Original Article

Indian Journal of Trauma and Emergency Pediatrics
Volume 9 Number 3, July - September 2017
DOI: http://dx.doi.org/10.21088/ijtep.2348.9987.9317.2

Effect of Vitamin C as an Adjuvant Therapy in Neonatal Sepsis

Rowshan Jahan Akhter*, B.H. Nazma Yasmeen, Md. Mahbubul Hoque***, M.A.K. Azad Chowdhury******

Abstract

Background: Neonatal sepsis is one of the major health problems throughout the world. The neonate is immunocompromised with incomplete development of multiple components of the immune system specially quantitative and qualitative deficiencies of the phagocyte systems. Vitamin C helps in eliminating, neutralizing and antagonizing toxins and mediators, by anti-inflammatory substances, and by immunomodulation. *Objective*: The aim of the study was to reduce the neonatal mortality from infection by using Vitamin C as an adjuvant therapy along with antibiotics. *Settings and Design:* This Randomized control trial was carried out in Dhaka Shishu (Children) Hospital during the period 1 April 2013-30th September 2014. *Methodology*: Neonates of 36 wks. or more gestational age and weighinge 2.5kg, presented with signs and symptoms of sepsis supported by positive CRP and or blood culture were assessed. All study patients were randomly divided into intervention group (Group A) and control group (Group B). In intervention group vitamin C, 100mg/kg was given for two consecutive days. *Results*: During the study period, total 279 neonates were assessed for eligibility and finally 137(68 in intervention group and 69 in control group) were enrolled after exclusion. There was significant difference in terms of cure (Both clinical and biochemical) was seen in 74.5% in group A and 25.5% in group B.) Mean decrease of CRP level in-group A was 42.44 (84.94%) mg/dl and in-group B was 14.39 (35.25%). There was statistically significant (P<0.001) decrease in CRP level in Intervention group along with clinical improvement. *Conclusion*: Vitamin C appears to be effective as an adjuvant therapy in neonatal sepsis. It maybe used as adjunct therapy in neonatal sepsis to reduce mortality and morbidity.

Keywords: Vitamin C.; Neonatal Sepsis; Adjuvant.

Introduction

Neonatal sepsis is one of the major health problems throughout the world. An estimated 4 million neonatal deaths occur around the world every year. Approximately 98% of these deaths occur in developing countries and two-thirds to three-quarters of neonatal deaths occur during the first week of life. These deaths are mostly attributable to infections, asphyxia, and consequences of prematurity and low birth weight and infections are a frequent and important cause of morbidity and mortality in the neonatal period. As many as 2% of fetuses are infected in utero[1], and 10% of infants are infected during the first month of life. The incidence of infection is higher in the neonatal period than at any other time in life, even if preterm babies are excluded[1]. In a study done in Neonatal unit, Dhaka Shishu Hospital showed 35% incidence of blood culture positive septicemia cases and 40% mortality among them[2].Overall mortality from septicemia varies between 26-40%[2]. Majority of preterm, LBW and asphyxiated newborn ultimately die of sepsis.

Reduction of death from neonatal sepsis will definitely contribute to a great extent to the reduction of neonatal mortality. This high mortality from sepsis necessities some new therapeutic effort to boost up

Author Affiliation: *Resident Medical Officer ***Professor ****Professor and Head, Department of Neonatology, Dhaka Shishu (Children) Hospital & Bangladesh Institute of Child Health, Sher-E-Bangla Nagar, Dhaka, Bangladesh. **Professor and Head, Department of Pediatrics, Northern International Medical College, Dhaka, Bangladesh.

Corresponding Author: B.H. Nazma Yasmeen, Professor and Head, Department of Pediatrics, Northern International Medical College, Dhaka, Bangladesh.
E-mail: prof.nazma.yasmeen@gmail.com, www.ProfNazma.com

Received on 09.08.2017, **Accepted on** 01.09.2017

immunity, to interrupt the toxin mediator cascades by supplemental measures.

