Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG)

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Summary

Background Sickle-cell anaemia is associated with substantial morbidity from acute complications and organ dysfunction beginning in the first year of life. Hydroxycarbamide substantially reduces episodes of pain and acute chest syndrome, admissions to hospital, and transfusions in adults with sickle-cell anaemia. We assessed the effect of hydroxycarbamide therapy on organ dysfunction and clinical complications, and examined laboratory findings and toxic effects.

Methods This randomised trial was undertaken in 13 centres in the USA between October, 2003, and September, 2009. Eligible participants had haemoglobin SS (HbSS) or haemoglobin Sβ⁰thalassaemia, were aged 9–18 months at randomisation, and were not selected for clinical severity. Participants received liquid hydroxycarbamide, 20 mg/kg per day, or placebo for 2 years. Randomisation assignments were generated by the medical coordinating centre by a pre-decided schedule. Identical appearing and tasting formulations were used for hydroxycarbamide and placebo. Patients, caregivers, and coordinating centre staff were masked to treatment allocation. Primary study endpoints were splenic function (qualitative uptake on ^{99}Tc spleen scan) and renal function (glomerular filtration rate by ^{99m}Tc-DTPA clearance). Additional assessments included blood counts, fetal haemoglobin concentration, chemistry profiles, spleen function biomarkers, urine osmolality, neurodevelopment, transcranial Doppler ultrasonography, growth, and mutagenicity. Study visits occurred every 2–4 weeks. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00006400.

Findings 96 patients received hydroxycarbamide and 97 placebo, of whom 83 patients in the hydroxycarbamide group and 84 in the placebo group completed the study. Significant differences were not seen between groups for the primary endpoints (19 of 70 patients with decreased spleen function at exit in the hydroxycarbamide group *vs* 28 of 74 patients in the placebo group, p=0·21; and a difference in the mean increase in DTPA glomerular filtration rate in the hydroxycarbamide group versus the placebo group of 2 mL/min per 1·73 m², p=0·84). Hydroxycarbamide significantly decreased pain (177 events in 62 patients *vs* 375 events in 75 patients in the placebo group, p=0·002) and dactylitis (24 events in 14 patients *vs* 123 events in 42 patients in the placebo group, p<0·0001), with some evidence for decreased acute chest syndrome, hospitalisation rates, and transfusion. Hydroxyurea increased haemoglobin and fetal haemoglobin, and decreased white blood-cell count. Toxicity was limited to mild-to-moderate neutropenia.

Interpretation On the basis of the safety and efficacy data from this trial, hydroxycarbamide can now be considered for all very young children with sickle-cell anaemia.

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Introduction

Sickle-cell anaemia is characterised by haemoglobin polymerisation that results in sickle-shaped red blood cells, vaso-occlusion, haemolytic anaemia, and vasculo-endothelial dysfunction, causing pain, organ injury, and early mortality. Clinical symptoms begin in the first year of life, with a physiological decline in fetal haemoglobin concentration. Higher concentrations of fetal haemoglobin are associated with fewer pain crises[1] and improved survival.[2] Hydroxycarbamide is an antineoplastic drug that inhibits ribonucleotide reductase, increases fetal haemoglobin concentration in red blood cells, and has other potentially beneficial effects, including improved nitric oxide metabolism, reduced red cell–endothelial interaction, and decreased erythrocyte density.[3] 15 years ago the double-blind placebo-controlled Multi-Center Study of Hydroxyurea (MSH) in adults with severe sickle-cell anaemia showed that hydroxycarbamide substantially reduced episodes of pain and acute chest syndrome, admissions to hospital, and transfusions.[4] Subsequently, smaller studies have shown similar benefits and few toxic effects in school-age children and adolescents.[5]

In 2000, the US National Heart, Lung, and Blood Institute (NHLBI) awarded a competitive contract to test in a clinical trial whether hydroxycarbamide given to

Panel 1: Definitions of adverse events

Acute chest syndrome
Clinical syndrome characterised by a new pulmonary infiltrate and at least three of the following: chest pain, temperature greater than 38·5°C, tachypnoea, wheezing, or cough.

Pain event
Pain in the arms or legs, back, abdomen, chest, or head with no other explanation, lasting at least 2 h, and requiring non-steroidal anti-inflammatory or narcotic analgesia. Events managed at home were included.

Dactylitis
Pain and tenderness with or without swelling, limited to the hands and feet.

Splenic sequestration
Increase in palpable spleen size by 2 cm or more below the costal margin from the last examination, accompanied by a decrease in haemoglobin of 20 g/L or more, or 20% or more from steady-state values.

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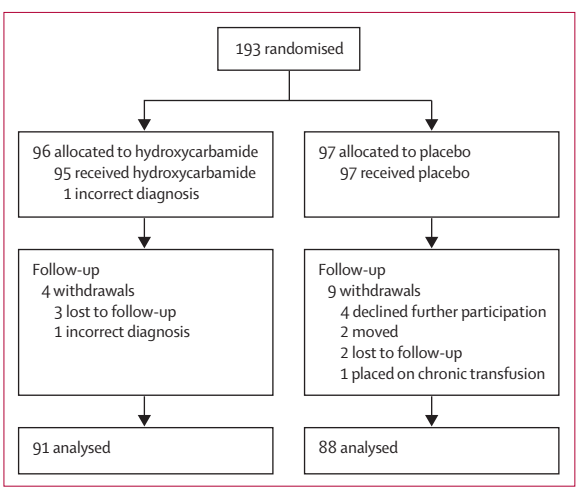

