MASSIVE BLOOD REPLACEMENT IN NEONATES AND CHILDREN

BY

H. G. SCHROEDER AND A. R. FORBES

SUMMARY

Seventeen neonates and small children underwent the operation of wedge excision spinal osteotomy for the correction of gross kyphosis. The operation involved massive blood loss, exceeding 50 per cent of estimated blood volume in all patients, and exceeding 150 per cent in two, with no operative mortality. The anaesthetic technique and management of massive blood replacement in these cases is described. The general problems associated with massive blood transfusion in small subjects are reviewed and discussed. Maintenance of normothermia, and replacement of measured loss with warmed fresh blood with buffering of the acid load are amongst the main recommendations.

Massive blood transfusion, although the subject of exhaustive studies in recent years in adults (Boyan and Howland, 1962; Burton and Holderness, 1964; Holmes, 1966; Burton, 1968), has not been accorded the attention it merits in neonates and infants. The latter, because of innate physiological differences from the adult, present the anaesthetist with special problems, not confined to those of proportion. The present communication is an account of the management of massive blood transfusion during surgical correction of gross kyphosis, with consideration of the difficulties involved.

MATERIAL AND METHOD

The cases presented in this series consist of seventeen neonates and small children with meningomyelocoele and associated hydrocephalus, who have developed gross kyphoscoliotic spinal deformity.

The meningomyelocoele was closed at birth in all cases and the hydrocephalus satisfactorily controlled by a functioning Spitz-Holter valve. The surgical operation was that of excision wedge spinal osteotomy (Sharrard, 1968), which consists of complete resection of the vertebral bodies contributing to the defect, through a posterior approach, continuity of the spine being restored by clipping together the hemivertebrae from each end of the resection. On average one and a half to two and a half vertebrae are excised in order to achieve a functional correction of the deformity. Because of the close proximity to the vertebral venous plexus, there is considerable loss of blood which cannot effectively be diminished by the employment of a hypotensive anaesthetic technique.

The patients can be divided into two groups by age and weight.

Group A. Seven neonates, aged 9 hours to 5 days and weighing 4-6 lb. (2-3 kg).

Group B. Ten small children, age 1½ to 1½ years but weighing 19-55 lb. (10-27 kg). The older children in this group were grossly underweight for their chronological age.

Anaesthetic technique.

Cases in Group A were premedicated with atropine 0.2 mg and vitamin K, 1.0 mg intramuscularly, 40 minutes pre-operatively.

Endotracheal intubation was performed while the neonate was awake, usually following pre-oxygenation; the patient then breathed a mixture of nitrous oxide and oxygen (50 per cent) with halothane vapour to induce surgical anaesthesia. Anaesthesia was maintained by IPPV using a modification of the Ayre T-piece—type 2(a) as described by Harrison (1964)—and an EGC (Sheffield) paediatric ventilator (Mushin et al., 1969).

In Group B, following atropine (0.6 mg) and trimeprazine tartrate 1 mg/lb. (2 mg/kg) oral...
premedication, anaesthesia was induced using either nitrous oxide, oxygen and halothane, or thiopentone 2 mg/lb. (4 mg/kg) followed by suxamethonium 0.5 mg/lb. (1 mg/kg) according to the child's age, and preference. The trachea was then intubated and anaesthesia maintained by IPPV with nitrous oxide, oxygen and tubocurarine hydrochloride 0.3 mg/lb. (0.6 mg/kg) and intermittent halothane, using a Barnet ventilator.

**Position during surgery.**

All patients were placed on the operating table in the prone position, using rolled towels or sandbags to support the shoulders and pelvis, allowing free movement of chest and abdomen.

**Conservation of heat during surgery.**

The patients were laid on a water blanket through which was circulated water from a thermostatically controlled warming bath set to 38–39°C. A mercury thermometer gave a continuous reading of the bath temperature, whilst the blanket temperature and oesophageal temperature were monitored by electric thermometers. A gradient of 2°C was maintained between bath water and patient.

