RANDOMIZED CONTROL TRIAL ARTICLE

Role of melatonin in management of hypoxic ischaemic encephalopathy in newborns: A randomized control trial

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Abstract

Objective: To find out the effect of melatonin as adjunct therapy on outcome of admitted newborns presenting with hypoxic ischaemic encephalopathy.

Methods: This randomized controlled trial was conducted at King Edward Medical University, Lahore, Pakistan, from October 2016 to March 2017, and comprised newborns with gestational age of 34 weeks or higher who fulfilled the definition of hypoxic ischaemic encephalopathy and presented within 12 hours of birth. The severity of hypoxic ischaemic encephalopathy was assessed by Thompson score. The subjects were randomised into standard treatment group and intervention group which received melatonin 10mg orally via nasogastric tube at admission. Newborns were followed for 28 days to see the effect of melatonin in terms of survival rate. Data was analyzed using SPSS 20.

Results: There were 80 newborns with overall mean gestational age of 36.81±1.7 weeks and mean birth weight of 2578.75±536 grams. Each of the two groups had 40(50%) subjects. In the intervention group, 35(87%) subjects and 26(65%) cases in the standard treatment group survived (p=0.03).

Conclusion: Administration of melatonin as an adjunct therapy in the management of newborns with hypoxic ischaemic encephalopathy led to improved survival rate.

Keywords: Newborn, Hypoxic ischemic encephalopathy, Melatonin, Survival rate. (JPMA 68: 1233; 2018)

Introduction

Hypoxic ischaemic encephalopathy (HIE) remains an important cause of neonatal morbidity and mortality, especially in resource-limited countries. The reported prevalence of HIE is 0.5-1/1000 live births in developed countries, while it escalates up to 100-250/1000 live births in developing countries.[1] Globally 23% of the early neonatal deaths are primarily due to HIE.[2] Worldwide, asphyxia causes almost one quarter of the 3.6 million neonatal deaths each year.[3] In urban Pakistan, the neonatal mortality rate was 47 per 1000 live births, while 26% of the total deaths were only due to birth asphyxia.[4] A study[5] from Karachi reported neonatal mortality rate as 34/1000 live births; 64% were due to HIE, whereas another sudy[6] reported 16% neonatal mortality attributed to HIE.

According to the World Health Organisation (WHO), birth asphyxia is defined as, "the failure to initiate and sustain breathing at birth".[7] There is no gold standard tool for HIE. The various clinical scoring/staging systems were designed to classify the encephalopathy associated with birth asphyxia. Thompson score is one such system being used for this purpose with 96% specificity.[8] Birth asphyxia leads to two-stage injury; an instantaneous phase of injury to neuronal cells, followed by the second stage mainly due to inflammatory cytokines, oxidative damage and apoptosis. Babies who suffer from birth asphyxia may develop severe and permanent neurological deficit in the form of cerebral palsy (CP), epilepsy, mental retardation, learning, visual and hearing impairments etc.

Optimal management of HIE includes prompt resuscitation, continued supportive care (thermal regulation, fluid / electrolytes, blood glucose homeostasis and control of seizures).[9] However, even with optimal management, approximate half the newborns with moderate to severe encephalopathy may either die or develop severe disability.[10]

N-acetyl-5-methoxytryptamine (melatonin) is an endogenously produced indolamine primarily produced by pineal body.[11] It is a naturally appearing neuroendocrine molecule released as a result of environmental light-dark cycle. Various studies have explored promising role of melatonin as anti-oxidant, anti-inflammatory and in immune modulation.[12,13] Melatonin is usually metabolised in liver and excreted by the kidneys. Melatonin crosses the blood-brain barrier freely with good efficacy and safety profile.[14] No significant untoward effect of melatonin has been reported yet even with higher doses.[15]

In the last few years, melatonin has become the

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promising option to minimise the neurological sequelae secondary to HIE.[16] A study[17] demonstrated that melatonin was neuro-protective in a newborn mouse model of excitotoxic white matter lesions mimicking HIE. Similarly, one study[11] also concluded that early administration of melatonin in HIE newborns may ameliorate the brain injury. The study, also showed that only one patient (1/15) died in the melatonin group, while four (4/15) died in the control group.[11] Another study[18] clearly showed that the oxygen-free radicals were markedly raised in asphyxiated newborns than those without asphyxia, and there was marked reduction in the level at 12 and 24 hours of life after getting melatonin. It also documented that 30 per cent of asphyxiated newborn who did not receive melatonin died within 72 hours, whereas all the asphyxiated newborns who received melatonin survived.