Figure 1: **Trial profile**

	Hydroxycarbamide (N=96)	Placebo (N=97)
Age (months)	13·6 (2·7)	13·5 (2·8)
Boys	44 (46%)	40 (41%)
Sickle-cell disease type		
HbSS	94 (98%)	93 (96%)
Hb Sβ⁰thalassaemia	2 (2%)	4 (4%)
Hospitalisations before study enrolment	65 (68%)	70 (73%)
Dactylitis before study enrolment	31 (33%)	39 (41%)
Pain events before study enrolment	25 (27%)	26 (27%)
Acute chest syndrome before study enrolment	3 (3%)	5 (5%)
Splenic sequestration before study enrolment	5 (5%)	10 (11%)
Transfusion before study enrolment	10 (11%)	17 (18%)
Spleen scan uptake		
Normal	8 (8%)	13 (13%)
Present but decreased	73 (76%)	72 (74%)
Absent	15 (16%)	12 (12%)
GFR (mL per min per 1·73 m²)	126 (39)	124 (30)
Haematological measurements		
Haemoglobin concentration (g/L)	90 (13)	92 (13)
Percentage of haemoglobin as fetal haemoglobin	25·9% (8·5)	26·0% (8·5)
White blood-cell count (×10³ per μL)	14·3 (5·3)	14·3 (5·9)
Platelet count (×10³ per μL)	365·5 (125·2)	375·0 (126·7)
CNS measurements		
Transcranial doppler ultrasound time-averaged mean maximum velocity (cm/s)	124 (22)	120 (22)

Data are mean (SD) or number (%) unless stated otherwise. HbSS=haemoglobin SS. GFR=glomerular filtration rate.

Table 1: **Baseline patient characteristics**

infants with sickle-cell anaemia for 2 years slows or prevents organ damage. In a pilot trial (HUSOFT),[6] very young children with sickle-cell anaemia tolerated a liquid hydroxycarbamide formulation (20 mg/kg per day), and had improved blood counts and fetal haemoglobin concentrations compared with predicted age-specific levels.[6] After 2 years, splenic radionuclide uptake was absent in only 47% of children, although 80% absence was predicted, leading to the choice of splenic function as a primary endpoint for the Pediatric Hydroxyurea in Sickle Cell Anemia (BABY HUG) trial. Because glomerular filtration rate (GFR) is abnormally increased early in life in children with sickle-cell anaemia, and can lead to progressive renal dysfunction,[7] we also assessed the effect of hydroxycarbamide on GFR as a primary endpoint.

We designed the BABY HUG trial to determine whether hydroxycarbamide safely prevents early damage to the spleen and kidneys in infants with sickle-cell anaemia. We also aimed to assess the effect of hydroxycarbamide on adverse clinical events, blood counts, additional aspects of organ function, and toxic effects.[8]

Methods

Patients

Participants aged 9–18 months were recruited between October, 2003, and September, 2007, at 13 trial centres in the USA. After written informed consent was obtained from their parents or guardians, potential study participants were assessed to establish eligibility and baseline status. An ombudsman was present at each site to promote understanding of the risks and demands of study participation. An unmasked so-called primary endpoint person monitored laboratory values and assisted in clinical management, and a feasibility and safety pilot study was done to assess toxicity in the first 40 participants.[8] Initial assessments were repeated at study exit.

Eligible participants had HbSS or Sβ⁰thalassaemia, and were enrolled irrespective of clinical severity. All participants received standard age-appropriate care for sickle-cell anaemia, including penicillin prophylaxis, pneumococcal immunisation, and parental education.

Participants were excluded for transfusion within 2 months; height, weight, or head circumference less than the fifth percentile; mental developmental index (MDI) less than 70; or abnormal transcranial doppler ultrasound (TCD) velocity.[8]

Ethics approval was obtained from a National Institutes of Health Protocol Review Committee and from each local centre's institutional review board.

Randomisation and masking

Participants were randomly assigned to either hydroxycarbamide (20 mg/kg per day) or placebo for 2 years, in a 1:1 ratio.[8] The randomisation sequence was pre-decided by a randomisation schedule developed for each clinical site by the medical coordinating centre. Double-blind randomisation was done with an automated telephone response system and the use of a random three digit kit number for each enrolled participant. The kit number, which was linked to the assignment sequence, was used by the drug distribution centre to ship the appropriate study drug to the clinical site pharmacy. Hydroxycarbamide and placebo powders had the same appearance and packaging and the liquid formulations had the same appearance and taste. Hydroxyurea and placebo were distributed to clinical centres in encoded kits. Local pharmacists reconstituted powder with syrup and water to a concentration of 100 mg/mL,[9] and dispensed a 35-day supply. As in the HUSOFT trial,[6] there was no dose escalation. Participants, caregivers, and medical coordinating centre staff were masked to treatment allocation.

Procedures

Masked readings of splenic uptake on ^{99m}Tc-sulphur colloid liver-spleen scans were categorised qualitatively as normal, decreased (but present), or absent. We proposed that a decline in splenic uptake (from normal to decreased or absent, or from decreased to absent) would occur 50% less frequently in the hydroxycarbamide group than in the placebo group. GFR with ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) plasma clearance was chosen as a coprimary endpoint, with an anticipated 0·6 SD difference.[10] Assessment of this

	Hydroxycarbamide	Placebo	Difference* (95% CI)	Effect size	p value†
Decreased spleen function at exit (compared with baseline)	19/70‡ (27%)	28/74‡ (38%)	–11% (–26 to 5)	–28%	0·21

*Difference in the proportion of evaluable patients with decreased splenic function in the hydroxycarbamide group versus the placebo group. †p value is from Fisher's exact test, comparing distributions between the two treatment groups. ‡Per protocol, excludes patients who had absent splenic uptake at entry and those who did not have spleen scan results at exit. An intention-to-treat analysis with multiple imputations was done, which produced the same results (data not shown).