In contact with the anterior aspect of the patient's trunk was a sheet of aluminium foil, replacing the traditional diathermy pad. Aluminium foil has the advantage of being an excellent conductor of heat and avoiding the need for electrode jelly. All pads or pillows were placed beneath the warming blanket. The e.c.g. was monitored throughout on an oscilloscope using standard limb leads.

**Blood loss measurement and replacement.**

Before commencement of surgery a reliable intravenous infusion of Hartmann's solution was established into scalp, umbilical or hand vein. Through this, blood was replaced from a 100-ml calibrated chamber, or by means of a syringe and three-way tap. Blood was warmed before transfusion, by immersion of the bottle in the warming bath and by circulation through an extension tubing taped in contact with the warming blanket.

Blood loss was measured at frequent intervals, using the haemoglobin dilution extraction technique described by Alsop, Emery and Zachary (1963). A correction factor of 25 per cent was applied to allow for the occult loss unmeasured by this method (Thornton et al., 1963; Caceres and Whittenbury, 1959). Loss was replaced using ACD blood, which was as fresh as possible. Positive balance was maintained in anticipation of sudden haemorrhage. In addition to the corrected total measured blood loss, Hartmann's solution was infused in quantities of up to 10 per cent of estimated blood volume. When the total amount of blood lost could not be replaced during the surgical procedure, the deficiency was made up in the immediate postoperative period.

**Calcium administration.**

Exogenous calcium was given intravenously commencing after blood loss had reached 100 ml. Calcium gluconate 1 ml of 10 per cent solution was given for the first 100 ml of blood loss and 0.75 ml for the second and subsequent 100 ml volumes.

**Sodium bicarbonate administration.**

Sodium bicarbonate was given at intervals throughout the operation, as an 8.4 per cent solution (1 m.equiv/ml) intravenously, in the ratio of 0.5 m.equiv/lb. (1 m.equiv/kg) body weight per 25 per cent estimated blood volume lost, commencing therapy after loss of 25 per cent of estimated blood volume (EBV).

An accurate blood and fluid balance chart was returned to the recovery ward with each case.

Duration of operation, including anaesthetic time, varied from 3½ to 4½ hours. Postoperatively patients in Group A were managed prone in an abdominal sling in heated humidified incubators. Patients in Group B were nursed in a plaster shell, prone, on split pillows. The patients were extubated and recovered from the anaesthesia in the prone position.

Investigation of all patients was routine preoperatively and 2–3 hours postoperatively, in respect of haemoglobin, haematocrit, urea, electrolytes and acid-base state. Where indicated these investigations were repeated 24 hours later. Acid-base estimations were made using the Astrup microtechnique on capillary blood samples.

**RESULTS**

**Blood loss.**

Estimated blood volume was calculated as 40 ml/lb. (90 ml/kg) body weight (Mollison, Veall
and Cutbush, 1950). In figure 1 the measured blood loss values are shown plotted against the estimated blood volume, for each patient. In ten patients the measured blood loss lay between 50 and 100 per cent of the estimated blood volume, in five cases between 100 and 150 per cent, and in two cases the measured loss exceeded 150 per cent of estimated blood volume (178 and 182 per cent).

In no case was the measured loss less than 50 per cent of the estimated blood volume.

There was no significant difference between Groups A and B in the percentage of estimated blood volume lost (P>0.01).

**pH results.**

By plotting the pre-operative pH values against the postoperative pH values (fig. 2) it is seen that in all except one case of Group B the pH was maintained within the accepted normal range. The pH estimations of Group A showed a wider distribution, those slightly outside the accepted normal range being on the mildly alkalotic side at 7.46 postoperatively. This is no more than a mild physiological insult and is within the figure of 7.52 quoted following exchange transfusion by Calladine and associates (1965).

**Carbon dioxide tension.**

The mean change in PaO₂ between pre- and postoperative values was 2 mm Hg (SD 8), all but two of the readings falling within the range of 32-46 mm Hg. There was no clear pattern of change, there being five falls and twelve rises in carbon dioxide tension.