In newborns with birth asphyxia, institutions of early measures for prompt diagnosis and management should be ensured to improve the outcome. The current study was planned to assess the role of melatonin as adjunct therapy on the outcome of newborns presenting with HIE. The underlying hypothesis was that early administration of melatonin as an adjunct therapy to the newborn suffering from HIE may ameliorate brain injury, resulting in earlier clinical recovery and better survival.

Patients and Methods

This randomised controlled trial was conducted in the Neonatal Section of the Department of Paediatrics at King Edward Medical University, Lahore, Pakistan, from October 2016 to March 2017. After approval from the institutional review board, newborns were enrolled using non-probability convenient sampling. The sample size of was estimated by using 5% level of significance, 90% power of test with expected percentage HIE patients as 66% and control group as 33%.[11]

Newborns presenting within 12 hours of birth with gestational age of 34 weeks or higher, consistent with case definition of HIE, admitted to neonatal unit from home or public/private hospitals were included, while those having features other than HIE at admission were excluded. The diagnosis of HIE was based on clinical features alone, and the severity of HIE was assessed by Thompson score[8] (Table-1).

Informed consent was obtained from the parents. Socio-demographic data was recorded for age, gender, gestational age, place and mode of delivery, and birth weight. The newborns were randomly allocated by computer-generated numbers to either the standard treatment group or the intervention group (melatonin). All the newborns were given standard treatment of birth asphyxia, which included oxygen therapy, intravenous (IV) fluids, intensive monitoring, broad-spectrum antibiotic cover for possible role of infection and control of fits if required. In addition to standard therapy, newborns in the intervention group received single dose of 10mg melatonin via nasogastric (NG) tube at admission. Effect of the intervention on survival of study cases was closely monitored till 28 days of age. Babies who left against medical advice (LAMA) or did not complete the study period were excluded.

Data were analysed using SPSS 20. Descriptive and inferential statistics were calculated as per the type of variable and outcome respectively. Chi-square was applied to compare treatment response between the groups. $P \leq 0.05$ was considered significant.

Results

There were 80 newborns with 40(50%) in each of the two

Table-1: Thompson Score.

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
LOC	Normal	Hyperalert, Stare	Lethargic	Comatose
Fits	None	< 3 Per Day	> 2 Per Day	
Posture	Normal	Fisting, Cycling	Strong Distal Flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± Bites	
Respiration	Normal	Hyperventilation	Brief Apnea	IPPV (Apnea)
Fontanel	Normal	Full, Not Tense	Tense	

Maximum Score = 22, Mild HIE: 1-10, Moderate HIE: 11-14, Severe HIE: 15.
LOC: Level of consciousness.

Table-2: Baseline demographic information of study groups (n = 80).

	Standard Treatment Group (40 cases)	Intervention Group (40 cases)	P-value
Gender			
Male	17(39.5%)	26(60.5%)	0.07
Female	23(62.2%)	14(37.8%)	
Place of birth			
Public sector Hospitals	10(25%)	8(20%)	0.783
Private sector Hospitals	19(47.5%)	22(55%)	
Home deliveries	11(27.5%)	10(25%)	
Mode of delivery			
SVD	29(72.5%)	28(70%)	1.00
C-Section	11(27.5%)	12(30%)	
Weight at admission			
<2500g	18(45%)	12(30%)	0.371
2500-3500g	20(50%)	26(65%)	
>3500g	2(5%)	2(5%)	
Gestational age			
34-36 weeks	18(45%)	17(42.5%)	0.99
≥37 weeks	22(55%)	23(57.5%)	
HIE grading			
Mild	4(10%)	6(15%)	0.79
Moderate	16(40%)	15(37.5%)	
Severe	20(50%)	19(47.5%)	

SVD: Single vaginal delivery
C-Section: Caesarean section.

Table-3: Clinical Outcome in Study Groups (n = 80).

