

## Preoperative transfusion in patients with sickle-cell disease



The preoperative management of children and adults with sickle-cell disease frequently includes transfusion of red blood cells to reduce the risk of procedure-related morbidity and mortality.<sup>1,2</sup> Perioperative disorders, including suboptimum hydration, acid-base imbalance, and poor oxygenation, can lead to substantial complications, such as acute chest syndrome, painful crises, and infections. Maintenance of good perioperative conditions,<sup>3</sup> use of advanced surgical techniques (eg, laparoscopy) and optimum anaesthesia practices, and reductions in the duration of hospital stays might mitigate these risks.

Jo Howard and colleagues<sup>4</sup> undertook the long-needed<sup>5</sup> Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) prospective, randomised trial of preoperative transfusion compared with no preoperative transfusion in patients with sickle-cell disease who were scheduled to undergo low-risk or medium-risk surgery. Children and adults with haemoglobin SS (HbSS) or  $\text{S}\beta^0$ thalassaemia sickle-cell-disease subtypes were enrolled. Patients with haemoglobin concentrations lower than 65 g/L and oxygen saturation less than 90%, who were undergoing or had a history of renal dialysis, had a history of acute chest syndrome in the previous 6 months, or had received a blood transfusion in the previous 3 months were excluded, as were children with a clinical history of stroke. The trial was terminated early because of safety concerns when a marked increase in severe adverse events (almost all acute chest syndrome) was seen in the no-preoperative-transfusion group. Allo-immunisation was seen in only one patient, possibly because of extended red-blood-cell phenotyping that included full-Rhesus phenotype (Cc/D/Ee) and K1 antigen. Preoperative blood transfusion did not eliminate the need for intraoperative or postoperative transfusions.

Randomised controlled trials such as TAPS are difficult to do because, owing to various reasons such as socio-economic and health circumstances, recruitment is challenging. In this multinational study, 343 patients were screened but only 70 (20%) were successfully recruited. Only around a third of excluded patients were deemed ineligible. Other prominent reasons for exclusion were decisions by the treating clinicians (73 [21%]), refused consent (58 [17%]), and logistical reasons (43 [13%]). The main reasons for ineligibility were transfusion

within the previous 3 months (58 [59%]), haemoglobin concentration lower than 65 g/L (16 [16%]), and acute chest syndrome within the previous 6 months (12 [12%]). The proportion of patients who declined to participate was similar to that in the cholecystectomy substudy of the National Preoperative Transfusion Study.<sup>6</sup> Of those excluded from TAPS by clinicians, 32 (44%) were scheduled to undergo orthopaedic surgery. This finding suggests that the clinicians believe that orthopaedic procedures are associated with increased risk.<sup>7</sup> The data from TAPS provide important information that can be used to improve enrolment of patients with haemoglobinopathies in future trials; useful approaches might be to improve dissemination of relevant information to treating clinicians and potential participants, employ a neutral ombudsman, and ensure adequate financial support to address logistical problems.

Several important issues were not fully addressed by the TAPS study. How to manage patients with high baseline haemoglobin concentrations (90 g/L or higher), which is expected in around a quarter of patients with the HbSS subtype, remains unclear. The study protocol called for exchange transfusion (in the preoperative-transfusion group) for such patients, but only five were enrolled, which was too small a number to draw any clear conclusions on efficacy. Additionally, the option of using a series of small simple (top-up) transfusions over 4–6 weeks was not explored. This approach might accomplish the same goals as exchange transfusion

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without the technical difficulties, although it is done at the cost of exposure to a greater number of units of transfused cells.

A related question that was not addressed was the management of individuals with the haemoglobin SC (HbSC) sickle-cell-disease subtype. Data from the Cooperative Study of Sickle Cell Disease<sup>3</sup> indicated that sickle-cell-related surgical complication rates are similar in patients with the HbSC and HbSS subtypes undergoing abdominal surgery or orthopaedic procedures. For example, individuals with the HbSC subtype who underwent cholecystectomy or splenectomy had a sickle-cell-related complication rate of 9%, compared with 8% in those with the HbSS subtype. Among patients with the HbSC subtype who underwent abdominal procedures, preoperative transfusion was associated with no sickle-cell-related complications, whereas no transfusion was associated with a 35% complication rate (acute chest syndrome or vaso-occlusive crises). Most patients with the HbSC subtype have baseline haemoglobin levels of at least 90 g/L and, therefore, how to manage patients with high haemoglobin concentrations is also pertinent in these patients.

How patients who are scheduled to undergo low-risk operations (placement of pressure-equaliser tubes, dental extractions, insertion of indwelling vascular access lines, etc) should be managed could not be answered by TAPS. The number of patients who underwent low-risk surgery was only 13 and, therefore, subgroup analysis was not possible.

The TAPS investigators conclude that patients with HbSS who have baseline haemoglobin concentrations lower than 90 g/L and are scheduled to undergo low-risk or medium-risk surgery should receive preoperative transfusion to reduce the risk of perioperative acute chest syndrome. This conclusion is consistent with data from the randomisation-declined, transfusion-refused arm of the National Preoperative Transfusion in Sickle Cell Disease Study,<sup>6</sup> in which the sickle-cell-related complication rate among patients with cholecystectomy who received no transfusion was 32%. Further conclusions from TAPS were constrained by nearly 80% of potential participants not being recruited.

Whether the financial resources for future randomised trials of transfusion management of surgery in individuals with sickle-cell disease will be available is

uncertain. Therefore, lower-quality evidence, such as that obtained by registries, might offer the best data with which to address unanswered questions. The UK National Haemoglobinopathy Registry has been set up to improve treatment services through the collection of data on the demographic characteristics, treatment, and disease complications of patients with haemoglobinopathies. Support by the National Heart, Lung and Blood Institute for a US registry with a biorepository (by consent) is being preceded by a surveillance pilot study (Registry and Surveillance System for Hemoglobinopathies [RuSH]). This effort responds to the National Heart, Lung and Blood Institute Strategic Plan, which aims to further understanding of the clinical mechanisms of diseases and thereby improve prevention, diagnosis, and treatment. Both of these national initiatives could provide important information about potential predictors of surgical outcomes, including genomic features that affect responses to sepsis,<sup>8</sup> prediction of renal failure,<sup>9</sup> and links to asthma, to help determine future transfusion practices.

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