**Bicarbonate levels.**

Change in bicarbonate level proved impossible to predict, rises balancing falls. Mean change was a rise of 2 m.equiv (SD 3). It emerged, however, that the rise in pH seen in Group A was not attributable to bicarbonate excess, as in one case only was the postoperative bicarbonate value higher than the pre-operative.

**Serum potassium level.**

There proved to be a wide variation in potassium values, no clear pattern being discernible. The mean change was 0.1 m.equiv/l (SD 0.8). The results in Group B remained within the accepted range of 3.5–5 m.equiv/l, but in Group A values tended to be high both pre- and post-operatively, the highest value recorded being 6 m.equiv/l.
Calcium.

Calcium levels were not measured. As prevailing techniques of measurement do not differentiate between ionized and bound calcium, they have little to offer as aids to management, especially when they must of necessity be retrospective values.

Haemoglobin and haematocrit.

The haemoglobin level and haematocrit showed a slight fall in postoperative values, perhaps indicating that replacement should be with measured whole blood, rather than ACD blood. This would mean an additional correction factor of 20 per cent on measured blood loss. However, another contributing factor to the fall in haemoglobin level could be the low accepted haemoglobin value of stored donor blood (65-75 per cent). The method of measurement of blood loss depends on the constancy of the haemoglobin level of the patient throughout the operation. Any tendency for the haemoglobin level to fall would lead to an underestimation of blood loss, with possible under-replacement of transfused blood.

Temperature conservation.

Except for one case mentioned below, there was no significant fall in temperature recorded during the procedure. This would suggest that measures used to warm both the patient and the infused blood were adequate.

Morbidity and mortality.

One of the neonates whose temperature on admission had been 96°F, and had fallen to 95°F during the procedure, subsequently developed sclerema; this is a recognized complication of hypothermia and surgical procedures (Reader and Williams, 1962; Bower, Jones and Weeks, 1960). The condition responded well to steroid therapy. An older child, following division of a large vertebral plexus vein and consequent sudden massive loss of blood, suffered a cardiac arrest; this was successfully treated by internal cardiac massage, intravenous injection of adrenaline and blood replacement. In a third child an air embolus resulted in severe bradycardia with heart block; this responded to external cardiac massage and administration of atropine intravenously.

Thus the surgical procedure is not without risk, requiring constant vigilance on the part of the anaesthetist.

In the present series there was no operative mortality. One child died 8 days postoperatively of bronchopneumonia, giving a peri-operative mortality of 6 per cent. One child developed postoperative sputum retention which resolved in 24 hours. Seven children from Group B were given blood postoperatively. In the others a dextrose-saline infusion was continued. Postoperative ileus was not seen, sixteen children taking oral fluids within 24 hours and one within 48 hours. All the children maintained a good urine output postoperatively. In one case only was the postoperative urea level above 40 mg/100 ml and this had fallen from 46 to 30 mg/100 ml by the second day.

DISCUSSION

Stewart (1962) has suggested that massive blood replacement consists of the replacement of one-half of the patient's blood volume within 1 hour. The operation of wedge excision osteotomy of the spine qualifies for this definition, as the major part of the blood loss and replacement occurs over a short period, of 30–60 minutes duration, when the vertebrae are being excised. This definition encompasses exchange transfusion, which consists of replacement of twice the patient's blood volume in 2 hours (Diamond, Allen and Thomas, 1951), and with which some parallels with massive blood replacement in neonates are drawn.

Both massive blood replacement and exchange transfusion consist of the rapid infusion of unphysiological ACD blood sometimes leading to a deterioration in electrocardiographic appearances and the condition of the patient (Van Praagh, 1961; Frank and Miraflor, 1968) and well reported as a cause of cardiac arrest due to asystole or ventricular fibrillation (Howland, Boyan and Schweitzer, 1956; McLean and van Tyn, 1961; Boyan and Howland, 1962; Le Veen et al., 1960). The reason for this is probably a combination of the factors examined below.

