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Original Article

Evaluation and Prognosis of Neonates with Asphyxia Treated by Hypothermia

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ABSTRACT

Background: Asphyxia is a perinatal incident of high mortality rate. Therapeutic hypothermia in both the head and the whole body has been proposed as an effective method in this regard. In this study, we compared these methods in neonates with asphyxia.

Methods: In this study, 16 neonates with asphyxia in two hospitals including Alzahra Hospital (head hypothermia) and Taleghani Hospital (whole body hypothermia) underwent therapeutic hypothermia for 72 hours. Temperature was maintained precisely controlled by several sensors. Moreover, body cooling was performed on the trunk and limbs of the neonates. The temperature and vital signs were controlled every hour while biochemistry and coagulation tests were performed regularly. Furthermore, the early and late complications of the patients, including developmental disorders, were closely evaluated. The two groups were compared using Chi-square and Mann Whitney U Test via SPSS software V.16 and the P value of less than 0.05 was considered significant.

Results: In total, 16 cases with the gestational age of 38±2 weeks were enrolled in this study. Of the 9 cases of head cooling, one expired and 2 others experienced mild developmental disorders. Of the 7 neonates of whole body cooling trail, 3 expired, one experienced minor developmental disorders and one case showed major signs of developmental disorders. No significant differences were found in terms of the feeding time (head group 5±2, body group 8±5 days) and the discharge time (head group 15±8, body group 14±5 days) of the studied neonates.

Conclusion: The head hypothermia method seems to be associated with a lower mortality compared to the whole body method. However, the difference was not statistically significant in the sample size above. Therefore, performing such procedures on larger samples could confirm the findings of this study.

Keywords: Asphyxia, Cooling, Hypoxic ischemic encephalopathy, Neonates

Introduction

In developing countries, perinatal Asphyxia occurs at a rate of 10 to 20 per 1000 live births while in developed countries, it happens at an approximate rate of 3 to 5 per 1000 live births. Asphyxia-related mortality rate fluctuates between 24% to 61%.

The brain is the organ most damaged by hypoxic-ischemic encephalopathy which is divided into three major categories of mild, moderate and severe. It has been reported that 10% to 20% of neonates with moderate injuries die while 30% to 40% are likely to experience neurological defects. In the severe form, it is reported that 50% to 60% of the neonates die and almost all the surviving cases will experience neurological complications (1).

Until recent years, the treatment of hypoxic-ischemic encephalopathy was restricted to supportive therapy and there were no specific treatments available for this condition. However, hypothermia has been considered as an efficient therapeutic method to reduce the mortality associated with hypoxic-ischemic encephalopathy within the past decade (2).

The mechanism of injury in ischemic hypoxia mainly involves oxygen deprivation in the tissues followed by anaerobic glycolysis of glycosylated phosphate deficiency and an increase in calcium, free radicals and such stimulators of the nervous system as glutamate. If the process is not drawn to a close, cell death is likely to occur through apoptosis (3).

In 1930, Temple Fay and colleagues used cold therapy for the first time in order to treat cancer, sepsis, brain tumors, Hodgkin's disease and drug-resistant, intractable pains (4). The mechanism of

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hypothermia in preventing tissue damage involves a reduction in the metabolic demand of the tissue and the cytokines level while preventing cell apoptosis (5, 6).

Materials and Methods

By prospective, non-randomized, regular sampling, 16 neonates were selected with the gestational age of >35 weeks, an APGAR score of <6 within 5 minutes after birth, pH<7.1 in the umbilical cord blood and base deficit of <-16 mmol/L.

Within the first six hours, we conducted renal function tests, coagulation tests, blood cultures and liver function tests and umbilical cord blood gas samples were also recorded within the first hour. Consequently, all the neonates were found to be eligible for hypothermia treatment and so, they were classified into two treatment groups.

The first group consisted of the subjects undergoing selective head cooling and the second group included the subjects treated by total body cooling using cold water bags.

