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GUIDELINES FOR NEONATAL & PAEDIATRIC TRANSFUSION

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INTRODUCTION

Paediatric surgical patients often need volume replacement with blood or blood products during the perioperative period [1]. One of the leading causes of morbidity and mortality during this period is hypovolaemia secondary to blood loss [2], and blood is important for oxygen delivery [3, 4], metabolism of drugs and immunity[3]. A significant change in circulating blood volume and cellular constituents affects these basic functions as well as cardiovascular properties, hence hypovolaemia should be promptly addressed [3]. However, transfusion of blood products in this population is associated with increased risks of harm and complications, when compared with adults [1, 2, 5, 6].

The risks involved can either be infectious or non-infectious, with non-infectious risks being associated with greater chances of transfusion reactions and increased mortality [6]. The three leading causes of mortality are transfusion- related acute lung injury (TRALI), transfusion- associated circulatory overload (TACO) and haemolytic transfusion reactions (HTR)[7] [5, 6]. Acute reactions may vary from mild urticaria to moderately severe fever and rigors to life threatening situations such as sepsis, anaphylactic reactions and the three above-mentioned reactions, TRALI, TACO and HTR [7].

The number of patients requiring transfusions is growing, while the donor pool remains unchanged or is slightly decreasing [8] and as mentioned above, the associated risks involved with transfusion of blood and blood products are plentiful and can be life-threatening [6, 7], so guidelines to assess the appropriateness of paediatric transfusion are essential.

PHYSIOLOGICAL AND HAEMATOLOGICAL VARIANCES FROM ADULTS

A neonate's haemostatic system is not well developed at birth, and matures during infancy [9].Children have higher rates of cardiac output and circulating blood volume, increased oxygen consumption and higher metabolic rate[1].Neonatal haemoglobin levels are affected by the timing of the clamping of the umbilical cord and they reach a steady state by the age of 2-3 months [1, 3, 9].

Haemoglobin concentration is higher if clamping of the cord is delayed, and deteriorates by the age of 3 months as a result of reduced red cell production [3]. Foetal haemoglobin (Hb F) constitutes 70% of total Hb in term infants, and having a higher affinity for oxygen with a leftwards shift of the oxygen haemoglobin dissociation curve, Hb F thereby reduces delivery of oxygen to the tissues [1].

Neonates are born with a relatively normal platelet count [3, 9], which may have impaired function for the first 2-3 weeks of life [3]. The low levels of procoagulant proteins, plus dysfunctional fibrinogen and plasminogen, place them at a higher risk of bleeding when compared with adults, as these factors lengthen the prothrombin time (PT) and activated partial thromboplastin time (APTT) [3, 9].

Table 1: NORMAL HAEMATOLOGICAL PARAMETERS[3, 10]

	Preterm	Term	Adult
Haemoglobin (g/dL)			
Birth	14 - 24	14 - 24	-
3 months	8 - 14	8 - 14	-
6 months- 6years	10 - 14	10 - 14	-
7- 12 years	11 - 16	11 - 16	-
Adult	-	-	11.5 - 18
Platelets (x10^9/litre)	150 -450	150 -450	150 -400
PT (seconds)	11 - 22	10 - 16	11 - 14
APTT (seconds)	28 -101	31 - 55	27 - 40
Fibrinogen (g/litre)	1.5- 3.7	1.7- 4.0	1.5- 4.0
Blood volume (ml/kg)	90 -100	80 - 85 (75 - 80)[a]	65 - 75

[a] Blood volume by the age of 6months
PT, prothrombin time; APTT, activated partial thromboplastin time.

TRANSFUSION THRESHOLDS

Transfusion threshold describes the lower limit of haemoglobin level at which a transfusion is considered. A balance has to be maintained between severe anaemia and increasing the risk of morbidity and mortality by exposing a patient to donor blood unnecessarily [3].

