Serum Albumin Concentrations and Clinical Disorders by Gestational Ages in Preterm Babies

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Purpose : The aim of this study was to determine the reference ranges of serum albumin levels depending on the gestational ages of preterm infants. We also intended to compare the mean serum albumin levels between groups of preterm infants that did not develop clinical disorders later, and groups that did develop clinical disorders such as respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity, apnea and bronchopulmonary dysplasia. We also examined the significance of serum albumin as a predictor for the development of clinical disorders.

Methods : The records of 208 neonates with gestational ages from 23 weeks to 41 weeks were reviewed retrospectively. The mean albumin concentrations with reference ranges by gestational ages were determined. Statistics for each two of group were compared. Logistic regression analysis was used to model odd ratio, and 95 percent confidence interval as a mean of the association between predictors and outcome.

Results : Serum albumin levels were at 23-24 weeks gestation was 2.36 g/dL, rising to 3.43 g/dL in full term babies. There were significant mean differences between the clinical groups and control groups for each clinical disorder such as respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity and apnea in premature babies of 30-36 weeks of gestation. Low serum albumin appeared to be associated with increased risks of clinical disorders.

Conclusion : The normal serum albumin levels in preterm infants should be defined according to the gestational ages. Lower albumin levels increase the risks of the later development of clinical disorders, which are common in premature infants. **(Korean J Pediatr 2005;48:148-153)**

Key Words : Serum albumin, Preterm neonates, Respiratory distress syndrome, Intraventricular hemorrhage, Retinopathy of prematurity, Apnea

Introduction

Albumin comprises 50% of the protein content. The physiological functions of serum albumin includes the binding and transport of substances such as fatty acid, ions, thyroxine, bilirubin and amino acids, and the effect on colloid osmotic pressure from the serum albumin accounts for 60-80% of the osmotic pressure. Albumin has an effect on vascular permeability, and it has a role as a free radical scavenger and for anticoagulation[1]. At our neonatal intensive care unit, the serum albumin concentration is routinely measured and this is done in almost every hospital. Hypoalbuminemia is a common finding in preterm (less than 37 weeks) neonates. An older child with a serum albumin level below 3 g/dL is classified as having hypoalbuminemia, and serum albumin levels in preterm infants are significantly lower than for full term infants[2].

Hypoalbuminemia occurs in a number of clinical situations including the acutely ill infant, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, hydrops fetalis and edema[3]. Albumin contributes to the antioxidant capacity of the plasma; therefore, lower levels of albumin may lessen the total plasma antioxidant capacity. This may be of importance for premature infants who are at risk for disease processes where reactive oxygen species play an important role, such as respiratory distress syndrome, chronic lung disease, and intraventricular hemorrhage[4].

In lung disease of the newborn, alveolar capillary mem-

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brane permeability is increased and high albumin levels are present in the alveolar aspirates; pulmonary edema is also found in such clinical situations[5]. The leakage of protein into the alveolar space interferes with lung function. It has been suggested that albumin infusion should increase the capillary colloid pressure, thereby resulting in a decrease in the flow of fluid out of the capillaries[6]. However, it could be argued that the capillary leak will not be altered by albumin infusion and that increasing the amount of intravascular albumin will increase the amount of fluid that leaks out of the circulation, and so increase the edema[3]. In addition the alveolar leakage of protein into the alveolar space inactivates surfactant[7].

Little was known about the normal ranges of albumin in preterm infants, particularly for Korean preterm infants. Moreover, there is an increasing body of evidence about the potential problems of albumin infusion to the preterm infant.

The aim of this study was to determine the reference ranges of serum albumin concentrations depending on the gestational ages of premature infants. We also wished to compare the mean serum albumin levels between groups of preterm infants that did not developed clinical disorders later and groups that did develop clinical disorders such as respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity, apnea and bronchopulmonary dysplasia. We also examined the significance of the levels of serum albumin as a predictive factor for the development of the above mentioned clinical disorders, respectively.