After they were neurologically evaluated within 6 hours of birth, both groups underwent hypothermia with the rectal temperature maintained between 33° to 35°C. The subjects' blood glucose and vital signs including blood pressure, heart rate and respiratory rate were supervised every six hours. Furthermore, electrolytes and cell counts were monitored on a daily basis.

In the neonates of the head-cooling group who were under ventilator, the inspiratory air temperature was maintained at 37 ° C and a warmer temperature of 35° C was also set for the skin sensor.

After 72 hours of hypothermia, re-warming continued for six hours. In case of severe bleeding or refractory hypertension, the neonate would be excluded from the study. Eventually, the cases were followed-up at the age of 8-22 months by reviewing the changes in the results of Ages & Stages Questionnaire (ASQ).

All the results were recorded in numeric or percentage terms. Qualitative variables were analyzed using Chi-square and Mann-Whitney U test was utilized for quantitative variables. The collected data were analyzed via SPSS software V.16 and a P value of less than 0.05 was considered as statistically significant.

Results

In total, 16 neonates over 35 weeks of gestational age with intrapartum asphyxia were enrolled in this study from June 2012 to June 2013 in Alzahra Hospital (9 cases) and Taleghani Hospital (7 cases). Head cooling was the method of choice in Alzahra Hospital while in Taleghani Hospital, whole body cooling technique was applied.

The subjects consisted of 10 female and 6 male neonates. The mean gestational age of the neonates was 38 ±2 weeks, with a minimum of 35 and a maximum of 41 weeks. The average weight of the neonates was 3000±700 g, with a minimum of 2300 and a maximum of 4100 g. The length of hospital stay for the head-cooling group and the whole body cooling group was 15±8 days and 14±5 days, respectively. The difference was not considered to be statistically significant (P=0.8).

Oral feeding in these neonates started on the fourth day for an average of six days in total and for a maximum of 24 days. The onset age of breast feeding in the head-cooling group and the whole body cooling group was 5±2 days and 8±5 days, respectively. The difference was not considered to be significant (P=0.5).

The first-minute APGAR score of the neonates was under 3 in 93% of the cases and in 7%, it was higher than 3. In none of the cases the score was over 7. Moreover, the fifth-minute APGAR score was below 3 in 70% of the neonates and it was between 3 and 6 in 30%. Of all the neonates in this study, 10 cases were born via vaginal delivery while 6 cases were born via Cesarean section.

The complications associated with the treatment of these neonates are depicted in Table 1.

The mean umbilical cord PH at birth in the head hypothermia group and the whole body hypothermia group was 7 and 7.1, respectively. The difference was not considered to be significant (P=0.1).

Furthermore, 8 out of 16 neonates required mechanical ventilation. The ventilation period was 25 hours on average, with a minimum of 6 and a maximum of 76 hours.

On the other hand, the mortality rate in the neonates with asphyxia treated by either head cooling or whole body hypothermia was 4 out of 16 (25%).

Table 1. The side effects observed during hypothermia therapy

Side effect	bradycardia	convulsion	hypotension	sclerema	Renal failure
Number of cases	9	7	5	1	1

In the head-cooling group, 1 out of 9 and in the whole body cooling group 3 out of 7 neonates died. Developmental assessment was conducted by ASQ in 10 cases of 12 surviving neonates through a follow-up period in the areas of social functioning, communication, fine and gross motor skills and problem solving. The follow-up revealed that 4 neonates had mild to severe neurological complications.

Of the neonates who were treated by whole body cooling, only one was found to have a severe degree of developmental impairment in all the assessed areas. In addition, two neonates of the head-cooling group were found to have mild impairments. One of them showed mild developmental impairment in two areas of problem solving and emotional connection and the other was found to suffer from mild impairment in problem solving.

In the whole body hypothermia group, one neonate was found to have mild gross motor skill impairment. Moreover, hypoglycemia was observed in one case which was reduced to 18 mg/dl on the first day, increased to 41mg/dl on the second day and reached 58mg/dl on the third day. According to the obtained results, hyperglycemia was observed at a higher incidence rate in 3 cases. No deaths occurred in either the hyperglycemic or hypoglycemic neonates.