Provided they remain haemodynamically stable, a healthy child can tolerate a drop in haemoglobin level to 7-8 g/dL if they have a normal cardiac output and maintain adequate delivery of oxygen to the tissues [2, 3, 8, 11]. Oxygen delivery to tissues (DO_2) is a product of arterial oxygen content (CaO_2) and cardiac output, and under normal circumstances, if the Hb concentration decreases, CaO_2 also decreases, but DO_2 remains stable due to an increase in cardiac output. If this lower limit of Hb is breached, one loses the ability to compensate, and DO_2 will diminish and oxygen extraction will escalate [8].

Normovolaemia can be sustained with the use of crystalloids and colloids [5, 11]. Crystalloids reach the interstitium faster than colloids, hence are more appropriate to use in interstitial losses. Colloids are better suited to replace intravascular losses [5]. Unnecessary fluid resuscitation should be avoided as it can potentially be harmful. Resuscitation ought to be physiologically guided [12, 13]. To prescribe intravenous fluids, a practical method was created *(Table 3)*, based on the estimated metabolic requirements for patients at rest. In theory in an awake child, 1 ml of water is needed to metabolise 1 kcal. The “4-2-1 rule” was formed as a weight-based rule for maintenance fluid therapy in paediatric patients which took into account insensible skin, respiratory tract and urinary losses [11].

Table 2: TRANSFUSION THRESHOLDS[2, 3]

BLOOD PRODUCT	CLINICAL CONDITION	TRANSFUSION THRESHOLD
RBC	**Infant < 4months of age**	**Haemoglobin (g/dL)**
	Preterm/term born anaemic	12
	Chronic oxygen dependency	11
	Severe pulmonary disease	12-14
	Late anaemia stable patient	7
	Acute blood loss >10% EBV	12
RBC	**Infant >4months of age**	**Haemoglobin (g/dL)**
	Stable infant	7
	Infant/ child critically unwell	7-8
	Infant/ child with perioperative bleeding	8
	Infant/child with cyanotic congenital heart disease (have increased oxygen demand)	9
	Child with thalassaemia major (to slow bone marrow stimulation)	9
	Child with sickle cell disease (>9g/dL if previous CVA)	7-9
	Child with sickle cell disease for major surgery (aim for 9 – 11g/dL and HbS <30%, <20% for thoracic or neurosurgery)	9
Platelets		**Platelets (x 10^9/litre)**
	Neonate with bleeding	50
	Sick neonate not bleeding	30
	Stable neonate not bleeding	20
	Stable infant >4months/ child	10
	Infant/ child ICU	20
	Any infant/ child for invasive procedure or surgery	50 - 100
FFP	Neonate/ child with bleeding, DIC or prior to an invasive procedure	APTT and PT >1.5 control for age
Cryoprecipitate	Neonate/ child with bleeding or DIC not corrected with FFP	Fibrinogen < 1 g/litre

Table 3: 4-2-1 RULE AND DAILY MAINTENANCE FLUID ACCORDING TO WEIGHT [11]

WEIGHT (kg)	HOURLY FLUID REQUIREMENTS	DAILY FLUID REQUIREMENTS
<10	4 ml/kg	100 ml/kg
10-20	40 ml + 2 ml/kg above 10 kg	1000 ml + 50 ml/kg above 10 kg
>20	60 ml + 1 ml/kg above 20 kg	1500 ml + 25 ml/kg above 20 kg

MAXIMUM ALLOWABLE BLOOD LOSS

It is important for the anaesthetist to be able to estimate the amount of blood a patient may be allowed to lose prior to needing a blood transfusion .This is achieved by estimating the child's circulating blood volume *(Table 4)* and incorporating it into a mathematical equation [2, 3, 13].

