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Research Article

Topiramate for Peri-Operative Neuroprotection in Infant Heart Surgery

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Abstract

Objective: To test feasibility and to generate preliminary data regarding dosage, safety and efficacy of topiramate for neuroprotection in neonates requiring cardiothoracic surgery.

Study Design: An open pilot trial of topiramate versus no topiramate in 24 term infants requiring cardiac surgery in the first month of life. Topiramate levels, number of missed doses, possible adverse effects, plasma S100β and Bayley III scores at 9 and 18 months were analyzed.

Results: Among the 12 infants who received topiramate, median number of doses prior to surgery was 4.5 and after surgery was 7. No adverse effects related to topiramate administration were noted. Mean topiramate levels were 3.7 μg/mL at 3 days and 5.5 μg/mL at 1 day after surgery. S100β levels and Bayley III scores were not significantly different between the two groups.

Conclusion: Administration of topiramate in the peri-operative period for infants with congenital heart disease is feasible. The serum topiramate levels were low, suggesting that the dose was too low in this population. No adverse effects or benefits of topiramate were noted. The study was not powered to determine effect of topiramate on developmental outcomes but facilitates sample size calculations for future studies.

Keywords: *Neuroprotection; Topiramate; Congenital Heart Disease; Infant*

Introduction

Congenital heart disease is the most common birth defect, occurring in 6 of 1000 live births [1]. Mortality in these infants has decreased significantly due to advances in surgical techniques and post-operative care [2]. Despite these advances, a significant number of children requiring early surgery for congenital heart disease demonstrate neurodevelopmental delays. Neurodevelopmental impairment in this population is likely multi-factorial with prenatal, perinatal, and peri-operative insults and genetic and socio-economic factors contributing. Brain injury in infants with congenital heart disease requiring surgery in the first month of life varies with the type of congenital heart disease and surgical procedure performed with rates as high as 70% [3,4]. Early post-operative magnetic resonance imaging (MRI) showed periventricular leukomalacia in 48%, infarct in 19%, and parenchymal hemorrhage in 35% of infants studied [5]. In another study, post-operative MRI at 1 to 2 weeks showed brain injury in over half of the neonates [6]. Neuropathology of infants who died after cardiac surgery showed that all of the 38 infants examined had signs of hypoxic-ischemic brain injury [7].

During hypoxic-ischemic brain injury, excessive release of glutamate causes influx of sodium and calcium into neurons through NMDA, AMPA and kainate receptors, ultimately causing cell death through activation of proteases, endonucleases, and other apoptotic mediators. Several agents have been proposed as possible neuroprotective agents for hypoxic-ischemic encephalopathy including allopurinol [8,9], xenon gas [10], N-acetylcysteine [11,12] and levetiracetam [13]. However, none of these agents appear to be ideal due to either lack of efficacy in infants with congenital heart disease [9], little safety data in infants, or difficulty in administration. Topiramate blocks glutamate AMPA and kainate receptors, but not NMDA receptors. Topiramate is commercially available, is easily administered in an enteral solution and has limited evidence of safety and efficacy in infants making it an attractive therapy for neonates. Administration of topiramate has been shown to reduce hypoxic-ischemic brain injury in piglet and rat models [14-16]. Topiramate has been administered to infants for short courses in hypoxic-ischemic encephalopathy and for long-term treatment of epilepsy without significant adverse effects [17,18]. As a first step towards testing the hypothesis that blocking glutamate receptors with peri-operative administration of topiramate reduces brain injury in infants requiring cardiothoracic surgery for congenital heart disease, we performed a pilot study to test feasibility and to generate dosing and safety data plus preliminary data for sample size calculations based on two outcomes: plasma S100β levels (a marker of brain injury) and Bayley III developmental scores at 9 and 18 months.

Materials and Methods

The study was approved by the Institutional Review Board at University of California, Davis and registered at Clinicaltrials.gov (NCT01426542). Twenty-four infants with congenital heart disease were enrolled in an open prospective pilot trial of peri-operative topiramate between Jan 2011 and June 2014. Infants were eligible for enrollment if they were born at a gestational age ≥ 35 weeks with congenital heart disease requiring surgery within the first 30 days of life. Infants were excluded if they had apparent genetic syndromes or neurological abnormalities at the time of enrollment. At the time of informed consent, parents were given the option of participating in the study arm (topiramate 5 mg/kg once daily for up to one week before and one week after surgery) or the comparison arm (routine care but no topiramate administration). The topiramate dose was chosen based on a recommended starting dose for epilepsy and previous demonstration of tolerability in infants in conjunction with cooling for hypoxic-ischemic encephalopathy [17]. Plasma for S100β measurements was collected at enrollment, on post-operative day 1 and at 1 week after surgery in both groups. Plasma S100β measurements were determined using a commercial ELISA assay (EMD Millipore, Billerica, MA). We also measured serum topiramate levels for infants in the topiramate group when possible on day 3 of topiramate administration and on post-operative day 1. Infants had developmental follow-up at approximately 9 and 18 months of age. Infants were tested with the Bayley III Scales of Infant and Toddler Development at each developmental follow-up visit.