Discussion

Saeed et al. conducted Hypothermia on infant mice suffering from hypoxic-ischemic encephalopathy. The results indicated the therapy to improve weight gain as well as increase the chance of survival (7) in the mice. On the same subject, research has it that head cooling of the fetal sheep from 90 minutes to 5 hours for 72 consecutive hours after the injury could positively affect the prevention of complications caused by brain tissue ischemia and hypoxia (8).

Nakamura and colleagues claimed that cooling could be performed for 72 hours without leading to any complications in human neonates (9).

Between 1960 and 1970, comprehensive research was conducted on the effects of cold on the performance of neonates upon asphyxia. Initially, studying animal models revealed that the tolerance of cerebral hypoxia symptoms was higher in hypothermia compared to normal ambient temperature. Therefore, researchers generalized their findings to the treatment of human infants (10).

Based on the findings of a Meta-analysis of 200 neonates, Miller and colleagues (1971) stated that hypothermia could noticeably enhance the prognosis of these infants (11). Nevertheless, hypothermia performed on preterm neonates in the operation room might lead to complications (12). Consequently, the nursing care of neonates through proper cooling and re-warming is of paramount importance in order to achieve success in this therapeutic method. Although they presumed that cooling at a temperature of 33.5 ° C will not probably have much influence on the neonate, they concluded that this temperature was a safer option (13). According to their study, central temperature of 32 or lower could cause serious complications in the neonates.

The treatment principles (14) include warming the delivery room without utilizing hyperthermia and deciding on the use of the cooling-off technique afterwards. On the other hand, hypothermia on neonates has to be based on the degree of compliance with factors such as APGAR, gestational age and laboratory findings (13).

Among other complications associated with this therapeutic method are coagulation disorders which appear in the form of disseminated intravascular coagulation and hypoglycemia.

Regardless of the type, the mortality rate of hypothermia according to some studies may vary from 39% to 80% (15). The long-term complications of asphyxia were observed at the age of 6 months. However, in 78% of the cases, normal development was observed which was statistically significant (16).

In the current study, death occurred in 4 (25%) out of 16 cases of asphyxia over 35 weeks of gestational age. In one case, it occurred at 2 days of age during hypothermia whereas in other cases, death occurred after hypothermia. In total, 3 of 4 deaths occurred in the whole body cooling group while only one occurred in the head-cooling group.

The complications caused by this method of treatment according to our findings were as follows:

1) Hypoglycemia and Sclerema Neonatorum in one case;
2) Coagulopathy in 2 cases;

Generally, the short-term complications during the treatment were similar between the two cooling methods. In addition, the mean values of blood glucose and coagulation tests were similar in both groups.

The most common health problems in the course of our study were hypotension, bradycardia, seizures and kidney failure many of which could be the symptoms of asphyxia as well.

We studied the evolution of neonates with asphyxia by determining the late squeal of the subjects at 8-22 months of age.

When evaluated in five fields including gross and fine motor skills, problem solving, communication and social areas, severe developmental disorders were observed in one of the 12 survivors of the neonatal asphyxia. On the other hand, mild disorders were reported in 3 cases.

In the present study, 90% of the cases with asphyxia who were treated by head cooling or whole body cooling experienced normal neural development and no severe developmental delay was observed during the follow-up period.

Conclusion

Asphyxia is a fatal condition during the prenatal period which can lead to mortality and morbidity of up to 50% in spite of the availability of the cooling therapy. Through the whole body cooling method, 3 out of 7 neonates died while in the head-cooling group, there was only one death out of 9 cases.

In the remaining 12 cases, 3 showed some degree of developmental delay, one case had severe and two others experienced mild disorders between 8 to 22 months of age.

It seems that head cooling could be a more reliable method for neonatal asphyxia management. However, it is necessary that this study be repeated in a larger sample size as to confirm the findings.

Conflict of interest

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