MABL = EBV x (HbI – Hb t) / Hb av

MABL = maximum allowable blood loss
EBV = estimated blood volume (weight in kg x blood volume in ml/kg)
HbI = initial haemoglobin
Hbt = threshold haemoglobin
Hb av = average haemoglobin i.e. HbI + Hbt /2

The original equation had the initial haemoglobin as the denominator, but further studies revealed that with the administration of crystalloids or colloids intra- operatively, the amount of haemoglobin being lost was reduced in the face of haemodilution. [5]

Ongoing blood loss can be replaced with a crystalloid in a volume of 3:1 or with a colloid in a ratio of 1:1, until the target value (MABL) is reached. At this point, transfusion with red blood cells (RBC) should be initiated [11, 13].

Table 4: ESTIMATED BLOOD VOLUME ACCORDING TO AGE AND WEIGHT [1, 2, 11, 13]

AGE	ESTIMATED BLOOD VOLUME (ml/kg)
Premature infant	90-100
Term infant – 3months	80-90
Children older than 3months	70-80
Children over 2 years of age	70
Very obese children	65

ASSESSING BLOOD LOSS[3]

- Inspection of surgical field, floor and drapes
- Evaluating swabs by weighing them and measuring volume in suction bottles
- Assessing cardiovascular indices i.e. heart rate, blood pressure, central and peripheral temperature and capillary refill time
- Measurement of central venous pressure (use trends rather than single values)
- Arterial pressure waveform
- Monitor cardiac output (again the trends are of more value than isolated figures)
- Biochemistry: lactate level > 4mmol/l and base deficit > -4 (indicators of poor tissue perfusion)
- Determination of extraction ratio (ER) which requires sampling from arterial and venous blood at organ outflow, using an equation to calculate plasma flow in order to evaluate organ function.

  Extraction ratio = Pa – Pv / Pa

  Pa is the concentration in the renal artery
  Pv is the concentration in the renal vein