Evidence is emerging that parenteral administration of high-dose vitamin C may be a beneficial adjuvant therapy of severe sepsis and septic shock. An excessive inflammatory response indeed enhances metabolic turnover of vitamin C Vitamin C helps in eliminating, neutralizing and antagonizing toxins and mediators, by antiinflammatory substances, and by immunomodulation. Vitamin C is very cheap and easily available. As it is a water-soluble vitamin, it has least or no side effects.

Materials and Methods

This Randomized control trial was carried out in neonatology department of Dhaka Shishu (Children) hospital during the period 1st April 2013-30th September 2014 (one & half year). Ethical clearance was taken from Ethical Committee of Dhaka Shishu Hospital and BICH Dhaka.

During the study period total 279 neonates were assessed.In this study. *Inclusion Criteria* were: 36 weeks or more gestational ages and weight >2.5kg, presented with signs and symptoms of sepsis, (Lethargy, Reluctant to feed, Respiratory distress, Tachypnea,Hypothermia/Fever, Convulsion, Jaundice, Bleeding manifestation, Septic foci, Abdominal distension and Apnoea) and Positive C-reactive protein (CRP>20 mg/dl), and/or positive blood culture. *Exclusion criteria* were severe birth asphyxia with HIE-III, major congenital malformations, DIC and H/O malfeeding. Total 142 neonates were excluded from the study according to exclusion criteria.

After taking written consent, subjects were assigned into two groups, GroupA (intervention group, n=68) received Vit. C and standard treatment protocol, and Group B (Control group, n=69) received only standard treatment protocol. This division was done by lottery method.

After enrolment 13 patients had given Discharge on risk bond, 7 in group A and 6 in Group B. Finally 124 neonates completed the study 61 neonates in Group A (intervention group) and 63 in Group B (control group).

Injection Vitamin C (100mg/Kg) and standard treatment of sepsis was given to all neonates of group A for consecutive two days. But in group B only standard treatment of sepsis was given. On the 3rd day CRP of all neonates were done again.

Primary Outcome

Cured-CRP becomes negative on 3rd day along with clinical improvement.

Improved- CRP level decreased from the previous but still positive along with clinical improvement.

Not Improved- CRP increased from previous record along with no clinical improvement.

Secondary Outcome-*Hospital stay*

All records regarding history, examination finding, investigations report, follow up findings and outcome were recorded in a preformed data collection sheet. The data was analyzed according to standard procedure. SPSS Win version 17 program has been used for data analysis: Results of the findings was verified by doing standard test for significance like Unpaired student "t" test and Chi-Square (X2) tests and finding out the P value.

Results

The mean (±SD) age of group A (Intervention) and group B (Control) neonates, respectively, was 8.18±7.16 (range 1-27) and 9.08±6.55 (range 1-28) days. Mean (±SD) weight of group A and group B neonates, respectively, was 2803.25±291.79 (range 2500-3200) gm and 2904.13±290.50 (range 2500-3500) gm which was statistically not significant between both groups.

There were no significant differences in history and clinical features of sepsis between the two groups (Table 1).

Pretreatment mean (±SD) CRP level was 50.13±21.07 (range 21.00-96.00) in group A and 38.21±16.61 (range 23.00-90.00) mg/L in group B neonates. Mean difference was significantly high in group A (p<0.01). At day 3 post treatment, mean (±SD) CRP level in group A was 7.69±7.48 (range 3.50-80.20) and in group B was 23.82±19.01 (range 3.60-70.20)mg/L. Statistically the mean difference was significantly low in group A (p<0.001). Mean decrease of CRP level in group A was 42.44 (84.94%) mg/dl and in group B was 14.39 (35.25%). The mean decrease was significantly higher in group A (p<0.001) (Table 2).

In group A and group B neonates blood culture showed positive result in 19 (31.1%) and 17 (27%), and negative result in 42 (68.9%) and 46 (73%) (Figure 1). The mean hospital stay was significantly high (p<0.01) in group B (Table 4).