As this is a novel area of investigation, the sample size for this pilot study was chosen based on feasibility of completion assuming that less than 50% of parents of eligible infants would agree to participate with the goal of generating preliminary data to determine advisability of future larger trials. As such it was not powered to address the overarching hypothesis. Chi-square and student's t-tests were used to compare variables with a normal distribution. Non-normal data were either log-transformed or analyzed with the non-parametric Mann-Whitney Rank Sum test.

Results

A flow diagram of patients approached and enrolled is shown in figure 1. There were no statistical differences between the two groups in gestational age, gender, or mortality, but the infants in the control group had higher birth weight ($p = 0.02$) (Table 1). Cardiac lesions were quite varied among patients (Table 2).

Patients in the topiramate group received a median of 4.5 doses pre-operatively and 7 doses post-operatively. Topiramate levels were only able to be assessed in a subset of patients due to timing of surgery. The individual topiramate levels are presented in figure 2 panel A (mean pre-operative level 4.7 μg/mL and mean post-operative level 4.3 μg/mL). Of the 12 infants receiving topiramate, 5 achieved a thera-

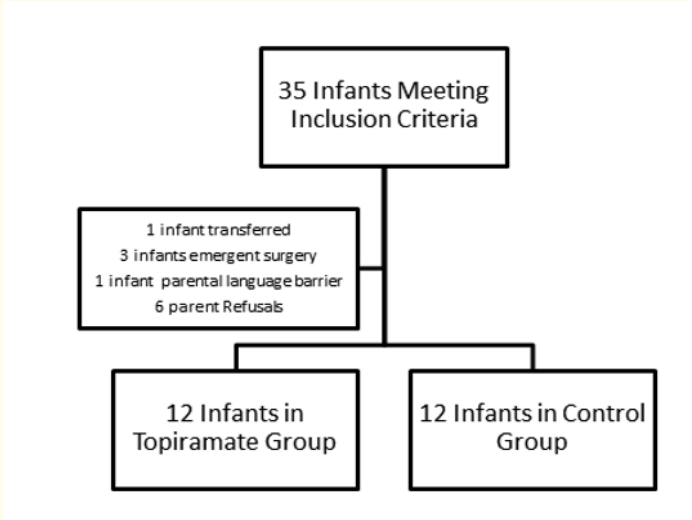

Figure 1: *Flow diagram of patient enrollment.*

	Topiramate (N = 12)	Control (N = 12)
Gestational Age at Birth(weeks), mean	39.5 (0.9)	39 (0.62)
Gender (M/F)	8/4	6/6
Birth Weight (kg), Mean (SD)	3.07 (0.41)	3.47 (0.43)
Lowest Pre-Op pH, Mean (SD)	7.24 (0.15)	7.24 (0.18)
Lowest Post-Op pH, Mean (SD)	7.27 (0.13)	7.25 (0.1)
Days in Hospital, Mean (SD)	28.3 (15.6)	40.4 (45.3)
Days in Hospital Post-Op, Mean (SD)	21.3 (14.4)	33.1 (46.8)
Deaths	2	3

Table 1: *Patient characteristics. No significant differences were noted between the two groups except for birth weight (p = 0.02).*

Lesion	Topiramate	Control
Hypoplastic left heart	2	3
Transposition of the great arteries	3	2
Interrupted aortic arch	3	0
Coarctation of the aorta	2	2
Critical aortic valve stenosis	0	1
Double outlet right ventricle	1	1
Double inlet left ventricle	0	1
Pulmonary valve atresia	0	1
Total anomalous pulmonary venous return	1	0
Truncus arteriosus	0	1

Table 2: *Cardiac lesions of enrolled infants by group.*

peutic level of ≥ 5 μg/mL, 1 had an early level of 4.3 μg/mL but did not have a level at post-operative day 1, 4 were clearly sub-therapeutic and 2 did not have any topiramate level measured. Metabolic acidosis is a known side-effect of topiramate, but there were no significant differences between the two groups in pre or post-operative pH on blood gases. No significant differences were noted in mortality, total hospital days, or post-operative days (Table 1).

Plasma S100β levels did not differ between pre-operative and post-operative timepoints (Figure 2, panel B) and did not differ between the two groups at any of the three time points (Figure 2 panel B, $p > 0.06$ Mann-Whitney test). We combined the data for all infants and found higher S100β levels post-operatively in 5 infants with intraventricular hemorrhage than in 19 infants who had no intraventricular hemorrhage. Infants with intraventricular hemorrhage on post-operative Day 1 had a mean (SD) S100β level of 423 (404) pg/mL while infants without intraventricular hemorrhage had a mean (SD) level of 33.5 (30.9) pg/mL (Figure 2 panel C, $p < 0.01$, T-test of log transformed data).