MASSIVE BLOOD LOSS AND MASSIVE TRANSFUSION

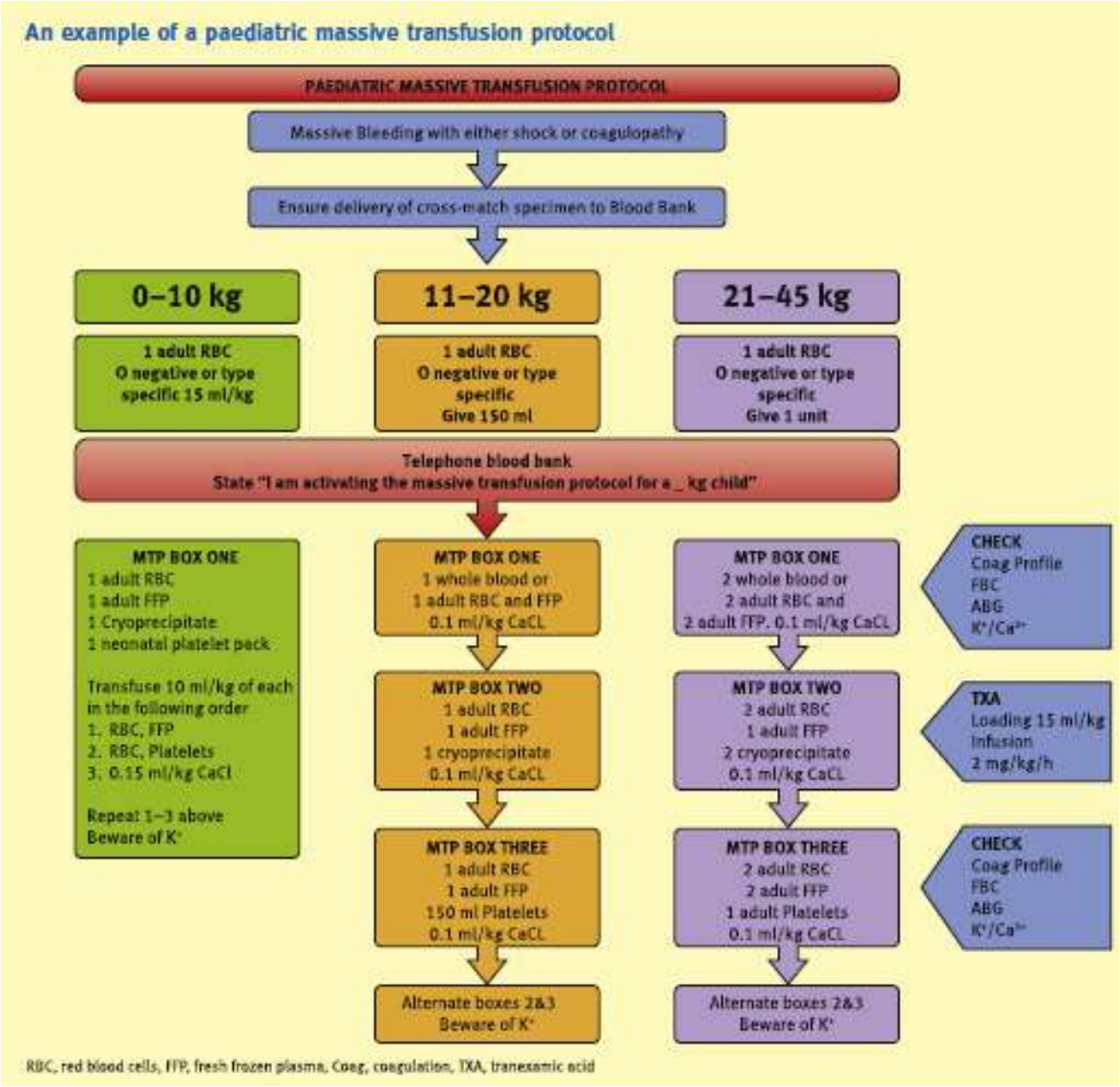
Massive blood loss is the loss of one or more circulating blood volumes within a period of 24hours [3, 11, 13], or half of the volume within three hours [3], which can result in coagulopathy secondary to haemorrhage. Early management of a massive bleed with the use of blood products such as fresh frozen plasma (FFP)/ freeze dried plasma (FDP) and platelets, in addition to packed red cells, improves the outcome of the patient [1, 3, 9, 14] .

Some guidelines suggest that FFP/ FFD and cryoprecipitate should be considered when more than 50% of one's blood volume has been replaced with red cells and state that their use, when more than 120% - 150% of the blood volume has been replaced, is mandatory [15].Massive transfusion protocols for paediatric patients are not well developed [11, 12], but the few that have been researched and implemented in various hospitals have had satisfactory results [3].

Massive transfusion roughly translates to transfusing 10 units of packed red blood cells in an adult, which when combined with infusions of crystalloid can result in irreversible coagulopathies [11, 13, 14]. In these patients, avoid hypothermia, hypovolaemia and acid-base abnormalities and ensure that all electrolyte abnormalities are corrected [14].

Protocols are aimed at providing a balanced amount of blood products, imitating whole blood, to the injured patient in order to treat haemorrhagic shock and coagulopathy[9] and should be readily available in all hospitals.

Figure 1: MASSIVE TRANSFUSION PROTOCOL [3]



TRANSFUSION OF BLOOD PRODUCTS

Red blood cell (RBC) transfusion

A preoperative full blood count should be done to evaluate haemoglobin, haematocrit and reticulocyte count [1].Transfusion with RBC must be performed based on restrictive rather than liberal haemoglobin levels, and infants under the age of 4 months of age must have type specific or O negative blood [11]. Transfusion with RBC increases arterial oxygen content and delivery of oxygen to tissues [8].Transfusion with autologous blood carries less risk than allogenic blood, so where possible, preoperative autologous donation of a patient's blood could prove beneficial [1, 16]. However, auto-donation could be challenging in the paediatric population as the child may require sedation and venous access may be problematic [16].