This study has shown significant difference in cure

Table 1: History and clinical features of the neonate of both groups

Parameters	Group A N=61(%)	Group B N=63(%)	p value
Delayed cry	25(41.0)	22 (34.9)	0.487^{ns}
Stopped feeding well	51(83.6)	59(93.7)	0.077^{ns}
Convulsion	24(39.3)	22(34.9)	0.610^{ns}
Excessive cry	6(9.8)	14(22.2)	0.061^{ns}
Lethargy	59(96.7)	59(93.7)	0.426^{ns}
Abdominal distension	7(11.5)	11(17.5)	0.344^{ns}
Severe respiratory distress	41(67.2)	40(63.5)	0.663^{ns}
Apnoea	15(24.6)	11(17.5)	0.330^{ns}
Severe chest indrawing	36(59.0)	35(55.6)	0.697^{ns}
Cyanosis	30(49.2)	32(50.8)	0.857^{ns}
Diminished reflexes	58(95.1)	56(88.9)	0.205^{ns}
Jaundice	12(19.7)	10(15.9)	0.580^{ns}

Table 2: Change in CRP level at day 3 from pretreatment level in the study groups

CRP (mg/L)	Group A N=61(%)	Group B N=63(%)	p value
Pretreatment			
Mean±SD	50.13±21.07	38.21±16.61	
Range	21.00-96.00	23.00-90.00	
Post treatment day 3			
Mean±SD	7.69±7.48	23.82±19.01	0.0001
Range	3.50-80.20	3.60-70.20	
Change from pretreatment level to post treatment day 3			
Mean	-42.44	-14.39	0.0001
Percent	-84.94	-35.25	

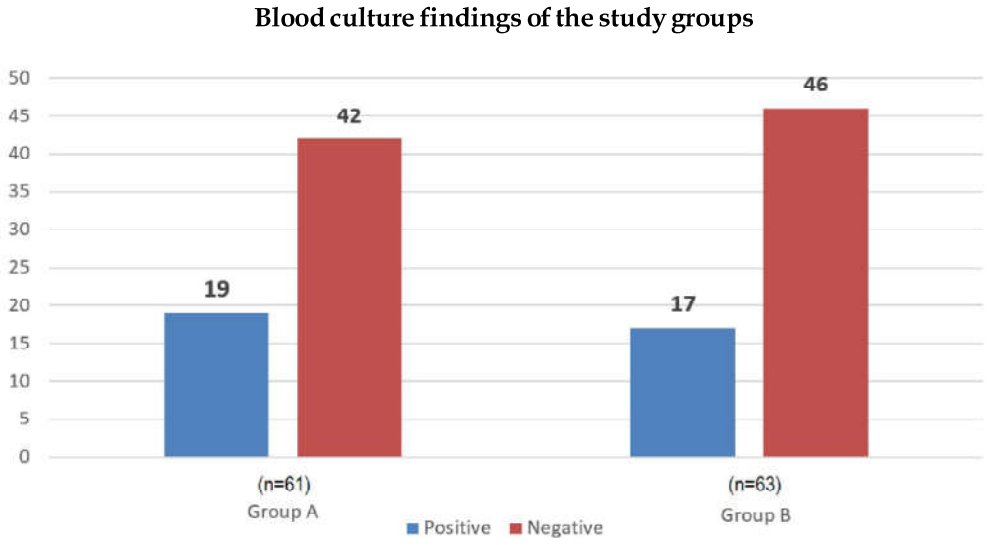

Fig. 1:

Table 3: Comparison of treatment outcome between the two groups

Outcome	N	Group A No. (%)	Group B No. (%)	*P* value
Cured	47	35(74.5)	12(25.5)	0.001^{**}
Improved	57	21(36.8)	36(63.2)	0.046^{ns}
No improvement	14	3(21.4)	11(78.6)	0.057^{ns}
Expired	6	2(33.3)	4(66.7)	0.688^{ns}

Table 4: Duration of hospital stay of the neonates

Hospital stay (days)	Group A (n=61)	Group B (n=63)	p value
Mean ± SD	6.38±2.27	9.98±4.14	0.0001
Range	4.0 12.0	6.0 23.0	

rate between intervention groups (75%) (Group-A) and control group (25%). (p=0.003) (Group-B) (Table 3).

