Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Importance of Melatonin in the Treatment of Hypoxic Ischemic Encephalopathy in Neonates

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Received: June 2020
Accepted: June 2020

ABSTRACT

Background: Objective: To determine the outcome of melatonin as an adjunct therapy on the results of newborns hospitalized with hypoxic ischemic encephalopathy. Study Design: A Randomized controlled trial. Place and Duration: In the Department of Paediatrics, Sahiwal Medical College & DHQ Teaching Hospital Sahiwal for one year duration from January 01 2019 to December 31 2020. **Methods:** This study includes neonates who meet the inclusion criteria of hypoxic ischemic encephalopathy and are admitted within twelve hours after delivery, with 34 weeks or above a gestational age. Is ischemic hypoxia and shows up inside 12 hours of birth. The hypoxic ischemic encephalopathy severity was evaluated by the Thompson score. Patients were randomly assigned to the standard treatment group and 10 mg melatonin oral intervention group by nasogastric tube on admission. The newborn was observed for 28 days to perceive the melatonin effects on survival. Data was recorded utilizing SPSS 20. **Results:** There were 100 newborns with 36.81 ± 1.7 weeks gestational age and 2578.75 ± 536 grams average normal birth weight. There were 50 (half) individuals in two groups. 31 (62%) cases in the standard treatment group and in the intervention group, 40(80%) cases were survived (p = 0.03). **Conclusion:** The utilization of melatonin as adjuvant therapy in the treatment of neonates with hypoxic ischemic encephalopathy prompted better endurance.

Keywords: Hypoxic ischemic encephalopathy, Melatonin, Survival rate.

INTRODUCTION

Hypoxic ischemic encephalopathy (IE) stays a significant reason for neonatal illness and mortality, particularly in regions with restricted assets.[1,2] While the revealed pervasiveness of HIE is 0.7-1.1/1000 live births in developed regions, it increments to 100-260/1000 live births in under-developing region.[3] Around the world, 23% of early neonatal mortality are predominantly brought about by HIE.[4,5] Globally, asphyxia causes almost a fourth of 3.6 million deaths of neonates every year.[6] In Pakistan, mortality of neonates was 46 for every 1000 live births, and 27% of all mortality were expected to be due to asphyxia during childbirth. One Karachi investigation discovered newborn mortality as 34/1000 live births; another study discovered 16% of neonatal mortality was due to HIE, and 64% were related with HIE.[7] As per the WHO, asphyxia from birth is characterized as "the failure to begin and keep up breathing at birth." There is no typical tool for HIE.[8] Different clinical/seriousness assessment frameworks have been created to classify encephalopathy related with asphyxia during childbirth.[9] The Thompson score is one of the frameworks utilized for this reason with a specificity of 96%. Birth asphyxia leads to injury in two stages; sudden phase of neuronal cell damage followed by a 2nd stage, primarily because of oxidative damage, apoptosis and inflammatory cytokines.[10] Infants experiencing asphyxia during childbirth can develop permanent and severe neurological deficits in the form of epilepsy, cerebral palsy (CP), learning, hearing impairment, mental retardation and visual impairment, etc. in the form.[11] Ideal HIE treatment includes continuous supportive care, rapid resuscitation (fluids / electrolytes, thermal regulation, seizures control and blood sugar homeostasis). Though, either with prime treatment, about half of neonates with modest to severe encephalopathy may progress towards severe disability or may die.[12]

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenously created indolamine released mainly by the pineal gland. It is a characteristic looking neuroendocrine molecule that is discharged because of the light-dark ecological cycle. A few examinations have researched the promising effect of melatonin in cancer prevention agent, immune modulation and anti-inflammatory. The liver normally metabolize the Melatonin and discharged by the kidneys.[11,12] Melatonin unreservedly crosses the blood-brain barrier with a safety profile and good efficacy. Even at high doses, no serious side effects of melatonin have been reported.

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As of late, melatonin has become a promising alternative to limit neurological sequelae optional to HIE. One examination indicated that melatonin was neuroprotective in a neonatal model of mouse and excitotoxic white matter lesions imitating HIE. Also, other investigation indicated that early organization of melatonin in newborn children with HIE can improve brain injury.[13] The examination additionally indicated that just a single patient (1/15) of the melatonin group died, whereas 4 died in the control group. Additional investigation distinctly indicated that free oxygen radicals expanded essentially in newborns with asphyxia than who were not asphyxiated and there was a reasonable decrease in level at twelve and twenty four hours in the wake of taking melatonin.[14] It was additionally reported that 30 percent of babies with asphyxia passed away within 72 hours, and every asphyxiated newborns got melatonin endure.