Materials and Methods

The records of 208 neonates with gestational ages from 23 weeks to 41 weeks that were born between January 1997 and June 2003 at Wonju Christian Hospital, Wonju, Korea, were retrospectively reviewed. Gestational ages were grouped from 23 weeks at 2 week intervals, and the last group included neonates of the gestation ages from 37-41 weeks.

The following subject parameters were collected : birth weight, gestational age, serum albumin concentration at 2 hours of age, and the presence or absence of clinical disorders such as respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity, apnea and bronchopulmonary dysplasia.

The diagnostic progress and the X-ray observation confirmed the respiratory distress syndrome. The respiratory distress syndrome was confirmed in a preterm newborn with respiratory difficulty, including tachypnea, chest retraction and cyanosis that persist or progress over the first 48-96 hours of life and a characteristic X-ray appearance that uniform reticulogranular pattern and peripheral air bronchogram. The brain ultrasound test was examined at the 7th day from the birth to observe for any hemorrhage within the areas such as the germinal matrix, the intraventricle, and the ventriculitis. The infants were diagnosed with the apnea if the discontinuity of breath was more than 20 seconds or when the combined appearance of symptoms such as the cyanosis and the arrhythmia regardless of the breath stopping period were present. The retinopathy of prematurity was confirmed under the guideline of the International Classification of Acute Retinopathy of Prematurity by the fundoscopic examination after 4 weeks from birth by the ophthalmologist. The infants who required the artificial respiration after either 36 weeks gestation period or 4 weeks from the birth were diagnosed as the bronchpulmonary dysplasia.

Serum albumin concentration was measured by the Bromocresol green method with the specimen being taken within 2 hours after birth. The mean albumin concentrations with reference ranges (95% confidence limits) by the gestational ages were determined. The clinical groups consisted of babies with each of clinical disorders such as respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity, apnea and bronchopulmonary dysplasia. The control group consisted of babies without each of these clinical disorders. Statistics for each two of the groups were compared by independent t tests. Logistic regression analysis was used to model the odds ratios, and a 95% confidence interval was accepted as a measure of the association between the predictors and outcome. All calculations were done on SPSS for windows; SPSS Inc., Chicago, Ill., USA.

P values <0.05 were regarded as significant.

Results

The mean albumin concentration in newborn babies rose from about 2.36 g/dL in 23-24 week gestation babies to about 3.43 g/dL in full term babies. The reference ranges (95% confidence limits) of the serum albumin concentration

was 1.74-2.94 g/dL in babies of 23-24 weeks gestation, and it was 3.32-3.56 g/dL in full term babies (Table 1).

The mean serum albumin concentration at 23-24 weeks gestation was around 2.36 g/dL, rising to about 3.43 g/dL in mature babies. The means and standard deviations in respect to the gestational ages are shown in Fig. 1. The overall analysis indicated that the albumin concentration increased as the gestation period was extended. Table 2 shows the mean values and standard deviations of serum albumin concentrations of the clinical groups and control groups. There were significant mean differences between the clinical groups and control groups for each clinical disorder including respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity and apnea in premature babies of 30-36 weeks gestation. However, there was no significant mean difference between the clinical group and control group for bronchopulmonary dysplasia in premature babies of 30-36 weeks gestation.

There were 61 premature babies of less than 32 weeks gestation. There was no significant differences of the mean albumin concentrations between the clinical group and control group for respiratory distress syndrome (clinical group, 2.36±0.42 g/dL, n=54; control group 2.64±0.34 g/dL, n=7), intraventricular hemorrhage (clinical group, 2.41±0.37 g/dL, n=17; control group, 2.39±0.44 g/dL, n=37), retinopathy of prematurity (clinical group, 2.54±0.41 g/dL, n=10; control group, 2.31±0.42 g/dL, n=44), apnea (clinical group. 2.38±0.22 g/dL, n=54; control group, 2.5±0.5 g/dL, n=7), bronchopulmonary dysplasia (clinical group, 2.46±0.31 g/dL, n=54; control group, 2.39±0.43 g/dL, n=7). There was no significant difference between the two groups for retinopathy of prematurity in babies of more than 37 weeks gestation age because there was only one case of retinopathy of prematurity among the 32 babies.