The South African National Blood Service suggests the use of small volume red cell transfusions (10-20 ml/ kg). Blood bank pre-transfusion testing in the first 4 months of an infant's life differs from adults. A complete crossmatch is not essential if there are no clinically significant red cell antibodies in the infant or maternal plasma, and the direct antiglobulin test is negative. However, re-confirmation of ABO and Rh-D group is needed each time a neonate requires a transfusion [15].

Blood component therapy

<u>Platelets</u>

Platelet transfusion is indicated only in an acute bleed with an estimated loss of > 40% of the circulating blood volume or for an invasive procedure where the platelet count is < 50 x 10^9/l [1, 2, 15].If the bleeding risk is increased then strongly consider administering platelets under the following circumstances[15] :-

- < 1000 g and < 1 week old
- Clinically unstable (i.e. labile blood pressure)
- Previous major bleeding
- Current minor bleeding
- Coagulopathy
- Planned surgery or exchange transfusion
- Major bleeding, where the platelet count is < 100 x 10^9/l

The suggested dose is 1 – 2 units/10 kg or 10 – 15 ml/kg [1, 2] .

<u>Fresh frozen plasma (FFP)</u>

In cases of Vitamin K deficiency, liver disease, disseminated intravascular coagulation or dilutional coagulopathy where coagulation factor deficiency is noted, FFP becomes invaluable. The suggested dose is 1 unit/10 kg or 10 – 15 ml/kg [1, 2, 8, 15].

<u>Cryoprecipitate</u>

This blood product contains 80 units of factor VIII, von Willebrand factor (VWF), factor XIII, fibrinogen (150 – 250 mg) and fibrinonectin. It is indicated when fibrinogen levels fall below 150 mg/dl with active or microvascular bleeding or in the face of massive bleeding. The suggested dose is 1 unit per 5 – 10 kg body weight [1, 2].

Table 4: BLOOD PRODUCT TRANSFUSION VOLUMES

BLOOD PRODUCT	FORMULA FOR VOLUME TO BE TRANSFUSED
RBC	
1 unit ~300 ml	Once MABL reached, administer 0.5 ml PRBC for every 1 ml of blood loss to maintain at threshold level
Paedipak = 1 unit divided into 4 or 8 small packs	To increase the Hb: 5 ml of PRBC (Hct 0.6) will raise Hb by 1 g/dl Volume to be transfused = Desired Hb (g/dl) x Wt (kg) x 5 Most top-up volumes are 10-20 ml
Platelets	
Apheresis unit (1donor) ~ 215 ml	Massive blood loss 1 blood volume loss = 40% fall in platelet count
Pooled unit (4 donors) ~300 ml	2 blood volume loss = 60% fall in platelet count 3 blood volume loss = 70% fall in platelet count
	Transfuse after 1- 1.5 blood volume loss Child < 15 kg = 10-20 ml/kg Child >15 kg = 1 apheresis or pooled unit
Fresh frozen plasma	
Pathogen inactivated	Check clotting profile after 1 blood volume loss
1 unit = 200 ml	Transfuse after 1- 1.5 blood volume loss APTT/PT > 1.5 x normal 10 – 20 ml/kg
Cryoprecipitate	
1 unit = 20- 50 ml	0.75 blood volume loss = 50% fall 5 – 10 ml/kg Maximum = 10 units

COMPLICATIONS OF MASSIVE BLOOD TRANSFUSION

One unit of packed RBC may be equal to a child's entire circulating volume and thus they may experience complications more often, such as hyperkalaemia, metabolic acidosis, hypomagnesaemia, hypocalcaemia and variations in the haemoglobin-oxygen dissociation curve [1, 2].

Hyperkalaemia

This is a very serious complication due to administration of old stored red blood cells and may cause cardiac arrhythmias and arrest. It is advisable to request RBC collected no more than a week before and to transfuse at a rate of 1 ml/kg/min. Arrhythmias may be treated using 1 meq/kg of sodium bicarbonate, 60 mg/kg calcium gluconate or 20 mg/kg calcium chloride intravenously [1, 2].