In neonates with asphyxia during childbirth, early measures ought to be taken for convenient finding and therapy to improve results.[15] This examination was intended to evaluate the role of melatonin as adjuvant therapy in neonatal with hypoxic ischemic encephalopathy. The essential speculation was that early organization of melatonin as adjuvant therapy to the hypoxic ischemic encephalopathy infant could improve brain injury, bringing about fast recuperation and better endurance.

MATERIALS AND METHODS

This randomized controlled trial was held in the Department of Paediatrics, Sahiwal Medical College & DHQ Teaching Hospital Sahiwal for one year duration from January 01 2019 to December 31 2020. The ethical committee has approved the study and non-probability convenient sampling was used to select patients. The sample size was assessed using a significance level at 5% and power of test at 90% with probable hypoxic ischemic encephalopathy patient's percentage as 66% and control group as 33%.

According to the HIE case definition, babies who admitted at 34 weeks or more within 12 hours after delivery hospitalized to the neonatal unit were included. The ones with characteristics other than hypoxic ischemic encephalopathy were excluded at the time of admission. The HIE diagnosis was grounded solely on clinical symptoms, and the hypoxic ischemic encephalopathy severity was evaluated by Thompson score [Table 1].

Table 1: Thompson Score.

Sign	0	1	2	3
LOC	Regular	Stare, Hyper alert	Exhausted	Comatose
Tone	Regular	Hypertonia	Hypotonia	Flaccid
Posture	Regular	Cycling, Fisting	Strong Distal Flexion	Decerebrate
Fits	Regular	< 3Per Day	> 2Per Day	
Grasp	Regular	Poor	Not present	
Moro	Regular	Partial	Not Present	
Fontanel	Regular	Full, Not-Tense	Tense	
Suck	Regular	Poor	Lacking ± Bites	
Respiration	Regular	Hyperventilation	Transitory Apnea	IPPV (Apnea)

Parental consent was attained. Sociodemographic data were recorded like age, gestational age, sex, place of birth and type of birth, and weight at birth. Newborns were randomly assigned to a standard treatment group or intervention group (melatonin) with computer generated numbers. All newborns received standard postnatal asphyxiation treatment, including intravenous (IV) fluids, oxygen therapy, and broad-spectrum antibiotic coverage for the possible infection, intensive monitoring, and fits control when needed. In adding to the standard treatment, infants from the intervention group were given a 10 mg melatonin in single dose from the nasogastric tube (NG) after ingestion. The impact of intervention on the endurance of the studied cases were diligently supervised up to 28 days of life. Infants who did not finish the study and objected to medical advice (LAMA) were omitted from the study.

The SPSS version 20. 0 was used for data analysis. Inferential and descriptive statistics were determined according to the type of variable and the result. A Chi-square was used to parallel responses among groups. P value less than 0.05 was taken significant.

RESULTS

There were 50 patients in both groups. 36.81 ± 1.7 weeks was the overall mean age of gestation and 2578.75 ± 536 grams was the average weight at birth. The males were 53 (53%) and females were 47 (47%). 49 (49%) children were born in private maternity hospitals, at home 27 (27%) were born, and 24(24%) were born in government hospitals. Likewise, the HIE score was similar in both groups and there was no variance statistically in the basic demographic variables among the two groups [Table 2].

In terms of results, 19 (38%) children died in the standard treatment group and in the intervention group; 10 (20%) died (p = 0.03) [Table 3].

There were 14 (14%) newborns with mild HIE and all (100%) survived regardless of the group. Regarding HIE, mean mortality was not significant in the standard treatment group and in the intervention group (p = 0.60). However, in severe HIE 13 (54%) children in the standard group treated expired compared to 6 (26%) in the intervention group (p = 0.04) [Table 4]. Male neonates showed a

better survival rate of 23 (88.5%) in the intervention group compared to 11 (64, 7%) in the standard treatment group (p + 0.12).