Metabolic acidosis.

ACD blood, which contains 120 ml acid/citrate/dextrose preservative per unit, together...
MASSIVE BLOOD REPLACEMENT IN NEONATES AND CHILDREN

with high levels of pyruvate and lactate, has a pH when fresh of 6.8–7.0 falling within 21 days to 6.6 (Baue, Herman and Shaw, 1961). The average pH of 3-day-old blood may be as low as 6.5 (Barrie, 1964). Thus one unit of ACD blood has an absolute base deficit of 6–8 m.equiv (Howland, Schweitzer and Boyan, 1965).

When this blood is transfused slowly into an adult, there is a tendency to mild progressive metabolic alkalosis consequent on metabolism of the citrate in the Krebs cycle, but at rapid rates of infusion falls in base excess are found (Burton, 1968) giving metabolic acidosis. By buffering the high acid content with sodium bicarbonate 44.6 m.equiv/5 units blood Howland, Schweitzer and Boyan (1965) were able to abolish the tendency to acidosis, and reduce the mortality in patients receiving 20 or more units, from 38 to 8 per cent. However, in neonates undergoing exchange transfusion, it is usual to find a metabolic acidosis (Povey, 1964), which gives way after 2–3 hours to an alkalosis lasting a few days (Barrie, 1964). Calladine and associates (1965) found that the pH usually remained above 7.1 rising to 7.53. To avoid this acidosis, sodium bicarbonate 1 m.equiv/100 ml blood is recommended and shown to have little effect on the post-transfusion alkalosis (Barrie, 1965; Gandy, Partridge and Gairdner, 1968). THAM has been recommended as a buffer (Baue, Herman and Shaw, 1961) but bicarbonate would seem more rational in the face of a low standard bicarbonate.

This tendency to metabolic acidosis may be accentuated, under general anaesthesia, by pre-operative starvation, by depression of liver and kidney function, and by tissue response to trauma and accumulation of metabolic products. This applies particularly to the neonate, who commonly exhibits a low serum bicarbonate and reduced ability to deal with hydrogen ions (McCance and Hatemi, 1961).

The authors consider it rational to give sodium bicarbonate, in order to avoid the problems of poor perfusion, rise in potassium and reduction in myocardial efficiency attendant on metabolic acidosis. In our series of children who were given sodium bicarbonate 0.5 m.equiv/lb. body wt/25 per cent EBV lost, the highest postoperative pH was 7.46, the corresponding pre-operative value being 7.41.

Respiratory acidosis.

Acidosis may be accentuated by a respiratory component, the PaCO_2 of stored blood being 152–210 mm Hg (Howland and Schweitzer, 1965a), so that adequate pulmonary ventilation is essential. To protect against a rise in PaCO_2 the authors consider it necessary to use IPPV in any patient undergoing massive blood replacement. In the present series, using IPPV, no significant rise in PaCO_2 was seen.

Citrate and calcium.

