Fresh Frozen Plasma Use in a Neonatal Unit in South Africa

by M. Shukri Raban and Michael C. Harrison

SUMMARY

Background: Despite limited evidence, fresh frozen plasma (FFP) transfusions are a relatively common neonatal procedure.

Objectives: Quantify FFP usage in our unit; determine indications for transfusions and compliance with published guidelines.

Methods: Data were retrospectively collected on infants who received FFP from January 2009 to December 2013.

Results: Admissions totalled 10,912 infants during the study period. In total, 113 case notes were reviewed and 142 FFP transfusions were administered. Infants receiving FFP had a high mortality rate (54.87%) and an increased odds ratio for mortality 17.9 (95% confidence interval 12.0–26.6). In total, 75% FFP transfusions were compliant with guidelines. The difference between pre- and post-transfusion coagulation profile in 36.3% of infants was not statistically significant.

Conclusions: FFP was often used in accordance with published guidelines in our neonatal unit. However, the appropriate use and effectiveness of FFP in improving neonatal outcomes undermines the rationale for FFP usage in current guidelines.

KEYWORDS: Fresh frozen plasma, FFP, infant, transfusion, coagulation.

INTRODUCTION

Fresh frozen plasma (FFP) is human donor plasma produced either from a single whole-blood donor unit or obtained by plasmaphoresis [1].

Despite limited indications for the use of FFP in infants [2], FFP transfusions appear to be a relatively common neonatal procedure. Recent retrospective studies reported that 6 and 12% of admitted infants received FFP transfusions [3, 4]. In a prospective study by Motta et al., 8% of infants admitted to Italian neonatal intensive care units received one or more FFP transfusions [5]. Most concerning is the significant proportion of inappropriate use of FFP. Motta et al. reported 60% non-compliance with published guidelines with 63% of the transfused infants receiving FFP as prophylaxis, without evidence of haemorrhage [5]. Coagulation times in infants, particularly preterm, are longer than in adults and not necessarily related to the risk of bleeding [6]. Abnormal coagulation test results, in the absence of symptoms or haemorrhagic risk, are not an indication for an FFP transfusion [6].

There is limited outcomes-based evidence for the use of FFP transfusions in the neonatal population. The Neonatal Nursing Initiative assessed the routine use of FFP to treat coagulopathy in the absence of bleeding, and showed no reduction in morbidity or mortality [7]. A subsequent systematic review and
meta-analysis reported no improvement in clinical outcomes comparing FFP with colloid or no transfusion [8]. Consequently, we aimed to (i) quantify FFP usage in a South African neonatal unit and determine indications for the transfusions; and (ii) to determine compliance with published guideline recommendations.

METHODS
The study was conducted at Groote Schuur Hospital (GSH), a tertiary-level neonatal unit in Cape Town, South Africa. The study was approved by the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee.

Data were collected retrospectively of all infants who received FFP transfusions over a 5 year period from the 1 January 2009 to the 31 December 2013. The total number of FFP transfusions performed in the neonatal unit at GSH as well as the corresponding patient’s name and case notes number were extracted from the Western Province Blood Transfusion Service (WPBTS) database. The patient’s case notes were cross referenced and the following baseline data were collected: gestational age, birth weight, postnatal age at transfusion, need for ventilatory and inotropic support, mortality, pre-transfusion and post-transfusion coagulation tests if done and pre-transfusion platelet count if done. Pre-transfusion and post-transfusion laboratory tests were only considered if they were performed within 24 h before and up to 24 h after the FFP transfusion. The indications for the FFP transfusions were also collected. These were compared against the neonatal indications for FFP transfusions in the handbook, ‘Guidelines of the South African National Blood Transfusion Service’ [2]. These indications include: haemorrhagic disease of the newborn secondary to Vitamin K deficiency where the infant is actively bleeding; bleeding (or high risk of bleeding) and abnormal coagulation profile; treatment of congenital deficiencies of single clotting factors, when the specific concentrate is not available and the infant is bleeding; and infants with a coagulopathy about to undergo an invasive procedure. Data collection also included the type of haemorrhage as an indication for FFP transfusion. Haemorrhages were categorized into intraventricular haemorrhages (IVH) diagnosed by ultrasound and graded according to Papile [9] classification; pulmonary haemorrhage was defined as a significant amount of blood suctioned from the endotracheal tube with a chest radiograph consistent with pulmonary bleeding; gastrointestinal haemorrhage evident by blood suctioned from the stomach, gross or occult blood in the stools and minor haemorrhages, which included a history of mucocutaneous bleeds. Infant reference ranges of coagulation tests were based on published laboratory data [10–12].