Table 2: shows the study groups Baseline demographic data (n = 100).

	Standard Treatment Group (50 cases)	Intervention Group (50 cases)	P-value
Gender			
Male	22(41.5%)	31(58.5%)	0.07
Female	28(59.6%)	19(40.4%)	
Place of birth			
Public sector Hospitals	13(26%)	11(22%)	0.783
Private sector Hospitals	23(46%)	26(52%)	
Home deliveries	14(28%)	13(26%)	
Mode of delivery			
SVD	34(68%)	33(66%)	1.00
C-Section	16(32%)	17(34%)	
Weight at admission			
<2500g	21(42%)	15(30%)	0.371
2500-3500g	24(48%)	30(60%)	
>3500g	5(10%)	5(10%)	
Gestational age			
34-36 weeks	23(46%)	22(44%)	0.99
>37 weeks	27(54%)	28(44%)	
HIE grading			
Mild	7(14%)	9(18%)	0.79
Moderate	19(38%)	18(36%)	
Severe	24(48%)	23(46%)	

Table 3 shows the Study Groups clinical Outcome in (n = 100)

		Outcome		P-value
		Survived	Expired	
Group of treatment	Standard	31(62%)	19(38%)	0.03
	Intervention	40(80%)	10(20%)	

Table 4: Comparison of study groups based on clinical outcomes and HIE Grading (n = 100).

		Treatment group	Outcome		P-value
			Survived	Expired	
HIE grades	Mild	Standard Treatment Group	6(100%)	0(0%)	
		Melatonin Group	8(100%)	0(0%)	
	Moderate	Standard Treatment Group	15(75%)	5(25%)	0.6
		Melatonin Group	16(84%)	3(16%)	
	Severe	Standard Treatment Group	11(46%)	13(54%)	0.04
		Melatonin Group	17(74%)	6(26%)	

A better survival rate was noted in children born via C-section in the intervention group than in the standard treatment group (p = 0.08).

DISCUSSION

Despite advances in perinatal care, hypoxic ischemic encephalopathy vestiges a vital source of infant morbidity and mortality, especially in countries with restricted resources.[15,16] HIE results in severe and permanent neurodevelopmental deficits. HIE affected children place a significant burden on the whole country and on family members.[17] Although with optimum HIE administration, up to half of people with moderate to severe HIE can die or develop disability. Drug treatment remains a long-awaited need to minimize the degree of encephalopathy and improve clinical outcomes. Due to the wide therapeutic assortment, melatonin is a viable choice to improve brain damage secondary to asphyxia at birth. In an animal model; the neuroprotective importance of melatonin has already been verified.[18,19]

This is the only local analysis assessing the enhancement of clinical outcomes in infants with HIE who received newer treatment protocols, such as melatonin, when given early. However, there are few available literature on human studies of this intervention internationally. Melatonin was not related with significant side effects.[20]

Similarly, another study has shown that melatonin is beneficial in the treatment of infants with hypoxic ischemic encephalopathy. There was a major decrease in the concentration of free oxygen radicals after taking melatonin in asphyxiated newborns. This study also showed that 38% of asphyxiated children who were not given melatonin expired within 72 hours after birth, and all asphyxiated babies who took melatonin survived.

The present literature has its limitations and advantages. The study people was randomized to eliminate any likelihood of selection prejudice. Likewise, a positive melatonin group could not be associated with another disturbing factor.[21] Not being blind is another limitation in this study.

However, due to the small sample size, we were unable to determine the association of individual Thompson score variables (posture, tone, reflexes, convulsions and breathing).[22] So, bigger randomized controlled trials (RCTs) with extensive observations are desirable to instrument the long-awaited management to reduce the squeal of hypoxic ischemic encephalopathy. Huge multi-centre studies are necessary to verify the outcomes.[23]

CONCLUSION

The use of melatonin as adjuvant therapy in the treatment of neonates with hypoxic ischemic encephalopathy improved the short-term endurance ratio.

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How to cite this article: Mustafa S, Yasin M, Israr S, Abbas S, Parveen T, Kamal Z. Importance of Melatonin in the Treatment of Hypoxic Ischemic Encephalopathy in Neonates. Ann. Int. Med. Den. Res. 2020; 6(4):PE04-PE07.

Source of Support: Nil, **Conflict of Interest:** None declared