		Outcome		P-value
		Survived	Expired	
Group of treatment	Standard	26	14	0.03
		65%	35%	
	Intervention	35	5	
		87.5%	12.5%	

groups. The overall mean gestational age was 36.81±1.7 weeks and the mean birth weight was 2578.75±536 grams. There were 43(53.5%) boys and 37(46.5%) girls. Overall, 41(51.3%) babies were born in private maternities, followed by 21(26.2%) home deliveries and 18(22.5%) in public-sector hospitals. Similarly, HIE grading was comparable in both group, and there was no statistical difference in baseline demographic variables between the groups (Table-2).

In terms of outcome, 14(35%) babies died in the standard treatment group, while 5(12.5%) died in the intervention group (p=0.03) (Table-3).

There were 10(12.5%) newborns with mild HIE and all of them (100%) survived regardless of the group. In terms of moderate HIE mortality rate of standard treatment group 3 (19%) versus 1(6.7%) in intervention group was not significant (p=0.60). However, in severe HIE, 11(55%) babies of standard treatment group died compared to 4(21%) in intervention group (p=0.04) (Table-4).

Table-4: Comparison of study groups based on HIE Grading and clinical outcome (n = 80).

		Treatment group	Outcome		P-value
			Survived	Expired	
HIE grades	Mild	Standard Treatment Group	4(100%)	0(0%)	
		Melatonin Group	6(100%)	0(0%)	
	Moderate	Standard Treatment Group	13(81%)	3(19%)	0.60
		Melatonin Group	14(93.3%)	1(6.7%)	
	Severe	Standard Treatment Group	9(45%)	11(55%)	0.04
		Melatonin Group	15(79%)	4(21%)	

HIE: Hypoxic ischaemic encephalopathy.

Male babies showed better survival rate in intervention group 23(88.5%) compared to 11(64.7%) in the standard treatment group (p+0.12).

Babies born by Caesarean Section (CS) had better survival rate 10(83.3%) in intervention group compared to 5(45.5%) in the standard treatment group (p=0.08).

Discussion

In spite of advancement in perinatal care, HIE remains an important cause of neonatal mortality and morbidity, especially in resource-limited countries. HIE leads to permanent and severe neurodevelopmental disabilities. The children with HIE cause substantial burden to the family and the nation as a whole. Even with optimal management of HIE, up to half of those with moderate to severe HIE may either die or develop severe disabilities.[10] Pharmacological therapies to minimise the degree of encephalopathy and improve the clinical outcome remains a long-awaited need. Melatonin, due to its broad therapeutic range, is a feasible option to ameliorate the brain injury secondary to birth asphyxia. The neuro-protective role of melatonin in animal model has been demonstrated already.[14,17]

This is the first local study to assess the improvement in clinical outcome of babies receiving newer modalities like melatonin when administered early while compared to standard treatment group in newborns with HIE. However, internationally there is limited published evidence for human studies on this intervention as well. Melatonin has not been associated with noticeable untoward effects.

The present study showed higher mortality 14(35%) in the standard treatment group compared to 5(12.5%) babies in the melatonin group. Our results are comparable with one study[11] which also observed the favourable outcome with melatonin. In that study, 4/15(27%) babies died in hypothermia group, while only 1/15(7%) died in the melatonin group. The addition of hypothermia in both groups may be the possible cause of lower mortality in that study compared to our results. It also showed there was fewer incidence of white matter abnormalities and seizure activity in infants with melatonin group.

Similarly, another study[18] concluded that melatonin is useful in the management of newborns with HIE. There was significant reduction in oxygen free radical concentration in asphyxiated newborns after receiving melatonin. That study also showed 30 per cent asphyxiated babies who did not receive melatonin died within 72 hours after birth, whereas all the asphyxiated newborns who received melatonin survived.

The current study has its strengths and limitations. The study population was randomised to exclude the possibility of any selection bias. Similarly, the favourable outcome of melatonin group could not be related to other confounding factor as well. Non-blinding in this study is another limitation. However, we could not establish the correlation of Thompson score individual variables (tone, posture, fits, reflexes, respiration) due to the small sample size. Therefore, larger randomised controlled trials (RCTs) with extended follow-up are needed to implement a long-awaited feasible treatment to lessen the sequelae of HIE. Large multicentre trials are needed to generalise the results.

Conclusion

Administration of melatonin as an adjunct therapy in the management of newborns with HIE improved short-term survival rate.

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Disclaimer: Due to non-existence of RCT registration authority RCT Trial Number has not been allotted. The approval to conduct the study has been taken from local IRB.

Conflict of Interest: None.

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