Table 2: **Spleen function (primary endpoint)**

	Hydroxycarbamide				Placebo				Difference† (95% CI)	Effect size	p value‡
	N*	Entry	Exit	% difference	N*	Entry	Exit	% difference			
Mean DTPA GFR (mL/min per 1·73 m^2)	67	123	146	18%	66	125	146	17%	2 (–16 to 20)	0·04	0·84

DTPA=diethylenetriaminepentaacetic acid. GFR=glomerular filtration rate. *Total number of patients assessed for each endpoint. N differs from the number reported in table 1 because only entry values that are paired with exit values from the same patient are included. †Difference in the mean increase in DTPA GFR in the hydroxycarbamide group versus the placebo group. ‡p value is from a *t* test statistic comparing the exit versus entry difference in means between the two treatment groups.

Table 3: **DTPA GFR (primary endpoint)**

	Hydroxycarbamide	Placebo	Difference* (95% CI)	p value†
Pitted cell counts ≥3·5% at exit	41/86‡ (48%)	51/82‡ (62%)	–15% (–29 to 0·4)	0·06
Pitted cell counts ≥3·5% at exit (*vs* baseline)	..	..	..	0·03
Better (≥3·5% to <3·5% at exit)	9/85‡ (11%)	3/82‡ (4%)	7% (–8 to 22)§	..
Same	63 (74%)	55 (67%)	7% (–7 to 21)	..
Worse (<3·5% to ≥3·5% at exit)	13 (15%)	24 (29%)	–14% (–26 to –2)	..
HJB counts ≥300/10^6 red blood cells at exit	54/83‡ (65%)	67/85‡ (79%)	–14% (–28 to 1)	0·06
HJB counts ≥300/10^6 red blood cells at exit (*vs* baseline)	..	..	..	0·005
Better (≥300 to <300)	1/76‡ (1%)	0/82‡ (0%)	1% (–14 to 17)§	..
Same	59 (78%)	47 (57%)	20% (6 to 35)	..
Worse (<300 to ≥300)	16 (21%)	35 (43%)	–22% (–36 to –8)	..

HJB=Howell-Jolly body. *Difference of (exit to entry) percentages in hydroxycarbamide and placebo groups. †p value is calculated with Fisher's exact test under the assumption that proportions are equal in the hydroxycarbamide and placebo groups. ‡Total number of patients assessed for each endpoint. N differs from the number reported in table 1 because only entry values that are paired with exit values (from the same participant) are included. §CI is measured with the exact test calculation from a non-central hypergeometric distribution.

Table 4: **Splenic function at exit (secondary endpoint)**

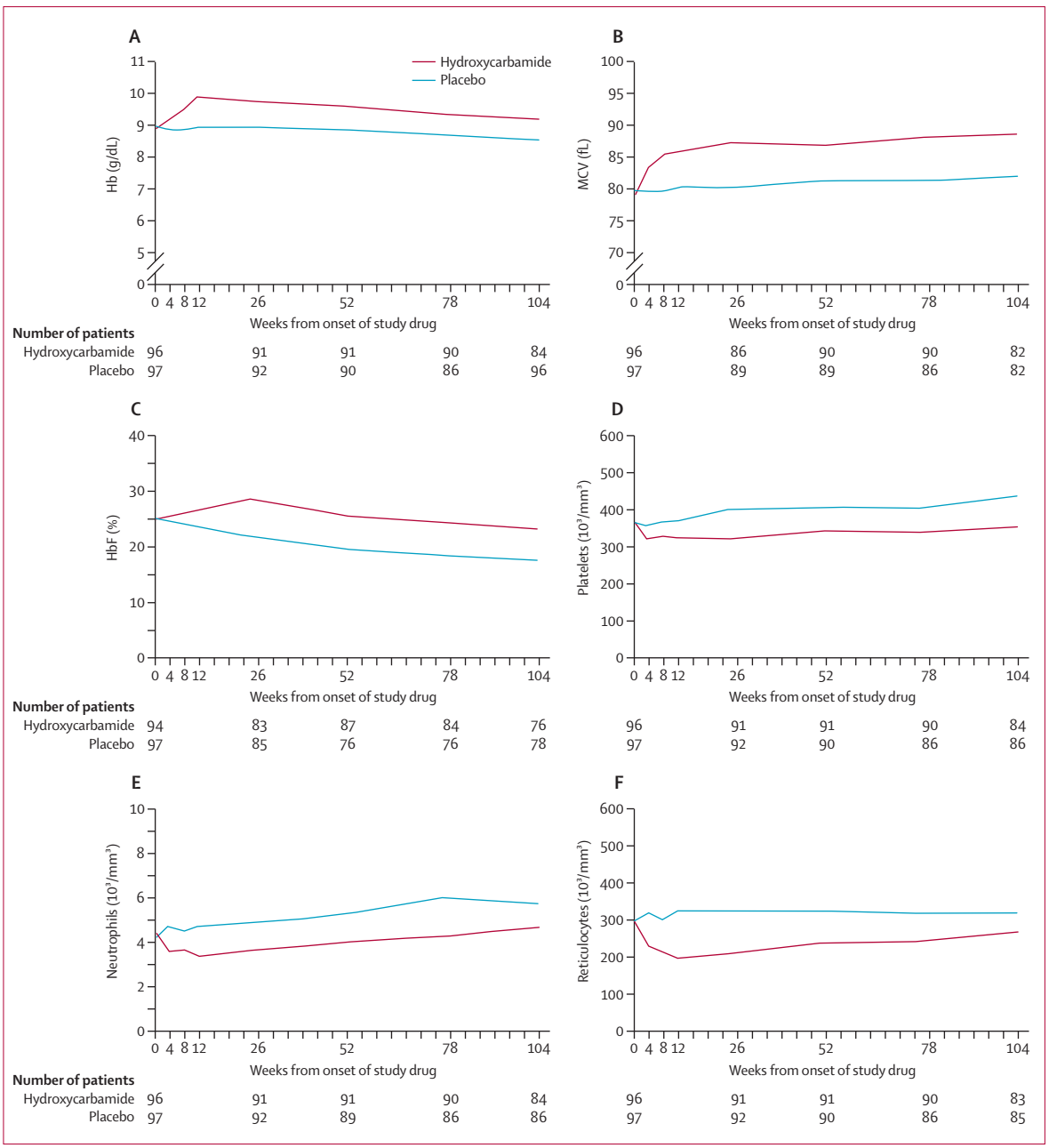

***Figure 2*: Longitudinal changes in mean haematological values in the hydroxycarbamide group versus the placebo group**
Panels show mean values over time from initiation of study drug for haemoglobin (A), MCV (B), fetal haemoglobin (C), platelet count (D), absolute neutrophil count (E), and absolute reticulocyte count (F). Blood counts were obtained every 2–4 weeks (although not all datapoints are shown), except for fetal haemoglobin, which was obtained every 6 months. The p values were 0·005 or less for all comparisons except for platelet counts (p=0·2). Hb=haemoglobin. MCV=mean corpuscular volume. HbF=fetal haemoglobin.

