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Effectiveness of vitamin C and E intervention on neuro-development of newborn baby with birth asphyxia: A randomized control trial.

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Abstract

Background: Antioxidants such as vitamin C and E acts by giving electrons to free radicals which acts as an extra electron stabilizer to preventing them from causing damage to the cells in the body.
Objectives: To assess the effectiveness of Vitamin C and E intervention on the neurodevelopment of birth asphyxiated newborn babies.
Materials and methods: The study design was non-randomized, matched control carried out at neonatal ICU among birth asphyxiated term neonates delivered at rural tertiary health care center located in the state of Maharashtra, India. The study duration executed from 1st January 2019 to 30th June 2019. A total of 100 participants were enrolled in the present study and followed over six months. A structured questionnaire was designed, validated and utilized to collect data from participants. The data was analyzed for descriptive and inferential statistics by using SPSS 20 statistical software.
Results: The mean blood levels of vitamin C and E were significantly higher in the study group as compared to control and also observed, those newborn babies received vitamin C and E, their blood levels were 5.8 and 5.2 times higher in the study group as compared to control as indicated by odd's rats respectively. Max, 74% of newborn babies who received Vitamin C and E were hospitalized for less than 5 days. The maximum, 83.3% participants from the intervention group showed normal neurodevelopment and provides 3.7 times protective phenomenon concerning neurodevelopment.
Conclusion: The study concluded that early administration of vitamin C and E in newborn babies serves as a protective shield for normal neurodevelopment.

Keywords: Vitamin C, Vitamin E, Birth asphyxia, New born, Neurodevelopment.

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Introduction

The antioxidants play an important role in reducing cellular oxidative stress. Antioxidants such as vitamin C and vitamin E work by giving electrons to free radicals; the extra electron stabilizes them, preventing them from causing further damage to the cells in the body. Despite the experimental evidence for a potentially neuro-protective role of ascorbic acid, the efficacy of this drug has not been studied in infants with hypoxic-ischemic encephalopathy. Vitamins C and E serve as proximate principles of a balanced diet rich in antioxidants essential for growth and development in the pediatric population. Vitamin E (α-tocopherol and β-tocopherol) can penetrate the cell membrane and provides a protective shield against lipid peroxidation. Vitamin C (ascorbic acid) also has antioxidant properties and act as an electron donor, which further resists the entry of other agents from becoming oxidized and quenching over production of FR [1].

There are few *in vitro* documents reported that Vitamin E intervention among the rat population using nervous tissue cultures can decrease lipid peroxidation increased the survival and neuritic extension of neurons. *In vivo*, prophylactic administration of vitamin E (α-tocopherol) has also been shown to have anti-inflammatory properties.

The study observed that the use of large doses of α-tocopherol significantly decreases the release of pro-inflammatory cytokines from cell lines that are exposed to lipopolysaccharide [2].

The highest concentrations of vitamin C in the body are found intracellularly in brain neurons and the brain is known to retain vitamin C preferentially in cases of deficiency. Animal experiments have demonstrated that vitamin C is crucial for early brain development. Several mechanisms may be involved in neuronal damage induced by vitamin C deficiency. Studies regarding the protective benefits of vitamins C and E in the perinatal period are limited.

Vitamin C deficiency is surprisingly common within the human population of the western world although cases of clinical scurvy are rarely reported. Vitamin C deficient sub-populations include pregnant women sharing blood vitamin C with their fetus, mothers, who convey their vitamin C deficiency to newborns during breastfeeding and a recent Mexican study found severe vitamin C deficiency in ~30% of young children (age 0-2 y).

Although not specifically related to vitamin C, infants exposed to intrauterine growth restriction have increased neuronal degeneration and learning disabilities and other studies have shown that supplementation with antioxidants such as vitamin C may improve survival in preterm babies.

In the developing brain, chronic malnutrition is a well-established contributor to deviation in neuronal function, including the development of the hippocampus and cognitive impairment in both humans and *in vivo* animal models. In guinea pigs, fetal malnutrition results in reduced numbers of hippocampal and cerebellar neurons, linking malnutrition to neuronal damage in the developing brain as well as the possible involvement of micronutrient deficiencies. Despite these reports, no detailed studies exist on the possible consequences of chronic, non-scorbutic vitamin C deficiency and its potential effect on brain development. However, studies by us have shown that young guinea pigs are more prone to oxidative stress than are mature animals and that the developing brain of neonatal guinea pigs is particularly susceptible to vitamin C deficiency because of rapid growth and an immature antioxidant defense system.

