Role of Citicoline in Treatment of Moderate to Severe Birth Asphyxia: A Pilot Project

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ABSTRACT

An observational cohort study was performed at Neonatal Intensive Care Units of two military hospitals to see the effects of citicoline in neonates diagnosed to have moderate to severe hypoxic ischemic encephalopathy. Twenty newborns fulfilling the inclusion criteria were selected for the study and were given injection citicoline *via* the IV route. The outcomes in the immediate newborn period, including neurological features and mortality, were studied. Only one baby, who was given injection citicoline, died during the study period and 19 babies were discharged and sent home after establishment of oral feeds. Citicoline was found promising in treatment of newborns with moderate to severe birth asphyxia.

Key Words: *Hypoxia, Ischemia, Birth asphyxia, HIE.*

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Neonatal hypoxic ischemic encephalopathy (HIE) is a common cause of brain injury secondary to perinatal asphyxia, affecting 1 to 8 per 1000 live full-term births. Approximately 25 – 30% of neonates having moderate to severe HIE develop permanent neurologic impairment.[1] HIE can be classified into three major categories, namely, mild (grade 1), moderate (grade 2) and severe (grade 3), according to Sarnat and Sarnat staging criteria. Neonates with mild HIE have a normal neurological outcomes.[2] However, severe HIE contributes to a higher risk of death in the immediate neonatal period as well as long-term neurologic disabilities, including cerebral palsy, mental retardation, learning disability, and epilepsy. Therapeutic hypothermia has been considered as standard treatment for neonates with moderate to severe HIE but is only partially effective.[3] Currently, well-established effective therapies are lacking and supportive medical therapies to maintain physiologic parameters remain the standard therapy. To curtail the high rates of neurologic morbidities caused by HIE, development of new therapeutic agents is needed.

Phosphatidylcolines are sphingolipids located in the cell membranes of nerve cells. They perform a key role in maintaining integrity of cell membrane and in regulating brain development.[4]

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Significant reduction in several phosphatidylcolines was observed after hypoxic–ischemic injury. Experimental studies, mostly on animal models and in adults, showed that citicoline can protect against neuronal apoptotic insults and attenuate brain damage.[5] Based on these animal and adult studies, citicoline appears a promising therapeutic option for treatment of neonates with HIE. A study carried out in China found that citicoline can have promising effects in improving neurological outcome of babies with HIE.[6]

Considering the promising effects of citicoline in adults with acute ischemic strokes and animal models, and the report from China, we evaluated its efficacy in neonatal HIE with the objective to assess whether citicoline would be efficacious in moderate and severe HIE in our setting where cerebral cooling facility is not available.

An observational cohort pilot study was designed to study the effects of citicoline on short term neurological outcome in babies with grade 2 and 3 HIE, at Neonatal Intensive Care Units (NICUs) of Military Hospital, Rawalpindi and Combined Military Hospital Quetta, from September 2020 to March 2021. Twenty newborns of both genders, of more than 32 weeks gestation, having grade 2 and 3 HIE, delivered indoor or received from outside hospital within 24 hours of birth and not having any major congenital malformations were enrolled in study through convenience sampling technique.

All newborn were given injection citicoline *via* the IV route at a dose of 15 mg per kg body weight every 12-hourly. The drug was given until suck reflex was established. Babies were observed for their neurological status, by observing their spontaneous movement and reflexes, laboratory studies

including plasma lactate, blood gases, and secondary evidence of hypoxia including the serum ALT, serum CK-MB, renal function tests, and PT/APTT were sent after 24 hours of delivery to look for multi-organ involvement.

Data was analysed in SPSS version 20. Descriptive statistics were used to calculate mean ± SD of numerical data, *e.g.,* age, gender and final outcome. For categorical data like duration of symptoms, neurological status, lactate levels, blood gases, and other laboratory results were analysed by their frequencies and percentages.

Of 20 newborns, 13 (65%) babies had grade 3 HIE, while 7 (35%) babies had grade 2 HIE. The mean birth weight was 3.03 ± 0.52 kg, mean gestational age was 38.25 ± 2.04 weeks. There were 13 (65%) males and 7 (35%) females. Nine babies were delivered through SVD, while nine were delivered through LSCS and two babies were delivered through vacuum extraction. The mean Apgar scores at 1 and 5 minutes were 2.90 ± 1.07 and 4.90 ± 1.16, respectively. The mean first-hour capillary blood pH was 7.03 ± 0.10, while mean lactate level was 9.30 ± 4.07. Nine (45%) babies required mechanical ventilation and 11 (55%) babies did not receive mechanical ventilation. Seizures occurred in 14 (70%), while six (30%) of the neonates remained seizures-free. Injection citicoline was well tolerated and there were no significant alterations in heart rate, oxygen saturation, respiratory rate or mean arterial pressure following injection citicoline.

Of 20 babies, only one died in neonatal period due to severe pulmonary hypertension. The first-hour capillary blood pH of this baby was 6.88 with serum lactate of 15 mmol/L and base deficit was 18 showing severe metabolic acidosis. His first and 5-minute APGAR scores were 01 and 03, respectively. He was placed on mechanical ventilation and given all possible treatment for pulmonary hypertension in the form of magnesium sulphate and sildenafil prior to his demise.

Nineteen babies survived and were discharged from our neonatal unit. The mean duration of hospital stay was 5.10 ± 2.337 days. The mean time for the establishment of the oral feeds or the development of sucking reflex was 18.95 ± 8.91 hours. All 19 babies were seizures-free at the time of discharge.

This was the first study of its kind where citicoline was used to treat moderate to severe birth asphyxia. The results are very promising as only one baby died during the study period.

Citicoline is a promising drug for the treatment of newborns with moderate to severe birth asphyxia. In this pilot study, it proved to be very effective as far as the duration of hospital stay, the frequency of seizures, and establishment of neonatal reflexes in the form of oral suck are concerned

Large, multicenter studies and randomised controlled studies with long term follow-up are required to establish a definitive role of citicoline in moderate to severe birth asphyxia.

ETHICAL APPROVAL:
Approval from hospital Ethical Committee was sought.

PATIENTS' CONSENT:
Informed written consents were taken from all the parents, whose newborns were considered to be eligible for the study.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AK: Conception and design, literature search, manuscript writing, data analysis and interpretation.
ZA: Conception of idea, literature search, critical revision.
AE: Data acquisition, analysis and interpretation, manuscript drafting.

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