endpoint was discontinued in May, 2009, because the monitoring board decided that further data gathering would be statistically futile. Secondary measures of splenic function were the quantitative ratio of nuclear decay counts in the spleen and liver, the proportion of red blood cells containing pits (small vacuoles normally removed by the spleen), and the proportion of mature red blood cells containing Howell-Jolly bodies.[11] Secondary measures of renal function were serum creatinine and cystatin C concentrations, urinalysis, and urine osmolality after limited fasting.[12] Investigations of the brain, lungs, hepatobiliary system, and growth and development were included as secondary endpoints or indices of toxicity; growth curves derived from Cooperative Study of Sickle Cell Disease (CSSCD) data were used to monitor height, weight, and head circumference. Neurodevelopmental

	Hydroxycarbamide				Placebo				Difference† (95% CI)	p value‡
	N*	Entry	Exit	% difference	N*	Entry	Exit	% difference		
Splenic function										
HJB (per 10^6 red blood cells)	76	663	1360	106%	82	495	1470	197%	−274 (−538 to −10)	0·04
Pitted cells (%)	85	4·3	5·7	32%	82	4·6	8·4	84%	−2·5 (−4·7 to −0·2)	0·04
Spleen:liver ratio of counts	84	0·36	0·28	−20%	79	0·38	0·20	−46%	0·10 (0·01 to 0·19)	0·03
Spleen volume (cm^3)	80	110	157	43%	80	98	132	34%	14 (−14 to 42)	0·33
Renal function										
Creatinine (mg/L)	69	2	3	10%	78	2	2	12%	−0·05 (−0·04 to 0·03)	0·77
Schwartz GFR (mL/min per 1·73 m^2)	69	192	218	13%	73	196	229	17%	−8 (−37 to 21)	0·60
Cystatin C (μg/mL)	39	0·91	0·92	1%	48	0·91	0·89	−3%	0·03 (−0·05 to 0·11)	0·42
Urine osmolality (mOsm/kg H_2O)	81	384	494	29%	84	400	454	13%	57 (3 to 110)	0·04
Urine pH	86	6·5	6·3	−2%	82	6·6	6·3	−4%	0·15 (−0·22 to 0·51)	0·43
Urine-specific gravity	86	1·010	1·012	0%	82	1·012	1·011	0%	0·002 (0·0004 to 0·004)	0·02
Total kidney volume (cm^3)	80	61	91	48%	79	58	97	67%	−9 (−16 to −2)	0·01
CNS										
TCD velocity (TAMM) cm/s	79	126	146	16%	79	118	150	27%	−12 (−18 to −6)	0·0002
Bayley MDI	85	97	97	1%	80	97	94	−3%	3 (−2 to 8)	0·22
Bayley motor PDI	85	97	101	5%	79	97	99	2%	2 (−3 to 7)	0·37
Growth										
Height (cm)	87	75·9	96·2	27%	82	75·7	96·2	27%	−0·2 (−1·0 to 0·6)	0·62
Weight (kg)	87	9·7	14·5	50%	85	9·6	14·3	49%	0·1 (−0·2 to 0·4)	0·53
Head circumference (cm)	85	46·9	50·3	7%	82	46·8	50·3	8%	−0·2 (−0·6 to 0·2)	0·44
Pulmonary										
O_2 saturation (%)	86	99	99	0%	86	99	98	−1%	0·6 (−0·04 to 1·2)	0·07
Laboratory results										
Haemoglobin (g/L)	79	89	91	3%	79	92	86	−7%	0·9 (0·5 to 1·3)	<0·0001
Fetal haemoglobin (%)	80	25·6	22·4	−13%	78	27·1	17·1	−37%	6·7 (4·8 to 8·7)	<0·0001
Mean corpuscular volume (fL)	79	80·2	92·2	15%	79	80·0	86·2	8%	5·7 (4·0 to 7·5)	<0·0001
White blood cells ($\times10^3$ per μL)	79	14·4	10·6	−27%	79	14·3	13·9	−3%	−3·4 (−6·0 to −0·9)	0·008
Absolute neutrophil count ($\times10^3$ per μL)	69	4·9	4·5	−7%	72	4·2	5·6	33%	−1·7 (−2·9 to −0·5)	0·005
Platelet count ($\times10^3$ per μL)	78	374	351	−6%	79	404	415	3%	−33 (−87 to 21)	0·23
Absolute reticulocyte count ($\times10^3$ per μL)	79	286	227	−21%	79	265	277	5%	−71 (−107 to −35)	0·0002
Reticulocytes (%)	80	9·2	7·9	−14%	79	8·2	10·0	22%	−3·1 (−4·5 to −1·8)	<0·0001
Total bilirubin (mg/L)	81	16	18	16%	85	16	23	46%	−0·5 (−0·8 to −0·1)	0·01

HJB=Howell-Jolly body. GFR=glomerular filtration rate. TCD =transcranial doppler ultrasound. TAMM=time-averaged mean maximum (velocity). MDI=mental developmental index. PDI=performance developmental index. *Total number of patients assessed for each endpoint. N differs from the number reported in table 1 because only entry values that are paired with exit values from the same patients are included. †Comparison of exit versus entry differences in hydroxycarbamide and placebo groups. ‡p value is calculated with Student's *t* test comparing the exit versus entry differences between mean values in the hydroxycarbamide and placebo groups.