Hypocalcaemia

Children with liver dysfunction are at higher risk of hypocalcaemia as they are unable to metabolize citrate present in stored blood, which chelates calcium [2, 11]. Hypocalcaemia is managed with calcium chloride 5 – 10 mg/kg or calcium gluconate 15 – 30 mg/kg [2].

Hypomagnesaemia

Magnesium is important for stabilizing the membrane potential and maintaining cardiac stability. Treatment in the face of cardiac arrhythmia is to administer 25 – 50 mg/kg magnesium sulfate[2].

Hypothermia

Due to the large surface area compared to their body weight, children lose heat more easily than adults. Hypothermia predisposes infants to hypoglycaemia, apnoea, reduction in drug metabolism, decreased delivery of oxygen to the tissues, and worsening coagulopathy which may ultimately result in death [1, 2, 11].

INTERVENTIONS TO REDUCE PERIOPERATIVE BLEEDING

Antifibrinolytics

The use of tranexamic acid, a synthetic analogue of lysine, at a dose of 20 mg/kg (bolus) and continuous infusion of 10 mg/kg/hr, significantly decreases blood loss by inhibiting the activation of plasminogen to plasmin [2, 9, 16].

Desmopressin

Desmopressin stimulates the release of von Willebrand factor (vWF) from endothelial cells (Weibel Palade bodies) by acting on the V2 receptor, thereby increasing the levels of vWF and coagulant factor VIII for up to 10 hours. It affects platelet activity through its adhesion to the vascular wall[2]. The recommended dose is 0.3 μg/kg IVI [2, 16].

Recombinant factor VII

This is very controversial in paediatric patients and thus should be reserved for refractory and uncontrollable surgical or traumatic bleeding where there are limited treatment options[2, 9].

Fibrinogen concentrate

Fibrinogen concentrate is indicated in perioperative and traumatic bleeding. It is also useful in patients with impaired fibrinogen synthesis due to liver failure [2].

Prothrombin complex

Factors II, VII, IX, X, anticoagulant factors Protein S and Protein C make up the prothrombin complex. It is primarily used to reverse Warfarin and to treat bleeding haemophiliac patients, but studies show that it is useful in managing perioperative bleeding refractive to the use of fresh frozen plasma, platelets and cryoprecipitate. The recommended dose is 20-30 UI/kg [(2)].

ALTERNATIVES TO BLOOD TRANSFUSION

In an effort to reduce the risks associated with transfusion of blood and blood products, blood conservation strategies can be implemented [(6)]. These include acute normovolaemic haemodilution, antifibrinolytics, controlled hypotension, intraoperative cell saver use, and preoperative autologous donations [(2, 6, 16)].

CONCLUSION

It is of vital importance that each hospital develop and follow a multidisciplinary protocol to combat massive bleeding, as haemorrhage is one of the leading causes of paediatric morbidity and mortality [2, 9]. Clinicians should be familiar with literature pertaining to haemorrhagic shock and the management of its sequelae i.e. hypothermia, acidosis and haemodilution [2]. Even though the safety of blood has been improved, there are still many risks associated with blood transfusions and they seem to be greater in the paediatric population [4, 6]. We need to improve blood product usage so as to avoid overuse, underuse and improper use [8].

Avoiding unnecessary transfusion also guides our practice of transfusing one unit of red blood cells at a time and reassessing the patient's condition, rather than requesting multiple units for a haemodynamically stable patient who is not actively bleeding.

Clinical judgement is critical in the decision to transfuse. Individual patient characteristics and symptoms should be incorporated into the decision making process. Ideal transfusion practice should offer enough RBC's to improve clinical outcomes while avoiding transfusion reactions following unwarranted transfusions.

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