Table 3 shows the results of binary logistic regression analysis for estimating the relative risks, as expressed by the odds ratio, for respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity, apnea and bronchopulmonary dysplasia associated with the serum

Table 1. Serum Albumin Concentrations by Gestational Ages (Total=208)

Gestation (weeks)	Numbers	Mean (g/dL)	95% confidence interval	
			Upper bound	Lower bound
23-24	7	2.36	2.97	1.74
25-26	26	2.26	2.42	2.09
27-28	28	2.53	2.67	2.4
29-30	21	2.82	2.96	2.68
31-32	28	2.86	3.02	2.71
33-34	34	3.24	3.35	3.13
35-36	32	3.43	3.55	3.32
>36	32	3.43	3.56	3.32

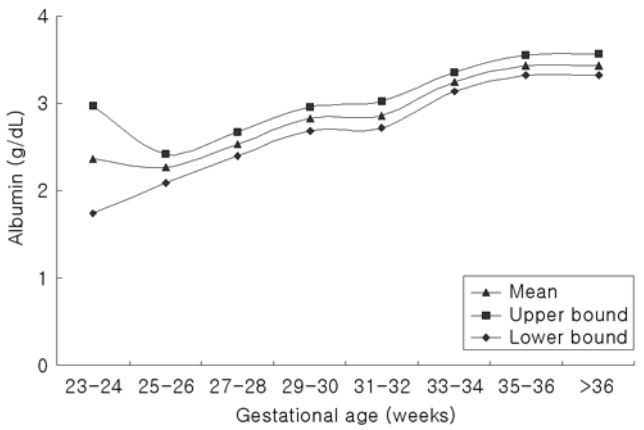

Fig. 1. Reference range of albumin concentration by gestational ages in newborn babies (95% confidence limits of results).

Table 2. Comparison of Serum Albumin Levels between Groups of Clinical and Control Groups in Gestational Age 30-36 Weeks

Clinical diagnosis	Serum albumin (g/dL)		*P*-value
	Clinical group	Control group	
RDS	2.85±0.36 (n=22)	3.23±0.39 (n=83)	<0.05
IVH	2.74±0.57 (n=6)	3.17±0.39 (n=99)	<0.05
ROP	2.69±0.33 (n=11)	3.2±0.39 (n=94)	<0.05
Apnea	2.85±0.34 (n=28)	3.26±0.38 (n=77)	<0.05
BPD	2.5 (n=1)	3.15±0.41 (n=104)	>0.05

n : number of cases
Abbreviations : RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity. BPD; Bronchopulmonary dysplasia

Table 3. Odds Ratios of Clinical Disorders by Binary Logistic Regression Analysis

Clinical disorders	B	Constant	SE	Odds ratio	95% confidence interval	*P*
RDS	-2.311	5.72	0.65	0.099	0.02-0.35	0.00
IVH	-2.42	4.37	1.07	0.089	0.11-0.72	0.02
ROP	-3.20	7.30	0.94	0.04	0.006-0.259	0.001
Apnea	-2.60	6.97	0.64	0.074	0.021-0.26	0.00
BPD	-3.936	2.96	2.9	0.02	0-6.49	NS

Abbreviations : B, estimated coefficient; SE : Standard error, RDS, neonatal respiratory distress syndrome; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; BPD, Bronchopulmonary dysplasia; NS, non significant

albumin levels of immediate postnatal period in premature babies of 30-36 weeks gestational age. A low serum albumin concentration appeared to be associated with the premature infants' increased risks of respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity, apnea and bronchopulmonary dysplasia.