Table 5: **Comparisons between entry and exit values (secondary endpoint)**

assessment (Bayley Developmental and Vineland Adaptive Behavior Scales) and neurological examinations were done every 6–12 months.[8] Potential for mutagenesis was measured with assays for variable, diverse, and joining (VDJ) immunoglobulin receptor rearrangement, flow cytometric quantification of young reticulocyte micronuclei, and chromosome and chromatid breaks.[13,14]

Infants were monitored every 2 weeks for adverse events and laboratory toxic effects until a tolerable dose was confirmed, and then every 4 weeks.[8]

Adverse clinical events included known complications of sickle-cell anaemia, such as pain, dactylitis, acute chest syndrome, stroke, priapism, sepsis or bacteraemia, splenic sequestration, hospitalisation, and transfusion. Serious adverse events were reviewed by an independent classification committee (panel 1 shows definitions).

Statistical analysis

All patients randomly assigned to a treatment group were analysed for the coprimary endpoints. Methodology for the collection and analysis of study endpoint data has been published previously.[8] Data analysis was done with the statistical package SAS (version 9.2). The α level for the coprimary endpoints was divided disproportionately, with 0·04 allocated to the spleen and 0·01 to the renal endpoint. A sample size of 100 patients per group provided greater than 95% power to detect an estimated proportion with worsening spleen function of 0·6 in the

	Hydroxcarbamide (N=96)		Placebo (N=97)		Hazard ratio (95% CI)*	p value†
	Events	Patients	Events	Patients		
Pain (all reports including pain)	177	62	375	75	0·59 (0·42–0·83)	0·002
Pain alone	63	37	121	55	0·54 (0·36–0·83)	0·004
Acute chest syndrome	8	7	27	18	0·36 (0·15–0·87)	0·02
Hospitalisation (for any cause)	232	69	324	84	0·73 (0·53–1·00)	0·05
Transfusion	35	20	63	33	0·55 (0·32–0·96)	0·03
Dactylitis	24	14	123	42	0·27 (0·15–0·50)	<0·0001
Stroke	0	0	1	1	..	0·31
Priapism	4	3	2	2	1·48 (0·25–8·84)	0·67
Sepsis or bacteraemia	3	2	6	5	0·40 (0·08–2·06)	0·26
Splenomegaly	127	32	88	36	0·87 (0·54–1·40)	0·56
Splenic sequestration	12	8	12	9	0·88 (0·34–2·27)	0·79
Gastroenteritis	26	18	70	41	0·35 (0·20–0·60)	0·0001
Death	0	0	0	0	..	..

*Hazard ratios and 95% CIs are generated from a Cox model. †p values are generated from the log-rank life test comparing the time to first event between the two treatment groups.

Table 6: **Adverse events**

control group versus 0·3 in the hydroxycarbamide group, assuming a two-sided type I error rate of 4%, and to detect a 60% difference in the exit versus baseline GFR measurements in the two groups, allowing a two-sided type I error rate of 1%. A group sequential design was used to adjust for 6-month interim-analysis reviews done by an independent data safety and monitoring board. Interim boundaries were widely set to enable the most powerful comparison to be done at the end of the study, should an interim boundary not be crossed during the trial. For secondary endpoints, a p value of 0·01 or less was considered significant.

Continuous variables are presented as means with SDs, and compared with the two-sample Student's *t* test. Categorical variables are presented as proportions, and compared with the Pearson χ^2 or Fisher's exact test. All adverse events were treated as either time to first event or a counting process event variable, and analysed with the log-rank life test or the counting process approach of Anderson and Gill.[15] Efficacy analyses were adjusted for baseline measurements. The generalised estimating equation method was used for analysing correlated or serially gathered data, and multiple imputation was used to adjust for missing data.

The trial is registered with ClinicalTrials.gov, number NCT00006400.

Role of the funding source

The NHLBI provided an initial draft of the study design. The study sponsors did not collect, analyse, report, or interpret data. Two employees of the NHLBI (JCG, MAW) contributed to the writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

193 infants with HbSS (n=187) or Sβ⁰thalassaemia (n=6), mean age 13·6 months (range 9–18), were randomly assigned to a treatment group at 13 clinical centres (figure 1). A temporary administrative clinical hold on all study activity occurred from March to June, 2006, because of a specified expiration date on one lot of treatment bottles. 179 (93%) participants who completed at least 18 months of the trial and at least one exit assessment were analysed; 167 (86%) completed the full study. 96 children were randomly assigned to hydroxycarbamide, and 97 to placebo, with no significant differences in age, sex, genotype, clinical severity of sickle-cell anaemia, laboratory values, or physical findings (table 1).

We recorded no significant difference between hydroxycarbamide and placebo groups for either of the primary endpoints (table 2, table 3). Qualitative spleen scans were worse at exit than at entry in 19/70 (27%) of those on hydroxycarbamide and 28/74 (38%) of those receiving placebo (difference 11%, 95% CI –26 to 5, p=0·21). GFR, measured by ^{99m}Tc-DTPA clearance, did not differ in the two groups (difference 2 mL/min per 1·73m², –16 to 20, p=0·84).

Quantitative measures of spleen function (Howell-Jolly bodies, pit counts, and ratio of spleen to liver count) suggested benefit from hydroxycarbamide when we compared exit versus entry differences between the hydroxycarbamide and placebo groups (table 4). By 1–3 months after starting study drug, blood counts differed in the hydroxycarbamide and placebo groups (figure 2, table 5). Haemoglobin and fetal haemoglobin concentrations were relatively stable in the hydroxycarbamide group between entry and exit, whereas normal age-related declines occurred in the placebo group. Infants in the hydroxycarbamide group had higher mean exit concentrations of haemoglobin (by 5 g/L), fetal haemoglobin (by 5·3%), and mean corpuscular volume (by 6·0 fL), and lower white blood cell, neutrophil, and absolute reticulocyte counts than did those in the placebo group (figure 2, table 5). Exit versus entry differences between the groups were significant (table 5).

