Transcranial Doppler Measures in Patients with Sickle Cell Disease At High Risk for Stroke and Receiving Hydroxyurea: The HyRetro Ancillary Study

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ABSTRACT

INTRODUCTION: Children with sickle cell disease (SCD) and increased transcranial Doppler (TCD) sonography velocity measures are at increased risk for stroke. Although chronic transfusion decreases this risk tenfold, this form of therapy is burdensome and includes risk of iron overload. Although it has been established that stroke risk is still present even after 30 months of transfusion therapy, the total length of transfusion therapy required is not known. Hydroxyurea (HU) therapy is effective in preventing SCD complications, although its effect in preventing SCD central nervous system complications is less clear and a matter of current investigation.

METHOD: During a clinical trial (STOP2), an ancillary study was conducted to examine TCD velocities in 76 patients with SCD receiving HU for a variety of indications. TCD measures were defined as the highest time-averaged maximum mean velocity of one of 8 measures from the following cerebral arteries – LMCA, LM1, LBIF, LDICA, RMCA, RM1, RBIF and RDICA – per STOP protocol.

RESULTS Results from 10 patients at high risk for stroke (defined as one or more TCDs ≥200 cm/sec) were evaluated for the present analysis. Average age at start of HU was 10.7 ± 3.2 standard deviation (SD) years; 6 were female. Eight did not receive chronic transfusion in STOP (4 randomized to observation arm in STOP, 4 observed but not randomized in STOP); and 2 were on transfusion (1 randomized to transfusion arm in STOP, 1 crossover in STOP/STOP2). Reasons for HU therapy included primary stroke prevention (n=6); secondary stroke prevention (TIA n=1; overt ischemic stroke n=1), vaso-occlusive or acute chest episodes (n=2). Averaged HU dose (available in 8) was 15 ± 3 mg/kg. Averaged measures, off and on HU for each patient, were used to calculate means. Averaged hematologic indices on treatment were as follows: white blood cell count, 10.2 ± 1.8 × 10^3/mm^3; hemoglobin, 8.1 ± 0.7 gm/dL; mean corpuscular volume, 105.6 ± 6.7 cu µm; reticulocyte count, 11.1 ± 2.3%. Averaged fetal hemoglobin (HbF), available in 8, was 16.1 ± 5.7%.One patient receiving HU for secondary stroke prevention suffered an overt stroke. This patient had a first overt stroke 24 months prior to start of HU therapy. MRI showed right frontal watershed and bilateral lacunar infarcts. Severe stenosis of the left MCA was noted. Patient had a repeat stroke 13 months after start of HU. MRI showed ischemia with watershed distribution of the left frontal lobe, stenosis of A2 and occlusion of A1 segments. Three TCDs before and two after start of HU were all >220 cm/sec. Overall, decreasing TCD velocities were noted in 60% prior to HU (STOP transfusion, n=2) and in 50% on HU (STOP transfusion, n=0).

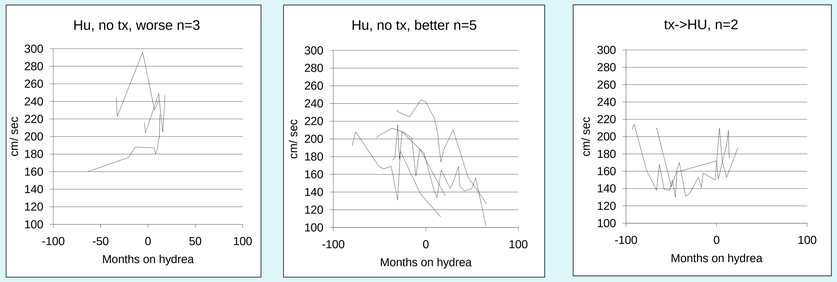
CONCLUSION. TCD velocities decreased significantly in high risk patients receiving HU that were not transfused in STOP. However, these results require cautious interpretation, as the number of patients is small and length of observation varied. Patients with very high TCD measures remain at risk. Further studies may elucidate whether there is a role for HU in patients with abnormal TCDs.

RESULTS

TABLE 1: Average follow-up and number of TCDs

Groups	Treatment	Follow-up (mo)	TCDs (n)
Not transfused in STOP (n=8)	Pre-HU	44 ± 23	5.3 ± 2.5
	HU	33 ± 24	5.0 ± 3.6
Transfused in STOP (n=2)	Pre-HU	64 ± 19	10.5 ± 0.7
	HU	19 ± 7	4.5 ± 0.7

FIGURE 1: TCDs over time in relation to start of hydroxyurea



RESULTS AND LITERATURE REVIEW

TABLE 2: TCD outcomes on hydroxyurea from current study (red) compared to previous studies

Abnormal (>200 cm/sec)	Author	Method	Year	Treatment	N	Mean pre TCD cm/sec	Mean post TCD cm/sec	p	Outcome description
	Bernaudin	TCD	2005	transfusion till normal, then HU	7	-	-		stayed normal 4 (57%)
	Kratovil	TCDi	2006	TX-> nothing (allo abs)-> HU	1	206	-		normal->abnormal->normal
	Gulbis	TCD	2005	HU	11	235+/- 25	204 +/-27	< .01	normal/conditional 2 (18%)
	Zimmerman	TCD	2008	HU maximum tolerated dose	6	216 +/- 14	173 +/- 31 cm	< .001	
	Lefèvre	TCD	2008	HU	21	235 +/-18	202 +/- 34	< .01	normal/conditional 8 (38%)
	STOP 1/2	TCD		HU	8	203+/-28	179+/-48*	< .01	normal 5 (62%)
	STOP 1/2	TCD		TX-> HU	2	160+/-0.5**	180+/-1.1		normal 0/conditional 2 (100%)
	Total				**50**				**normal/conditional 22 (44%)**
Conditional (170-199 cm/sec)	Kratovil	TCDi	2006	HU >=6 months	3	-	-		normal 2 (66%)
	Zimmerman	TCD	2007	HU maximum tolerated dose	15	-	-		normal 14 (93%)
	Total				**18**				**normal 5 (88%)**
Normal (<170 cm/sec)	Kratovil	TCDi	2006	HU >=6 months	48	125 +/- 32.3	111.2 +/- 29	< .001	
Combined (>140 cm/sec)	Zimmerman	TCD	2007	HU maximum tolerated dose, RMCA	37	166 +/-27	135 +/- 27	< .001	
	Zimmerman	TCD	2007	HU maximum tolerated dose, LMCA	37	168 +/-26	142 +/- 27	< .001	

*: Wilcoxon signed-rank test, p=0.008; ** TCD on transfusion, prior > 200 cm/sec

REFERENCES

Adams RJ, et al. N Engl J Med 1998;339:5-11.
Adams RJ, et al. N Engl J Med 2005;353:2769-78
Bernaudin F, et al. Pediatr Radiol 2005;35:242-248.
Gulbis B, et al. Blood 2005;105:2685-2690.
Kratovil T, et al. Pediatr Blood Cancer 2006;47:894-900.
Zimmerman SA, et al. Blood 2007;110:1043-1047.
Lefèvre N, et al. Blood. 2008 Jan 15;111:963-4;

SUPPORT

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