During infusion of ACD blood there is a linear association between the citrate levels in the body and the rate of infusion, rapid transfusion producing a peak, which will fall again in a warm, well-perfused patient, as the rate is slowed (Burton, 1968). The high levels of citrate associated with rapid transfusion will produce cardiovascular depression and reduction in cardiac output. This is shown by a rise in venous pressure and a fall in arterial pressure, associated with a fall in serum ionic calcium (Bunker et al., 1955) which can be reversed by administration of calcium chloride (Bunker, Bendixen and Murphy, 1962), or gluconate (Burton and Holderness, 1964). Thus Burton (1968) recommends administration of 10 ml of calcium gluconate 10 per cent per litre of blood, when 1.5–2 litres of blood is being given at a rate of 100 ml/min (equivalent to \( \frac{1}{2} \) EBV over 20 minutes). Howland, Schweitzer and Boyan (1964), on the other hand, reported the results obtained in a series of 872 patients receiving 2½ litres of blood or more, without exogenous calcium, with no cases of ventricular fibrillation. During a previous two-year period an unspecified number of patients received calcium and twenty instances of ventricular fibrillation were seen. They suggest that calcium is not only unnecessary, but dangerous. It is suggested that, although the serum ionic calcium level falls initially in the presence of excess citrate, it will rapidly rise again due to the mobilization of skeletal reservoirs (Howland, Jacobs and Goulet, 1960; Howland et al., 1957; Howland, Schweitzer and Boyan, 1964). This is the case in the experimental animal after administration of hypocalcaemic blood (Nakasone et al., 1954), albeit with a fall in body calcium, but evidence in man is inconclusive (Bunker, 1966).
In exchange transfusion, a fall in ionic calcium is found irrespective of total calcium, with no evidence of mobilization of calcium ion to combat it (Farquhar and Smith, 1958). Calcium gluconate is given as 1 ml of 10 per cent solution for each 150 ml blood exchanged (Allen and Diamond, 1957; Barrie, 1965). It is considered essential (Taylor et al., 1961) but there is some doubt as to its efficiency in raising the level of serum ionic calcium (Farquhar and Smith, 1958).

The role of calcium, then, is far from clear. Although it counteracts myocardial depression from a variety of causes (Churchill-Davidson, 1968), notably raised potassium (Taylor et al., 1961) and reduction of serum magnesium levels (Bajpai, Sugden and Sten, 1967), its administration would appear to be unnecessary and even dangerous in adults, unless during very rapid transfusion, or in the presence of citrate intoxication. The electrocardiogram in this situation may show depressed P wave, prolonged QT interval and depressed T wave (Nakasone et al., 1954), but this may be masked by the prolonged QT and raised T of hyperkalaemia (Taylor et al., 1961).

It is, however, suggested that children, especially the newborn, may not have adequate body stores of calcium on which to draw (Howland et al., 1957) and may exhibit impaired citrate metabolism, leading to a fall in serum ionic calcium and making calcium administration necessary (Dybkaer and Elkaer, 1964). The writers think it wise in the present state of knowledge to administer calcium prophylactically to children, and they have seen no cardiac dysrhythmia consequent upon its use.

**Potassium.**

The plasma potassium of stored blood rises from an initial 4–5 m.equiv/l. to 15 m.equiv/l. in 10 days and to 25 m.equiv/l. in 21 days (Dybkaer and Elkaer, 1964). In spite of the administration of hyperkalaemic blood, the authors have found, in common with others (Kliman, 1965; Bunker et al., 1955), no consistent rise in serum potassium. Possible reasons for this include the relatively small absolute amounts of potassium given, transfer to extracellular compartments, storage of potassium in the liver with subsequent excretion (Farquhar and Smith, 1958), and transcellular sodium/potassium exchange (Kliman, 1965).

High serum potassium has been found in exchange transfusions, possibly an accumulative effect (Farquhar and Smith, 1958), and during rapid transfusions in children (Craythorne, 1964). Schweitzer and Howland (1962), who found an incidence of hyperkalaemia of 5 per cent, state that it is not due to the volume of ACD blood transfused but to the presence of a low pH, coupled with tissue trauma. In this context, hyperkalaemia was taken as a serum potassium level exceeding 6 m.equiv/l.

It appears to be a reasonable assumption that, in the absence of massive tissue damage, buffered blood, less than one week old, should not lead to a significant rise in serum potassium.