DATA ANALYSIS
The WPBTS data were exported to a Microsoft Excel file. Data were analysed with Stata version 12 (Stata Corporation, College Station, USA). The characteristics of study infants were analysed by descriptive statistics. Continuous variables with symmetrical distribution were presented as mean and standard deviation. Comparisons between pre-transfusion and post-transfusion coagulation tests were performed using unpaired t-tests. The odds ratio (OR) for mortality was calculated using the mortality for FFP exposed infants, mortality for non-exposed infants and the number of FFP exposed and non-exposed infant survivors. Descriptive results are expressed as numbers and proportions (%). A p value <0.05 was considered significant.

RESULTS
During the 5 year period, 10,912 infants were admitted to the GSH neonatal unit. The WPBTS data identified 124 infants who received FFP transfusion during this period. Three infants were excluded; for one infant the FFP was prescribed but not administered as a senior clinician deemed that the infant was not for further escalation of care, the remaining two infants had blood issued by the blood bank but we could find no prescription for the FFP or proof of administration. We were unable to locate eight infant’s case notes. One hundred and thirteen case notes were reviewed in the final analysis and 142 FFP transfusions were administered (transfusion/patient ratio = 1.26).

The pre-transfusion characteristics of the infants are described in Table 1. FFP transfusions were
Table 1. Pre-transfusion patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Results</th>
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<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
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<tr>
<td>No. of infants &lt;28 weeks (%)</td>
<td>14 (12.4)</td>
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<tr>
<td>No. of infants 28–34 weeks (%)</td>
<td>72 (63.7)</td>
</tr>
<tr>
<td>No. of infants &gt;34 weeks (%)</td>
<td>27 (23.9)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>1190 (1020–1730)</td>
</tr>
<tr>
<td>Postnatal age at transfusion (days)</td>
<td>4 (2–8)</td>
</tr>
<tr>
<td>Dose of FFP (ml/kg)</td>
<td>15 (10–18)</td>
</tr>
<tr>
<td>Pre-transfusion INR</td>
<td>2.38 (1.85–4.05)</td>
</tr>
<tr>
<td>Pre-transfusion PTT (seconds)</td>
<td>59 (44.5–87)</td>
</tr>
<tr>
<td>Pre-transfusion fibrinogen (mg/dl)</td>
<td>2 (1.1–2.9)</td>
</tr>
<tr>
<td>Pre-transfusion platelets (×10^9/l)</td>
<td>106 (51–202)</td>
</tr>
<tr>
<td>No. of infants requiring mechanical ventilation (%)</td>
<td>98/113 (86.7)</td>
</tr>
<tr>
<td>No. of infants requiring inotropic support (%)</td>
<td>80/113 (70.8)</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td></td>
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<tr>
<td>Mortality in &lt;28 week infants (%)</td>
<td>6/14 (42.85)</td>
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<tr>
<td>Mortality in 28–34 week infants (%)</td>
<td>43/72 (59.72)</td>
</tr>
<tr>
<td>Mortality in &gt;34 week infants (%)</td>
<td>13/27 (48.15)</td>
</tr>
<tr>
<td>No. of infants presenting with haemorrhage (%)</td>
<td>41/113 (36.3)</td>
</tr>
<tr>
<td>Types of haemorrhage; number of infants (%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>25/41 (61.0)</td>
</tr>
<tr>
<td>IVH all grades</td>
<td>8/41 (19.5)</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>5/41 (12.2)</td>
</tr>
<tr>
<td>Subaponeurotic haemorrhage</td>
<td>3/41 (7.3)</td>
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*Mean (range) unless specified otherwise.

administered more often to preterm infants; 76.1% <34 weeks gestation with a mean gestational age of 31 weeks. Most of the FFP transfusions were administered within the first week of life; by day 3 postnatal age, 45.8% of FFP transfusion were administered, 60.6% by day 5, 81.7% by day 14 and 88.7% by day 28. Infants who received FFP had a high mortality rate (54.87%) and they had an increased OR for mortality 17.9 [95% confidence interval (CI) 12.04–26.6]. Of the 113 infants who received FFP, only 41 (36.3%) presented with haemorrhage; pulmonary haemorrhage the commonest cause.