The present study was conducted to measure the anti-oxidant levels and neurodevelopment in birth asphyxiated newborns before and after vitamin C and vitamin E administration [3].

Materials and Methods

The study design framed to carry out a present study was non-randomized pre and post-intervention with matched controls at neonatal ICU under the department of pediatrics. The study subjects were birth asphyxiated term neonates delivered at rural tertiary health care center located in the state of Maharashtra, India. The study duration was of six months and executed from 1st January 2019 to 30th June 2019.

Inclusion criteria

Term neonates (gestational age >37 weeks), birth asphyxia, Apgar score of <6 at 5 minutes and Clinical features suggestive of neonatal encephalopathy (coma, seizures or hypotonia).

Exclusion criteria

Pre-terms neonates (<37 weeks gestational age), healthy neonates crying immediately after birth and lethal congenital anomaly [4].

Sample size

A study was conducted by Rathee AVS, et al, observed the mean levels of antioxidants among the control group was 1.7347 ± 0.38 and in the study group 1.925 ± 0.53. Considering the given levels as a reference, we calculated the sample size as follows:

$N=2 \times (SD)^2 (Z1+Z2)^2/(M1-M2)^2$

M1=Mean test intervention, 1.70

M2=Mean control intervention, 1.94

S1=Standard deviation of M1, 0.38

S2=Standard deviation of M2, 0.53

S=Pooled SD, 0.461

1-α=Set level of confidence=0.95

1-β=Set level of power of test=0.8

Z1=Z value associated with alpha=1.644

Z2=Z value associated with beta=0.84

N=Minimum sample size=46

Hence to round up, in the present study, we enrolled 50 interventions and 50 controls each.

Ethical consideration

An institutional ethical clearance certificate was obtained before the commencement of the present study. Informed consent was obtained from the parents of the newborns before enrolling them in the study. The benefits of the administration of vitamin C and vitamin E will be explained [5].

Data collection

A self-designed, validated and structured questionnaire was used to collect the data from mothers of neonates as well as study participants. It datasheet includes demographic profile and relevant information of mother as well as a newborn baby before and after the intervention of vitamin E and C. Asphyxiated newborns were assigned into two groups as intervention and control one. The birth asphyxiated term neonates were received oral vitamin E and oral vitamin C as follows:

- Single-dose of vitamin E drops 200 IU within 6 hours of birth and
- Vitamin C tablet 250 mg in the pulverized form via infant feeding tube.

The asphyxiated newborns were divided into 3 groups based on Sarnat and Sarnat scoring into three stages of HIE *i.e.* HIE grade 1, HIE grade 2, and HIE grade 3 and they were compared with the controls in respected groups in context to biochemical parameters. The babies were followed for six months for a hospital stay as well as neurodevelopment [6].

Laboratory investigations

The venous blood in a quantity of 2 ml was collected in the plain bulb on the following days:

Sample 1: At the time of admission as baseline data.

Sample 2: 72 hours after administration of vitamin E and vitamin C.

Statistical analysis

The data were summarized into tables for frequency percentage distribution. Unpaired student t and *chi-square* test were practiced to identify the differences in the levels of Vitamin E and C.

The significant differences were considered when the p-value was less than 0.05 at a 95% confidence level by using statistical software SPSS Version 20 [7].

Results

In the present study, we assessed the mean blood levels of vitamin E before and after administration of vitamin E among the participants.

The mean blood levels of Vitamin E were significantly higher in the study group as compared to control after intervention as indicated by a p-value less than 0.05 at a 95% confidence level. The study also observed that those newborn babies received vitamin E at the time of the birth; their blood levels were 5.2 times higher than the control group (Table 1).

Mean vit. E levels	Study group	Control group	T-value	P-value
Before intervention	2.28 ± 0.11	2.22 ± 0.23	1.16	0.24
After intervention	3.89 ± 0.87	2.65 ± 0.57	5.21	0.001*

Table 1. Mean values of vit. E intervention in study and control group.

According to the mean blood levels of vitamin C were 3.89 and 2.65 in the study and control group after intervention and the difference was significantly higher in the study group as compared to the control.

The study also observed that those newborn babies received vitamin C, their blood levels were 5.8 times higher in the study group as compared to control as indicated by odd's ratio and p-value at 95% confidence level (Table 2).