Discussion

Sepsis is the leading cause of neonatal death [4]. In southern Asia, neonatal sepsis occurs among 8-38 per 1000 live births [5]. The clinical syndrome of sepsis is not a single homogeneous disease process but a generic term for a large group of diseases[6]. Management of neonatal sepsis should be focused on prompt recognition, early treatment and aggressive monitoring and thereby reduce the severity of the disease and its complications. Treatment is largely supportive and it is directed to preventing disease progression through antibiotic therapy and maintaining homeostasis by intravenous fluids, electrolytes and nutrition.

Despite appropriate management, the outcome is universally not good as the neonates are immune deficient in comparison to older babies. It is found that circulating levels of vitamin C (ascorbate) are low in patients with sepsis. Parenteral administration of ascorbate raises plasma and tissue concentrations of the vitamin and may decrease morbidity [7]. On the basis of this hypothesis that micro vascular function in sepsis may be improved by parenteral administration of ascorbate as an adjuvant therapy[7].

Very few studies have been done worldwide to see the effect of Vitamin C on neonatal sepsis. The first study was conducted in New York, USA by Kiran Vohra et al, in 1990 to see the improvement of neutrophil migration by giving systemic vitamin C in neonates.8 This study has shown significant increase in neutrophil chemotaxis after administration of vitamin C. No study has been conducted so far in Bangladesh on this topic.

This study showed significant improvement in mortality and morbidity of neonatal sepsis cases in intervention group with Vitamin C. Improvement were assessed by doing CRP on 3rdday (Table 3). This study has shown significant difference in cure rate between intervention group (75%) and control group (25%). (p=0.003) (Table 3).

Very recently a government trial on adult human sepsis was done in USA which showed that vitamin C supplement can reduce CRP in human sepsis [9]. Several human trials were done on sepsis on adult so far, but very few studies were done on neonates with sepsis.

A few population studies have shown inverse relations between vitamin or fruit and vegetable intakes and inflammation marker, including Creactive protein (CRP); interleukin 6; fibrinogen and coagulation factors VII, VIII, and IX; prothrombin fragments and thrombin-ant thrombin complexes [10]. Another prospective, randomized, double-blind, placebo-controlled trial in adult by Crimi E et al found decreased morbidity for severely burned patients who received a very high dose of parenteral ascorbate (1,584 mg/kg/day) [11]. Vitamin C has particular relevance to micro vascular barrier function. It strengthens and protects the immune system by stimulating the activity of antibodies and immune system cells such as phagocytes and neutrophills [12].

Sies and Wilhelm, et al stated that Vitamin C works by stimulating the immune system protecting against damage by the free radicals released by the body [13]. Neutrophil are important in phagocytising extracellular organisms. To kill these organisms, neutrophills need to be able to detect them and move towards them (chemo taxis), ingest them (phagocytosis) and kill them [2]. This is proved by Kiran et al study in 1990 who found significant neutrophil chemo taxis after giving Vitamin C in neonates with sepsis. Gaby and Singh reports that one hour after injection of 1 g of vitamin C to healthy individuals, the neutrophil motility and leukocyte transformation in the subject's blood increased significantly [14].

For neonatal sepsis, case fatality rates range from 13 to 86%, with the highest mortality rates reported in developing countries [5]. In Bangladesh, results from a study conducted in pediatric tertiary care center in Dhaka showed that the case fatality rate was 40% for the culture-positive neonatal sepsis cases even with appropriate management [3]. This study shows 36 culture positive cases of different organisms in both the groups out of 124 sepsis cases (Figure 1). Types and number of organisms were almost similar in both groups. Total 6 patients died and all were

blood culture positive.Number of death was low in intervention group (2) than control group (4). This study showed there was significant difference in hospital stay between two groups. In intervention group range of hospital stay was 4-12 days Mean±SD 6.42±2.28. and in control group range of hospital stay was 6-23 days Mean±SD 10.21 ±4.47. That is therewas significant reduction of hospital stay in intervention group then control group (p=<0.0001)(Table 5). Several medication as adjuvant therapy was tried in neonatal sepsis during last two decades. Among these Vitamin A and IVIG has shown significant role in the treatment of neonatal sepsis [8]. This study showed Vitamin C also has some role in improvement of neonatal sepsis as adjuvant therapy.