Exit versus entry differences in the hydroxycarbamide group also showed a trend towards higher urine osmolality and specific gravity, and lower total kidney volume compared with those in the placebo group. The increase in time-averaged mean maximum TCD velocity from baseline to exit was lower in the hydroxycarbamide group than in the placebo group (20 cm/s *vs* 32 cm/s). We recorded no differences between groups in the average Bayley MDI or Vineland scores for communication, daily living skills, socialisation, and motor skills (data not shown), although all five participants with an MDI less than 70 at exit had received placebo. Growth was not affected by hydroxycarbamide.

Acute event rates for the most common complications of sickle-cell anaemia differed substantially in the two groups (table 6). Pain was nearly twice as frequent and

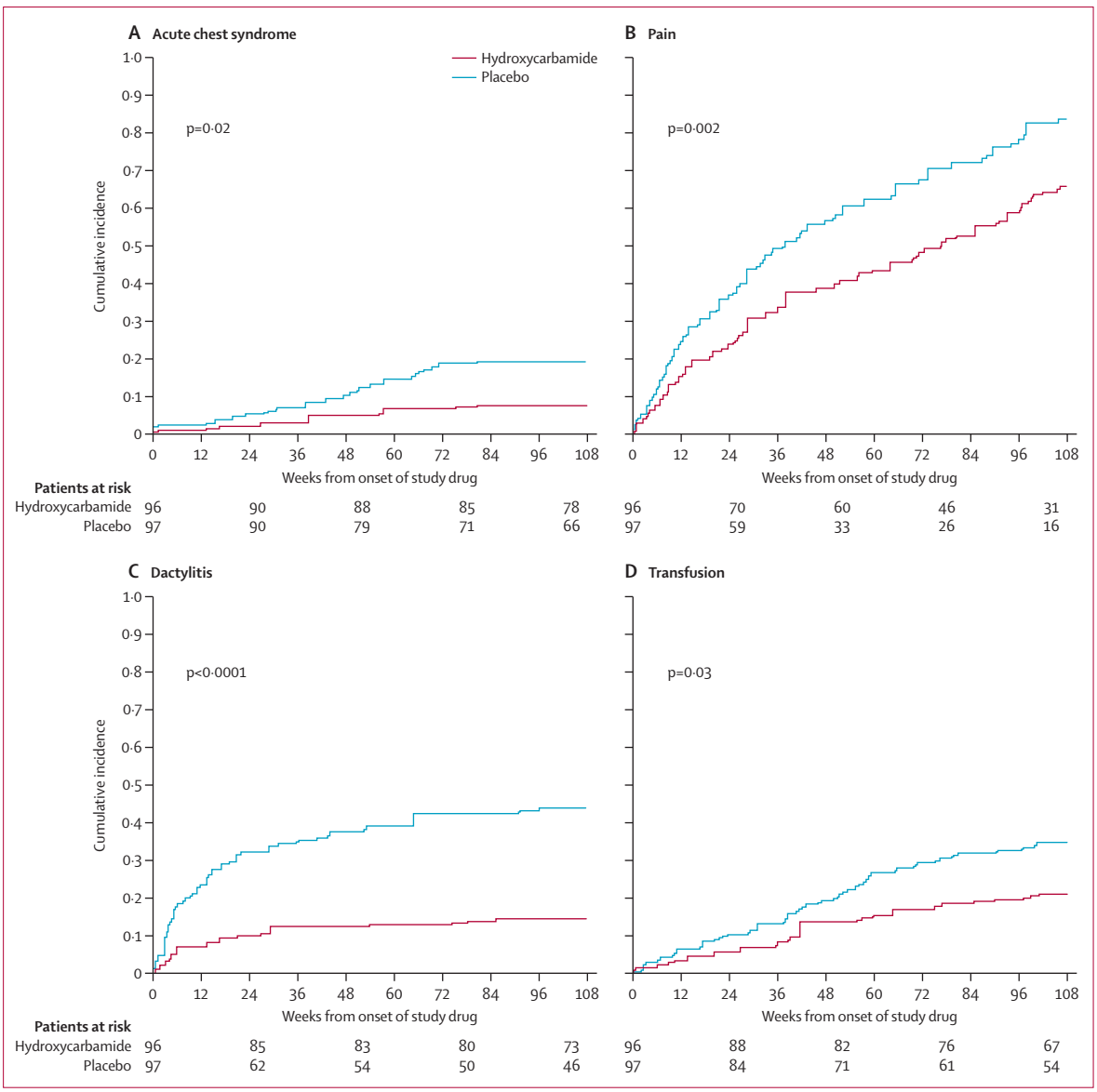

Figure 3: **Cumulative probability of adverse events in the hydroxycarbamide group versus the placebo group**
The cumulative probability curves were generated by the time to first event for acute chest syndrome (A), pain (B), dactylitis (C), and transfusion (D). The differences in the events between the treatment groups were assessed with the log-rank life test. The p values for cumulative probability curves were 0·02 for acute chest syndrome, 0·002 for pain, <0·0001 for dactylitis, and 0·03 for transfusion.

dactylitis five times more common in the placebo group. Acute chest syndrome was three times higher in the placebo group than in the hydroxycarbamide group. Hospitalisations and transfusions were marginally more common in the placebo group (table 6); most hospitalisations occurred for reasons other than pain (usually fever). Differences between the two groups were apparent by about 50 days (dactylitis), 100 days (pain), and 300 days (acute chest syndrome and transfusion) after treatment initiation (figure 3).