**Hypothermia.**

Rapid administration of cold stored blood (4°–8°C) will lead to a dramatic fall in the temperature of the recipient (Boyan and Howland, 1961), especially the anaesthetized infant (Harrison, Bull and Schmidt, 1960; Dybkjaer and Elkaer, 1964). A temperature of 30°C leads to a 30–40 per cent reduction in the rate of citrate metabolism (Bunker, 1966), with a concurrent fall in the rate of release of calcium ions. This may produce deterioration of tissue perfusion, metabolic acidosis and a tissue hypoxia accentuated by a shift to the left of the oxygen dissociation curve (Valtis and Kennedy, 1954). The importance of hypothermia in the production of transfusion arrest was stressed by Boyan and Howland (1963), the hypothermic heart being more susceptible to changes in the Ca++/K+ ratio (Marshall, 1962). However, if normothermia is actively maintained and the transfused blood warmed, the heart is not subject to a venous return of cold blood, adequate tissue perfusion is assured, citrate is metabolized, and acid-base, calcium and potassium derangements are minimized. Simply by warming the blood to body temperature, Boyan (1964) reduced the incidence of cardiac arrest during massive blood transfusion of 3 l./hour from 58.3 to 6.8 per cent. Dybkjaer and Elkaer (1964) found that the incidence of ventricular arrhythmias in children was reduced when blood warmed to 37°C was used; they recommend its use in all major operations in children.
On heating blood to 38°C, no alteration in serum potassium or increase in free haemoglobin is found (Howland and Schweitzer, 1965a, b), but it must not be heated above 40°C (Mollison, 1961). The available methods of blood warming are considered elsewhere (Besselring et al., 1965). In infants undergoing long operative procedures, with massive blood replacement, it is essential to warm both the blood transfused and the patient.

Clotting defects.

A haemorrhagic tendency, in the form of oozing from wound surfaces, although not encountered by us, may be found in association with transfusions of one blood volume (Boyan and Howland, 1962) in 4 per cent of patients (Howland and Schweitzer, 1965a). The circulation of a patient who has received one blood volume will contain 62 per cent ACD blood (Weiner and Wexler, 1946), deficient in factors V, VIII and platelets. Depression of factor VII, prothrombin and fibrinogen, and increased fibrinolysis may also be found. Where oozing occurs, this is not related to citrate, but to multiple defects of the above factors (Zucker et al., 1957).

Recommended treatment includes fresh frozen plasma for all factors except platelets, which are supplied by platelet-rich blood. Fibrinogen may be given in hypofibrinogenaemia, and aminocaproic acid in fibrinolytic states (Ulin, Gollub and Erlich, 1960). Aprotinin (Trasylol) may also be of value in haemorrhagic states (Today's drugs, 1966).

Recommendations.

The requirements of massive blood transfusion in neonates and infants are as follows:

1. Maintenance of normothermia by prevention of heat loss throughout the operation.
2. Warming to body temperature all blood transfused.
3. Fresh blood is ideal; stored blood should be less than 1 week old.
4. Maintenance of blood transfusion, through a reliable infusion, in positive balance, with constant reference to a reliable measurement of loss.
5. Buffering of the acid load of the blood by means of sodium bicarbonate 0.5 m-equiv/lb. (1 m-equiv/kg) body weight/25 per cent EBV lost.
6. Intravenous administration of calcium to combat depression of ionic calcium and citrate excess in a dose of 1 ml calcium gluconate 10 per cent for the first 100 ml of blood loss, 0.75 ml for the second and subsequent 100 ml.
7. Maintenance of adequate ventilation by IPPV as an essential protection against respiratory acidosis due to the high PaCO2 of ACD blood.
8. Pre- and postoperative monitoring of acid-base state.
9. Continuous electrocardiographic monitoring during anaesthesia.

REFERENCES


Dix-sept nouveau-nés et petits enfants ont subi une ostéotomie spinale à excision cunéiforme pour correction d’une grave kyphose. L’intervention a causé une perte massive de sang, dépassant 50 pourcent du volume sanguin estimé chez tous les patients, et dépassant 150 pourcent chez deux malades, mais n’a entraîné aucune mortalité opératoire. La technique anesthésique et la méthode de remplacement massif de sang, utilisées dans ces cas sont décrites. Les problèmes d’ordre général, associés à la transfusion massive de sang chez ces petits sujets sont revus et discutés. Le maintien de la normothermie et le remplacement de la perte mesurée par du sang frais préchauffé avec tamponnage de l’acidité figurent parmi les principales recommandations.