which is not responsive to the administration of calcium. Hyperkalemia: In patients who are massively transfused and in the neonatal population, extracellular potassium in RBC units increases from 1 mmol/L to nearly 30 mmol/L after 42 days of storage . This increases the risk for transfusion-associated hyperkalemia. Storage-associated changes in the membrane of the RBCs also make them less deformable, making it more diffcult for these RBCs to reach the microvasculature. These changes have led to a number of studies aimed at examining the efficacy and safety of aged RBCs in transfusion.

If there is risk of massive transfusion, ask for red blood cells collected less than a week ago. Hyperkalemia is one of the most feared complications in massive transfusions, particularly in children. There is a

progressive increase of extracellular potassium during the storage of red blood cells; the level of potassium measured in 1 unit of red blood cells after collection is 12meq/l; at 21 days it is 32meq/l and at 35 days the values are as high as 50meq/l.

Hyperkalemia represents by arrhythmia and can be treated by calcium , bicarb1meq/kg, dextrose insulin, hyperventilation and the use of beta mimetics.

Hypothermia: Children experience a higher heat loss due to their large surface area versus their bodyweight. Furthermore, they are particularly sensitive to hypothermia and to its deleterious effects such as: hypoglycemia, apnea, decreased drug metabolism, decrease oxygen delivery to the tissues, increased oxygen consumption, worsening of coagulopathy. **(40)**

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