Sepsis or bacteraemia occurred in two patients in the hydroxycarbamide group and in five in the placebo group. Episodes of splenic sequestration were equal in the two groups. Gastroenteritis occurred less frequently in those receiving hydroxycarbamide.

The only frequent toxicity, mild-to-moderate neutropenia (absolute neutrophil count 500–1249/μL³), occurred 107 times in 45 participants in the hydroxycarbamide group and 34 times in 18 participants in the placebo group (table 7). Recurrent or persistent neutropenia resulted in nine long-term dose decreases (to 17·5 mg/kg per day) in the hydroxycarbamide group and five in the placebo group (p=0·20). More severe neutropenia (absolute neutrophil count <500/μL³) was rare and not associated with invasive

	Hydroxycarbamide (N=96)		Placebo (N=97)		Hazard ratio*(95% CI)	p value†
	Events	Patients	Events	Patients		
ANC <500/μL³	5	5	2	2	2·5 (0·5–12·9)	0·26
ANC 500–1250/μL³	107	45	34	18	3·0 (1·7–5·1)	<0·0001
Thrombocytopaenia (platelet count <80×10³ per μL³)	12	11	8	7	1·6 (0·6–4·1)	0·32
Severe anaemia (haemoglobin <70 g/L plus ARC <80×10³ per μL³)	1	1	2	2	0·47 (0·04–5·21)	0·53
ALT (>150 U/L)	3	2	1	1	2·0 (0·2–22·3)	0·56
Bilirubin (>100 mg/L)	0	0	1	1	..	0·31
Creatinine (≥2×baseline plus ≥10 mg/L)	0	0	0	0	..	..
Skin and subcutaneous disorders	122	62	165	69	0·74 (0·52–1·04)	0·08

ANC=absolute neutrophil count. ARC=absolute reticulocyte count. ALT=alanine aminotransferase. Patient-years in the hydroxycarbamide group=189. Patient-years in the placebo group=185.*Hazard ratios and 95% CIs are generated from a Cox model. †p values are generated from log-rank life tests comparing the time to first event between the two treatment groups.

Table 7: **Toxic effects**

infection. Thrombocytopenia and reticulocytopenia were similar in the two groups. At study exit, chromosome and chromatid breaks did not differ in the two groups when compared with baseline levels, nor did we record any differences in VDJ recombination events or micronuclei assay results (data not shown).

Discussion

Hydroxycarbamide was safe and resulted in a decrease in common but serious adverse events, especially pain and dactylitis, as well as improved laboratory parameters. Several secondary measures of spleen, kidney, and CNS function suggested benefit, but these results were not conclusive.

BABY HUG is, to our knowledge, the first randomised, double-blind trial of hydroxycarbamide in children with sickle-cell anaemia (panel 2). It differs from all other paediatric trials (except for the pilot HUSOFT study) in that the participants were much younger at enrolment (mean age 13·6 months), and a severe clinical course (eg, three or more vaso-occlusive events in the previous year) was not a prerequisite for entry. No previous systematic reviews or meta-analyses of the effects of hydroxycarbamide on splenic or renal function in sickle-cell anaemia have been published. In our literature review we found two retrospective studies that showed modest preservation of splenic uptake in older children,[19,20] and a small prospective study that showed no effect.[21] Published data for the effects of hydroxycarbamide on renal function report possible effects on proteinuria and microalbuminuria.[22,23] One study found that GFR did not increase after 2 years of hydroxycarbamide treatment in preschool-aged children.[23]

Hydroxyurea did not prevent a reduction in splenic function assessed by qualitative spleen scan uptake. However, compared with previous reports, the decline in function on spleen scan occurred in a smaller than expected proportion in the placebo group (38%), and in an even smaller (but not significantly different) proportion (27%) of those treated with hydroxycarbamide. Because serum creatinine concentrations, often used to estimate glomerular function, are diminished in individuals with sickle-cell anaemia, we used ^{99m}Tc-DTPA clearance, which is a more definitive assessment of GFR that does not require urine collection. As expected, increased GFR for age was present at baseline,[7,10] and further increases were seen at exit, but hydroxycarbamide had no effect on glomerular hyperfiltration.

Possible explanations for the lack of difference between the hydroxycarbamide and placebo groups in terms of primary endpoints include: use of a fixed dose of hydroxycarbamide (20 mg/kg per day), which is lower than the usual maximum tolerated dose and perhaps clinically less effective;[3,24] the relatively short duration of the trial (perhaps with further compromise by the 3-month clinical hold), which could have been insufficient to see changes; the small number of participants; and suboptimum endpoint measurements, which might not have been sensitive enough to detect subtle changes in splenic and renal function. Unfortunately, at entry nearly three-quarters of participants were classified as the intermediate category of decreased but not absent splenic uptake on qualitative spleen scan; changes within this category could not be taken into account when analysing the primary endpoint. Of course, hydroxycarbamide might not prevent organ dysfunction in infants, or it might offer only some protection. An open-label follow-up study of this cohort that allows dose escalation is underway (NCT00890396). Of the 179 patients who completed at least 18 months of follow up in the BABY HUG trial, 163 (91%) are enrolled in the follow-up study. For 133 (82%) of these patients, their families have chosen to use open-label hydroxycarbamide, usually with an escalation to the maximum tolerated dose.

Three secondary measures of splenic function (liver count ratios, pit counts, and Howell-Jolly bodies) suggested benefit from hydroxycarbamide when adjusted for baseline values; the potential use of baseline pit counts and Howell-Jolly bodies from the BABY HUG study has been analysed.[11] Two secondary measures of renal function (urine osmolality and specific gravity) suggested benefit

from hydroxycarbamide. The greater total kidney volume on ultrasonography in the placebo group might indicate nephromegaly due to hyperfiltration. Moreover, hydroxycarbamide might favourably affect CNS pathology, which is a major problem in older children with sickle-cell anaemia. The average increase in TCD velocity, an established indicator of stroke risk in older children, was significantly less in those receiving hydroxycarbamide than in those receiving placebo, probably indicating the higher mean haemoglobin concentration in that group. Although the mean MDI was similar in the two groups, all five participants with scores lower than 70 at exit had received placebo.