Discussion

The clinical indication for measuring albumin concentration is usually to assess the nutritional status and liver function, or it is used in the investigation of a prolonged edema[8]. Little was known about the normal ranges for albumin concentration in preterm babies, particularly in those infants of less than 32 weeks gestation, until Cartlidge and Rutter's study in 1986[9]. They have reported the normal albumin concentration at birth, which showed a gradual rise from a mean value of 1.9 g/dL at 26 weeks gestation to 3.1 g/dL at full term.

Our results were similar to that study; we have shown that the albumin concentration is maintained at around 2.31 g/dL by 23-24 weeks gestation, and that this slowly rises to a level of about 3.43 g/dL at full term. These results agree with the concentration values found by Reading et al[8], who measured albumin concentration in premature infants and found a steady rise from 28 weeks gestation to full term.

Their results are 0.5-1 g/dL lower than ours at all gestational ages. We believe this discrepancy may be accounted for partly by the different biochemical testing method used to measure albumin[8]. However, we could not exclude other factors that might have affected this discrepancy.

Because it is a non-specific marker of illness, the use of a serum albumin measurement in reaching a diagnosis is of limited utility. However, the association of serum albumin concentration with the severity of illness and a poor outcome has long been recognized, and there are literally hundreds of studies in which the association has been demonstrated[1].

Goldwasser and Feldmam[10] reported that serum albumin concentration is inversely related to mortality risk over its entire range in a study of many populations comprising healthy subjects and patients with acute or chronic illness. They suggested that albumin concentration is a highly sensitive indicator of preclinical disease and disease severity, and it could be useful in the quantification of risk in a broad range of clinical and research settings. In this study, we tried to determine whether serum albumin concentration is an independent predictor of morbidity and if it could be useful in the quantification of risk for clinical disorders in the premature infant.

Moison et al[4] reported that hypoalbuminemia was present in all babies with respiratory distress syndrome at birth. In their study, this change in serum albumin may have been related to the changes in alveolar capillary permeability, and the increased alveolar capillary permeability contributed to the decreased plasma protein concentration. The albumin levels were significantly decreased with increasing FiO_2 and the increased duration of oxygen therapy. The decreased plasma albumin concentrations were also noted to have lowered the antioxidant capacity of the blood. Oxygen toxicity appeared to lower the plasma protein by increasing the pulmonary permeability[11].

We found that the serum albumin concentrations of the respiratory distress syndrome group were lower that of the control group without respiratory distress syndrome at the gestation age of 30-36 weeks. This was the same result as was noted by in the research of Moison et al[4] and Ebbesen and Nyboe[11]. Moreover binary logistic regression analysis demonstrated that each 1 g/dL difference in serum albumin concentration was associated with a 9.9% higher risk of respiratory distress syndrome.

There was no data suggesting a direct relationship between low serum albumin concentration and intraventricular hemorrhage. However, as was shown in Lackmann et al's study[12] on the oxygen radical diseases of prematurity, there was an increasing incidence of intraventricular hemorrhage, bronchopulmonary dysplasia and retinopathy of prematurity with low serum albumin levels: these diseases might have been affected by the lower antioxidant activity that resulted from a lower serum albumin concentration. Our findings demonstrated a lower serum albumin concentration in the intraventricular hemorrhage group and the retinopathy of prematurity group than in the groups without each of these disorders. Each decrement of -1 unit of albumin increased the risk of intraventricular hemorrhage and retinopathy by 8.9% and 4%, respectively. Each -1 g/dL of difference in the serum albumin concentration increased the risk of apnea by 7%. However, it is not obvious whether the level of serum albumin is the only specific factor causing these maladies, or if these diseases reflect

the poor general condition of the premature infant.

In our study, serum albumin concentration could not predict the development of bronchopulmonary dysplasia. Similarly, Moison et al[4] reported that lower albumin levels did not predict development of bronchopulmonary dysplasia with the specificity for Moison's results being 94%, and the sensitivity was 50%.