Conclusion

Vitamin C appears to be very effective as an adjuvant therapy in neonatal sepsis. However, large scale multi center similar study with Vitamin C should be carried out to substantiate our findings. It may be used as adjunct therapy in neonatal sepsis to reduce mortality and morbidity.

Acknowledgement

I am thankful to all the members of Dept. of Neonatology and Dept. of Microbiology, Dhaka Shishu (Children) Hospital for their kind cooperation.

Special note

This Article was presented (Oral) in the 12th Congress of Asian Society for Pediatric Research 2016, in Bangkok, Thailand on November, 2016. It won the **"Award of Excellence"** for Best Article. Source: facebook.com/pg/IMCPCThailand/photos/?tab=album&album_id=1185466551507257.

Reference

1. Afroza, S, Begum, F, Co-relation between Sepsis Score and Blood Culture Report in Neonatal Septicaemia. J Bangladesh Coll Phys Surg, 2008;26(2):79-82.
2. Hoque MM, Ahmed ASMNU, Halder SK, Khan MFH, Chowdhury MAKA. Morbidities of pretermVLBW neonates and the bacteriological profile of sepsis cases. PULSE 2010;4(1):5-98.
3. Honore PM, Jacobs R, Hendrickx I, De Waele E, Spapen HD. Adjuvant vitamin C treatment in sepsis —how many oranges a day keep (vasopressordependent) septic shock away? J Thorac Dis 2016;8(9):E993-E995.
4. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO estimates of the causes of death in children?Lancet. 2005;365:1147-52.
5. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. Arch.Dis.Child Fetal Neonatal Ed.2005; 90:F220-F224.
6. Marshall JC Sepsis; rethinking the approach to clinical research.J.Leukoc.Biol.2008;83:471-482.
7. Block G, Jensen C, Dietrich M, Norkus EP, Hudes M, Packer L. Plasma C-reactive protein concentrations in active and passive smokers: influence of antioxidant supplementation. J Am Coll Nutr 2004;23:141–7.
8. VohraK, Khan AJ, Telang V, Rosenfeild W, Evans HE. Improvement of neutrophil migration by systemic vitamin C in neonates.Journal of perinatology, 1990; 10(2):134-6.
9. Ascorbic Acid (Vitamin C) Infusion in Human sepsis [A service of the U S National Institute of Health]; Virginia commonwealth university, October 2012. Clinical Trials.gov identifier: NCTO434121.
10. Wannamethee SG, Lowe GD, Rumley A, Bruckdorfer KR, and Whincun PH. Associations of vitamin C status, fruit and vegetable intakes, and markers of inflammation and hemostasis. Am J Clin Nutr 2006;83:567–74.
11. Crimi E, Liguori A, Condorelli M, Cioffi M, Astuto M, Bontempo P, Pignalosa O, Vietri MT, Molinari AM, Sica V, Della Corte F, Napoli C. The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. Anesth. Analg. 2004;99:857–863.
12. Eberhard Kronhausen and Phyllis Kronhausen with Harry B. Demopoulos, M.D., Formula for Life, William Morrow and Co., New York, 1989.p.95.
13. Sies, H. and S. Wilhelm. Vitamins E and C, beta carotene and other carotenoids as antioxidants. Am.J. Clin. Nutr, 1995;62:1315S-1321S.
14. Gaby, S.K. and V.N. Singh, , Bendich, A., Singh,V. and Machlin, L. (eds.). Marcel Dedder,N.Y"Vitamin C," – Vitam intake and health: A Scientific Review, 1991.