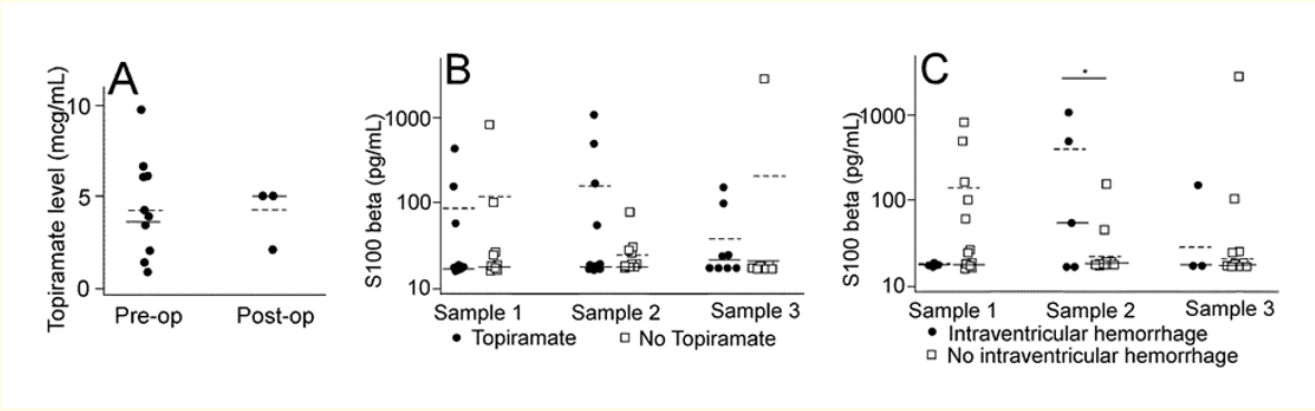

Figure 2: *A: Pre- and Post-operative topiramate levels in infants receiving 5 mg/kg once daily. B: Plasma S100b levels from infants treated or not treated with topiramate. C: Plasma S100b levels from infants with and without IVH. Solid bar represents median and the dashed bar represents the mean of the samples in each group. Y axes in B and C are logarithmic scales. * $p < 0.05$ T test of log transformed data.*

Bayley III scores did not differ between the two groups at either time point (Table 3). When patients were categorized as having either optimal (alive and all scores > 70) or not optimal (any score < 70 or deceased), there was no difference between the topiramate or control groups ($p = 0.67$).

	First developmental visit			Second developmental visit		
	Topiramate	**Control**	**P value**	**Topiramate**	**Control**	**P value**
Cognitive	103.6 (17.5)	106.7 (10.4)	0.66	90 (11.6)	86.7 (15.3)	0.85
Language	84.9 (13.8)	98 (9.6)	0.18	91.1 (15.30	75.7 (12.3)	0.16
Motor	95.2 (19.3)	91.3 (16.4)	0.78	89.2 (13.4)	91.3 (20.1)	0.86

Table 3: *All values are mean Bayley III scores (standard deviation).*

Discussion

Administration of topiramate in the peri-operative period for infants with congenital heart disease is feasible as demonstrated by the number of doses administered. The number of doses administered pre-operatively were variable due to the operative timing. However, the low serum topiramate levels suggest that future studies of topiramate for peri-operative neuroprotection in term infants with congenital heart disease should adopt a higher dose. No adverse effects of topiramate were noted, in particular metabolic acidosis was not increased in the topiramate group and there was no difference in mortality between groups. Changes in urea cycle intermediates and related metabolites along with case reports of hyperammonemia [19] and necrotizing enterocolitis [20] related to topiramate administration suggest caution in administering topiramate and consideration of monitoring of ammonia levels in infants receiving topiramate in future studies.

S100β has been used as a marker of acute brain injury in previous studies [21]. While no significant difference was noted in the S100β levels of control infants compared to infants who received topiramate, the marked increase in S100β in infants with intraventricular hemorrhage seen here is consistent with some previous observations [22]. However, at least one study of S100β as well as several other serum biomarkers including glial fibrillary acidic protein following pediatric cardiac surgery did not predict brain injury [23]. The variable results obtained with S100β as a biomarker of brain injury may relate to the severity and type of brain injury, as well as the timing after injury.

This pilot study has several limitations including the small sample size, the lack of randomization and blinding, and heterogeneity of cardiac lesions between the groups. Pilot studies are useful for assessing advisability and sample size of larger definitive trials and for generating mechanistic hypotheses to be tested. Since the S100β levels did not show a trend towards improvement in the topiramate group, a sample size calculation is not helpful. The two trends toward improved outcomes with topiramate do allow calculation of a sample size necessary to confirm a potential benefit. Assuming $\alpha = 0.05$ and $\beta = 0.1$, to confirm improvement in the Bayley language scale at 18 months of age of 15 points would require a sample size of 21 in each group and to confirm a shorter length of hospitalization after surgery of 12 days with topiramate administration would require a sample size of 31 in each group.

Conclusion

Administration of topiramate at a dose of 5 mg/kg/day to infants with congenital heart disease in the peri-operative period is feasible and did not demonstrate side effects or safety concerns. The study was not powered to detect differences in developmental outcomes. The low serum topiramate levels suggest that the chosen dose is too low for a neuroprotective benefit. Based on the data from this pilot study, a larger blinded randomized placebo-controlled study with a higher daily topiramate dose of 7.5 mg/kg (with at least 21 - 31 infants in each group) is warranted to further investigate the potential benefits of topiramate in this population.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the UC Davis Institutional Review Board.

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