Hydroxycarbamide and erythropoietin in the preoperative management of children with sickle cell anaemia undergoing moderate risk surgery

Surgery in patients with sickle cell anaemia (SCA) has a high complication rate. The Cooperative Study of Sickle Cell Disease in the USA found that overall mortality was 1·1% within 30 d of surgery (Koshy *et al*, 1995). In the same study, 22% patients with SCA undergoing cholecystectomy or splenectomy suffered complications including acute sickle pain (5·4%) and acute chest syndrome (2·8%) (Koshy *et al*, 1995). Preoperative transfusion is frequently used to try and reduce the risk of surgery, although its exact role is not established. In a randomised controlled trial, exchange transfusion was shown to confer no benefit over simple transfusion in moderate or low risk surgery (Vichinsky *et al*, 1995). However, it is not clear whether transfusion of any sort is of benefit in this sort of surgery, and this question is currently the subject of a randomised controlled trial (http://www.ctu.mrc.ac.uk/studies/taps.asp). The lack of evidence is particularly difficult when advising patients who do not wish to have blood transfusions for religious or personal reasons. We present three children with SCA undergoing surgery that declined transfusion and were managed with hydroxycarbamide and erythropoietin. All were already taking folic acid.

Patient 1 was a girl who had one hospital admission aged 4 years for acute anaemia caused by Parvovirus B19 infection and required a blood transfusion. When aged 7 years she had evidence of obstructive sleep apnoea and adenotonsillectomy was planned. Her steady-state haemoglobin preoperatively was 65–70 g/l and her transcranial Doppler (TCD) scan was normal. Her parents were Jehovah's Witnesses and wanted to avoid blood transfusion if at all possible. Following discussion of the risks and benefits of hydroxycarbamide and erythropoietin, combined therapy was started (Table I). The haemoglobin and HbF% increased and there were no adverse effects, such as hypertension, myelosuppression or renal dysfunction. The operation proceeded uneventfully with no surgical or haematological complications. Erythropoietin was stopped immediately postoperatively, and the hydroxycarbamide continued for a further 2 weeks.

Patient 2 was the sister of patient 1, and had two admissions in infancy with pain. She was admitted with acute anaemia aged 8 years secondary to Parvovirus B19 infection, necessitating blood transfusion. She had delayed speech and language development. A TCD scan at the age of 10 years was abnormal with a peak velocity of 205 cm/s in the left middle cerebral artery, confirmed on repeat scanning. A magnetic resonance imaging scan of her brain showed no evidence of ischaemic damage. The increased risk of stroke was discussed with her parents and in view of their religious beliefs the decision was taken to start hydroxycarbamide as an alternative to a transfusion programme. Her steady-state haemoglobin was 65 g/l prehydroxycarbamide treatment. An adenotonsillectomy was planned for obstructive sleep apnoea. Following discussion, it was decided to add erythropoietin preoperatively. A sustained rise in haemoglobin and HbF% was seen (Table I). There were no side-effects. The maximum intracerebral blood velocity, assessed by TCD scan, decreased while on hydroxycarbamide and was normal after 2 years. Erythropoietin was discontinued after surgery and the patient remained on hydroxycarbamide.

Patient 3 was a girl who had multiple admissions to hospital in the first 18 months of life with recurrent chest infections and splenic sequestration requiring transfusion at the age of 1 year. Aged 6 years she developed cholecystitis and was found to have gall stones. Over the next two years she had several further episodes of cholecystitis but her parents were reluctant to proceed with a cholecystectomy. Aged 8 years, her parents agreed to this operation, and the possibility of perioperative transfusion discussed, including the option of entering the TAPS (Transfusion Alternatives Preoperatively in Sickle Cell Disease) study. Her mother was desperate to avoid transfusion and the option of using preoperative hydroxycarbamide and erythropoietin was discussed. Her steady-state haemoglobin was 70–80 g/l pre treatment. Hydroxycarbamide and erythopoietin were both given for 1 month preoperatively with increases in haemoglobin and HbF% (Table I), and no toxicity. Laparoscopic cholecystectomy was performed uneventfully. She stopped hydroxycarbamide 1 week postoperatively.

The families of these children wanted to avoid blood transfusion if possible. However, in all three there were reasons for considering preoperative transfusion, including low haemoglobin (patients 1 and 2), abnormal TCDs (patient 2) and history of frequent episodes of acute pain and chest problems (patient 3). The combination of hydroxycarbamide and erythropoietin offers the potential benefit of a fairly rapid increase in haemoglobin and HbF levels, with additional antisickling benefits from hydroxycarbamide, including improved nitric oxide metabolism and reduced expression of adhesion molecules (Little *et al*, 2006). Although the laboratory changes were relatively small in our patients, they are likely to offer significant clinical benefit. In addition, the increased preoperative haemoglobin reduced the likelihood of postoperative transfusion, which is a particular problem following

Table I. Maximum changes in relevant haematological parameters associated with preoperative hydroxycarbamide (HC) and erythropoietin (EPO) use.

		Patient 1	Patient 2	Patient 3
Hydroxycarbamide mg/kg/d		16 3·5 months	30 long term	17 1 month
Erythropoietin IU/kg (twice/week)		100–200 2 months	100–200 2 months	100–200 1 month
Haemoglobin (g/l)	Steady-state	70 g/l	65	74
	Peak	83	79	81
	Change (%)	+19	+22	+9·5
HbF%	Steady-state	10·5	7·5	1·5
	Peak	13·8	11·2	4·5
	Change (%)	+38	+49	+200
Absolute HbF (g/l)	Steady-state	7·0	4·9	1·1
	Peak	11·0	8·8	3·6
	Change (%)	+57	+79	+227
Reticulocytes	Start HC/EPO	252	319	410
	Preop	343	158	385
	Change (%)	+36	−50	−6
Neutrophils	Start HC/EPO	3·6	6	3·8
	Preop	7·4	3·8	2·0
	Change (%)	+105	−37	−47
Lactate dehydrogenase	Start HC/EPO	505	692	513
	Preop	564	602	522
	Change (%)	+12	−13	+1·8

tonsillectomy. This approach may be useful in Jehovah's Witnesses or others with a very strong desire to avoid transfusion. Blood transfusion remains the treatment of choice in the management of complicated patients with sickle cell disease undergoing moderate risk surgery, but preoperative hydroxycarbamide and erythropoietin is a potential alternative, and could be studied in appropriate clinical trials.

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