Table 2 describes the indications for which the FFP transfusions were administered. One hundred and two (75%) of the FFP transfusion were judged to be in accordance with the ‘Guidelines of the South African National Blood Transfusion Service’ [2], whereas 34 (25%) were inappropriate transfusions. Among the appropriate indications for FFP transfusion, high risk of bleeding combined with coagulopathy was the commonest indication.

The total cost for the FFP transfusions was 57 440 ZAR (South African rand). For transfusions administered according to published guidelines, the cost totalled 43 772 ZAR whereas 13 968 ZAR was spent on inappropriate transfusions.

Table 3 compares the coagulation profile of the infant pre- and post-transfusion. In the infants <28 weeks and those >34 weeks the pre-transfusion and post-transfusion values did not show statistically significant differences. In the 28–34 week group of infants, FFP response was statistically significant for international normalized ratio (INR) and partial thromboplastin time (PTT) but was not for fibrinogen.
DISCUSSION

As opposed to erythrocyte and platelet transfusions, current recommendations for FFP transfusions are based on limited data [4]. Despite the paucity of evidence for efficacy, FFP transfusions remain popular among clinicians; Veljkovic et al. [13] reported that 60% recipients of FFP at the Institute for Mother and Child Health Care of Serbia were <1 year old. The GSH neonatal unit did not have a written standardized protocol to inform FFP transfusion decisions during the 5 year study period. These decisions were left to the discretion of the individual attending senior clinicians. Unlike previous retrospective studies [3, 4], our study found that only 1% of the infants admitted to the neonatal unit received FFP transfusions, significantly lower than previously reported.

A prospective study by Motta et al. [5] as well as retrospective studies by Baer et al. [3] and Puetz et al. [4] reported a remarkably significant non-compliance to published guidelines for FFP transfusion. Interestingly, 75% of the transfusions in our study were compliant with published guidelines. The risk of death in the FFP-transfused infants in this study is high, similar to Motta et al. [5] reporting OR for mortality 6.3 (95% CI 4.9–7.8) and 40% mortality reported by Altuntas et al. [18]. One explanation may
be that the FFP-transfused infants were sick, with many requiring cardiorespiratory support.

The FFP transfusions showed statistically significant improvement in infants 28–34 weeks gestational age but did not result in statistically significant differences in the coagulation profiles in 36.3% of infants in this study (infants <28 weeks and >34 weeks). This is not surprising as Abdel-Wahab et al. demonstrated that <1% of patients fully corrected PT/INR and only 15% partially normalized their PT/INR following FFP transfusion for mild coagulation abnormalities. Regarding the efficacy of FFP to correct abnormal coagulation profiles, Johnson et al. [19] note that the correction of the coagulation profile was neither predictable nor consistent; only 7 of 23 (30%) had a full correction of PT and activated partial thromboplastin time (APTT).

The dose of FFP may also contribute to its poor effect to correct the coagulation profile. An FFP dose of 10 ml/kg should raise most coagulation factor levels by only 10 U/dl (10%) [4]. If the pre-transfusion coagulation factors are significantly low, a dose of 10 ml/kg will be rendered ineffective. A total of 42.6% of infants received a dose of ≤12 ml/kg during the 5 year period.

CONCLUSION
Adopting and implementing evidence-based guidelines ensures safe patient care of high quality, while also allocating much needed resources cost-effectively. Achieving these goals for FFP administration is particularly challenging. Coagulation profiles in infants differ from adults and vary according to gestational and postnatal age [20]. In addition there are few studies in the neonatal population guiding the treatment of coagulation abnormalities and therapeutic targets [1]. The assessment of ‘high risk’ for bleeding is fraught with problems. ‘High risk’ is neither defined by gestational age nor severity of the coagulation abnormality. Reference ranges have been established by Andrew et al. [10, 11] and more recently by Christensen et al. [12]; however, the authors caution the use of these reference ranges pending further studies supporting its use in evidence-based protocols. Standard coagulation has a limited utility as a predictor of bleeding. Appreciating the limitations of the coagulation screening test is imperative as well as understanding that in vitro abnormalities of coagulation may not equate with in vivo failure of the clinical haemostasis and clinical coagulopathy [1]. Therefore, in practice FFP use should be confined to therapeutic rather than prophylactic use in the bleeding infant with a coagulation abnormality.

Further research is needed to objectively assist in the assessment and management of coagulation abnormalities in the non-bleeding infant.

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REFERENCES