POST-HOC ANALYSIS OF A PHASE 2 TRIAL OF N-ACETYLCYSTEINE FOLLOWING KASAI PROCEDURE FOR BILIARY ATRESIA

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Background: Biliary atresia (BA) is a neonatal liver disease characterized by impaired bile flow and is the most common indication for pediatric liver transplantation. The only identified treatment option thus far is a Kasai portoenterostomy (KP) which has variable success. Adjunctive therapies have been studied in an attempt to improve outcomes after KP, however none have demonstrated effectiveness. This phase 2 study assessed whether N-acetylcysteine (NAC) improved bile flow following KP. While the study did not meet the primary endpoint, there are many other markers of liver disease and injury that may have been affected by NAC.

Materials/Methods: This study was an open-label, single center, phase 2 trial of IV NAC begun within 24 hours of KP and administered for a total of 7 days following KP at Texas Children's Hospital from 2019-2021. It followed a minimax clinical trial design. The primary endpoint of the study was normalized total serum bile acids within 24 weeks of KP. The secondary endpoints were to examine the clinical effects of a short course of IV NAC on other clinical parameters in the first 24 months of life. To analyze these secondary endpoints, study participants will be matched 1:2 by age at time of KP with historical patients with BA. Statistical comparisons will be conducted between study participants and historical controls regarding markers of liver injury in the first week following KP, indicators of bile flow within the first six months following KP, frequency of liver transplantation within the first two years of life, and the occurrence of adverse events.

Results: Per the minimax trial design, the study was terminated early when the primary endpoint of total serum bile acids of <10 umol/L was not met. Comparisons will be made between study participants and historical controls to determine if a short course of IV NAC demonstrated any clinical benefit following KP.

Conclusions: This post-hoc analysis will determine whether there is any evidence that NAC may provide some clinical benefit following KP for infants with BA. Such results will also help guide future studies of NAC for infants with BA and other cholestatic conditions. Finally, the number and type of adverse events that occurred in infants while receiving IV NAC compared to historical controls will demonstrate that the side effect profile of this medication is acceptable.

Images / Graph / Table

Table 1. Demographics and characteristics of study cohort and historical controls matched for age at Kasai.

Characteristics	Historical Controls (n=24)	Study Participants (n=12)	p
Sex, % (n)			
Male	25.0% (6)	58.3% (7)	Chi
Female	75.0% (18)	41.7% (5)	Chi
Race, % (n)			
Asian	0% (0)	8.3% (1)	FET
Black	4.2% (1)	33.3% (4)	FET
White	95.6% (23)	58.3% (7)	Chi
Hispanic, % (n)	54.2% (13)	50.0% (6)	Chi
Gest Age <37 weeks, % (n)	4.2% (1)	16.7% (2)	FET
Congenital anomal(ies), % (n)	4.2% (1)	8.3% (1)	FET
Age at KP (days), mean±SD	35±21	36±22	MWU
Weight at KP (kg), mean±SD	3.9±0.4	3.8±0.5	MWU
Weight z-score at KP, mean±SD	-0.8±0.8	-1.2±1.3	MWU
Laboratory values at KP, mean±SD (n)			
AST (IU/L)	129±114	129±80	MWU
ALT (IU/L)	101±125	83±55	MWU
GGT (IU/L	583±465	381±313	MWU
Conjugated bilirubin (mg/dL)	2.9±0.9	2.6±1.0	MWU
Unconjugated bilirubin (mg/dL)	2.5±2.9	1.7±1.1	MWU
Total bilirubin (mg/dL)	9.6±4.5*	6.3±1.7**	MWU

* denotes values available from 11 historical controls
** denotes values available from 7 study participants