Most importantly, participants in the hydroxycarbamide group had substantial clinical benefit, including lower rates of pain and dactylitis, and decreases in the occurrence of acute chest syndrome, admission to hospital, and transfusion, in addition to improved haematological parameters. Proportionally, the decreases in pain, acute chest syndrome, admission to hospital, and transfusion seen in our unselected patients were very similar to those recorded in severely affected adults in the MSH trial,[4] which led the US Food and Drug Administration to approve hydroxycarbamide for adults with severe sickle-cell anaemia.

The reduction in clinical events and improved haematological parameters with hydroxycarbamide should improve long-term prognosis. Recurrent pain and acute chest syndrome and higher white blood cell counts were associated with early mortality in the CSSCD trial.[2] Haemoglobin concentrations lower than 70 g/L, increased white blood cell count during the second year of life, and dactylitis before age 1 year were associated with increased risk for severe outcomes later in life,[25] although these findings were not replicated in a more recent newborn cohort.[26] Higher haemoglobin concentrations, lower reticulocyte counts, and lower bilirubin concentrations in the BABY HUG hydroxycarbamide group indicate reduced haemolysis, which should diminish nitric oxide depletion and its deleterious vascular effects.

The only toxic effect we detected from hydroxycarbamide in this infant cohort was mild-to-moderate neutropenia, but we detected no significant differences in severe neutropenia or in the number of bacteraemia or sepsis events between the hydroxycarbamide and placebo groups. Despite some previous concerns,[17] hydroxycarbamide did not increase the frequency of splenic sequestration or have any detrimental effects on growth or neurodevelopment. With several assays for mutagenesis, no significant differences between the hydroxycarbamide and placebo groups were noted. Long-term follow-up of participants with sickle-cell anaemia, averaging 17·5 years for those in the MSH study,[27] 8 years for an adult Greek cohort,[28] 12 years (to date) for the HUSOFT participants,[29] and 8 years for the Duke paediatric cohort,[24] has not shown any unexpected toxic effects from hydroxycarbamide. In fact, extended use has probably improved survival in adults.[27,28] However, because the risk of neoplasia is unknown when hydroxycarbamide is begun early in life, long-term follow-up is crucial.

A National Institutes of Health Consensus Conference concluded that hydroxycarbamide is underused in adults with sickle-cell anaemia.[30] The laboratory and clinical benefits of hydroxycarbamide for children and adolescents with sickle-cell anaemia, coupled with an excellent short-term and long-term safety profile, suggest that hydroxycarbamide is also underused in young patients. Further follow-up of the BABY HUG cohort is now planned until 2016, when participants will be 9–13 years of age, and will provide valuable data for longer-term beneficial and toxic effects.

In conclusion, we believe that the results of the BABY HUG study should have a major effect on guidelines for the management of children with sickle-cell anaemia. On the basis of the safety and efficacy data from this trial, hydroxycarbamide therapy can now be considered for all very young children with sickle-cell anaemia whether or not they have clinical symptoms. Future monitoring of this approach should be improved by a sickle cell registry in the USA and a global sickle disease network.

Panel 2: Research in context

Systematic review

We searched PubMed for review articles with the search terms "sickle cell" and "hydroxyurea". Two systematic reviews were identified: one involving adults[16] and the other involving children.[17] Additionally, there was a recent Cochrane review of hydroxycarbamide for sickle cell disease.[18] Together, these reviews reported only two randomised controlled prospective trials of hydroxycarbamide in sickle-cell anaemia. Our own search of reported studies did not identify any additional randomised trials. The Multi-Center Study of Hydroxyurea (MSH) study was a high-quality, double-blind trial of hydroxycarbamide in 299 adults with severe sickle-cell anaemia, in which hydroxycarbamide treatment was associated with a significant reduction in pain, acute chest syndrome, hospitalisation, and transfusion in the treated group.[4] In the systematic review of the paediatric literature, 26 articles were assessed, but there was only one randomised trial (considered to be moderate quality), in which 22 assessable children (median age 8 years) with severe sickle-cell anaemia were treated in a single-blind 12-month crossover study; hydroxycarbamide resulted in decreased hospitalisations.[5] There were no randomised trials of the effect of hydroxycarbamide on organ function, nor any in infants.

Interpretation

Our study is the only double-blind prospective paediatric trial to investigate the effect of hydroxycarbamide in very young children with sickle-cell anaemia. Patients in our trial differed from those in other trials in two important ways: they were very young, and eligible irrespective of whether they had severe clinical course of disease. On the basis of the safety and efficacy data from this trial, hydroxycarbamide can now be considered for all children with sickle-cell anaemia, starting at an early age.

Contributors

WCW prepared the first draft of the report after discussion by the writing committee. FDA, JCB, RCB, JFC, RVI, STM, SR, ZRR, BWT, MAW, WCW, REW, and LWW participated in study design. JCB, RCB, JFC, THH, RVI, STM, SR, ZRR, SAS, CDT, WCW, REW, and LWW did patient recruitment and coordinated study site activities. JCB, RCB, JFC, BAF, THH, XH, RVI, RVK, AK, STM, CPM, SR, ZRR, SAS, BWT, CDT, MAW, WCW, REW, and LWW did data collection, analysis, and

interpretation, and BAF, XH, and BWT did data verification. JCB, RCB, JFC, BAF, JCG, THH, RVI, RVK, AK, STM, CPM, SR, ZRR, SAS, BWT, CDT, MAW, WCW, REW, and LWW did writing and editing. JCG administered the project. FDA oversaw neurodevelopmental data, and AK, ZRR, and REW supervised the central laboratories.

Conflicts of interest

We declare that we have no conflicts of interest.

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