Mean vit. C levels	Study group	Control group	T-value	P-value
Before intervention	2.73 ± 1.58	2.91 ± 1.43	0.49	0.62
After intervention	5.90 ± 1.24	4.08 ± 0.58	5.87	0.001*

Table 2. Mean values of vit. C intervention in study and control group.

This shows that 74% of newborn babies who received vitamin E and C were hospitalized for less than 5 days, whereas 88% of participants from the control group required more than 5 days hospital stay.

The hospital stay was significantly less in the intervention group as indicated by odd's ratio of 27 and p less than 0.05 at 95% confidence level (Table 3).

Hospital stay	Study group	Control group
<5days	37 (74.0%)	6 (12.0%)
>5 days	13 (26.0%)	44 (88.0%)
Chi-square value	31.9	
Odd's ratio	27	
Confidence interval	7.6 to 94.9	
P-value	0.0001*	

Table 3. Hospital stay after vitamin E and C intervention in study participants.

The neurodevelopment of study participants was assessed after the 3rd and 6th months of extra-uterine life. Among the study participants, 4% from the study group and 12% from the control group died before attainment of 6 months of extra-uterine life.

The maximum, 83.3% participants from the intervention group showed normal neurodevelopment as compared to the control, however, 40.9% of participants from the control group showed a delay in neurodevelopment and the difference was statistically significant as shown by odd's ratio of 3.7 and p-value, 0.03 at 95% confidence level (Table 4).

Neurodevelopment	Study group (n=48)	Control group (n=44)
Normal	40 (83.3%)	26 (59.0%)
Delayed	8 (16.6%)	18 (40.9%)
Chi-square value	4.56	
Odd's ratio	3.7	

Confidence interval	1.23 to 11.30
P-value	0.03*

Table 4. Neurodevelopment status after vitamin E and C intervention in study participants.

Discussion

The neurodevelopment of study participants was assessed after the 3rd and 6th months of extra-uterine life. The maximum, 83.3% participants from the intervention group showed normal neurodevelopment, however, 40.9% of participants from the control group showed a delay in neurodevelopment and the difference was statistically significant. The highest concentration of vitamin C in the human body is to be found intra-cellularly in brain neurons and acts as a precursor for neurodevelopment. The author, Maggini S, et al, in their study, discussed that vitamin C deficiencies could also compromise mental development in the early childhood period. A study conducted by H. Aly, et al observed comparatively lesser developmental delay *i.e.,* gross developmental and motor delay among the infants in whom vitamin C was administered as compared to control group. Several mechanisms may be involved in neuronal damage induced by vitamin C deficiency [8].

Animal experiments have been demonstrated that vitamin C is crucial for early brain development. *In vitro* evidence suggested that, in adult and fetal rat brain cultures, vitamin E can decrease lipid peroxidation and increase survival and neuritic extension of neurons. *In vivo*, prophylactic administration of vitamin E before hypoxia-ischemia can decrease the incidence of IVH. Protective effects on retinopathy of prematurity have also been reported with a reduction of ROP III+ from 5.3% to 2.8%. In a mouse model of Down syndrome, α-tocopherol suppresses lipid peroxidation in the hippocampus and ameliorates behavioral and cognitive impairments. α-tocopherol has also been shown to have anti-inflammatory properties. Administration of α-tocopherol, particularly in large doses, has been shown to decrease the release of pro-inflammatory cytokines from cell lines exposed to lipopolysaccharide [9].

Ascorbate deficiency in the postnatal mouse brain (in the presence of normal GSH levels) leads to diminished motor functions, yet an exaggerated response to a dopaminergic agonist. Ascorbate antioxidant effects are enhanced in conjunction with vitamin E. When vitamin E is oxidized, it forms α-tocopherol radical which is harmful, but vitamin C can mediate the return of α-tocopherol radical to α-tocopherol, thus regenerating α-tocopherol concentrations in plasma. In support of these findings, a study of transient intrauterine ischemia in pregnant rats showed that either vitamin E or vitamin C treatment alone, started before the ischemic insult, was able to decrease oxidative mitochondrial impairment in the fetal brain, but the improvement was greater when vitamins were administered together [10].

Conclusion

The study showed a significant reduction in hospital stay among intervention participants as compared to controls however, author Putzu A recorded no significant effect on the same and this difference could be due to critically ill patients participated in clinical trial. The study concluded that after administration of vitamin C and E, neonates showed a significant rise in blood concentration which serves as a protective shield for them to prevent form developmental delay as well as multiple organ damage and reduction in mortality.

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