Atkinson et al[13] have reported that hypoalbuminemia might cause a newborn's gut to be less resistant to insults such as bacterial over growth or a hypoxic ischemic event, which then predisposes the newborn to necrotizing enterocolitis. However, in our study, the number of babies with necrotizing enterocolitis was so small that we did not include cases of necrotizing enterocolitis in our study.

It has been advocated in the past that ill infants with respiratory distress syndrome should be given an albumin infusion whenever their serum albumin falls below 2 g/dL [14]. However, it is now recommended that care should be taken as an albumin infusion may be harmful. Albumin infusion has been associated with a significant reduction in the body weight in the newborn, but there were no changes associated with the respiratory status[15]. Fluid overload is another side effect of albumin administration.

Complications from fluid overload include patent ductus arteriosus, necrotizing enterocolitis and bronchopulmonary dysplasia. Also, as albumin is a blood product, it carries the potential risk of infection and adverse reactions.

Goldwasser and Feldman[10] showed that in adults, the serum albumin concentration is inversely related to the risk of death. Conversely, a review of the literature for albumin infusions in critically ill adults suggests that it may increase mortality in selected patients[16].

So there is still a lot of controversy about albumin infusion to treat hypoalbuminemia. This issue of albumin infusion will continue and further work is obviously needed.

We conclude that the normal albumin levels in preterm infants should be defined according to the gestational age. Serum albumin levels for premature babies of gestation 30-36 weeks in the respiratory distress syndrome group, intraventricular hemorrhage group, retinopathy group and apnea group were lower than in each group without these clinical disorders. Lower albumin levels increase the risks of the later development of respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity and apnea in premature baby of 30-36 weeks gestation. Unfortunately, the association between clinical disorders and serum albumin concentrations in preterm babies of less than 30 weeks gestational age remains undefined. It is clear that further studies on this issue, with a larger group of relevant subjects, need to be initiated.

국문 요약

미숙아에서 재태 연령에 따른 혈청 알부민치와 임상증상과의 관계

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목 적 : 혈장의 항산화 능력, 항혈전 작용, 혈관 투과성 등에 관여하는 알부민이 낮은 경우 호흡곤란증후군, 기관지폐 이형성증, 괴사성 장염, 뇌실 내 출혈, 태아수종 등이 동반되어 나타날 수 있으며, 특히 신생아의 폐질환에서는 폐 모세혈관의 삼투성이 증가하고 폐포 흡인액에서 알부민이 증가되어 폐부종이 발생될 수 있으나 이때 저알부민혈증의 교정을 위해 알부민을 투여하는 것은 오히려 알부민 누출을 증가시켜 부종을 증가시킬 수도 있고 폐 표면활성제의 작용을 저해하여 나쁜 결과를 초래할 수도 있다. 그러므로 저자들은 미숙아에서 출생 직후 재태 기간에 따른 알부민의 정상범위를 결정하고, 신생아 호흡 곤란 증후군, 뇌실 내 출혈, 미숙아 망막증, 무호흡, 기관지폐 이형성증 등의 임상증상이 발생된 군과 대조군의 알부민치를 비교하고, 출생 직후의 알부민치가 이들 질환의 발생을 예측할 수 있는지를 후향적으로 조사하고자 하였다.

방 법 : 1997년 1월부터 2003년 6월까지 원주기독병원에서 출생한 재태 23-41주의 신생아 208명을 대상으로 출생시 체중, 재태 기간, 생후 1일의 혈중 알부민치를 의무기록을 검토하여 조사하고, 최종 진단에서 신생아 호흡 곤란 증후군, 뇌실 내 출혈, 미숙아 망막증, 무호흡, 기관지폐 이형성증 유무를 조사하여 이들 임상증상이 있었던 군과 없었던 대조군으로 나누어 혈중 알부민치를 비교하였다.

결 과 : 혈중 알부민치는 재태 기간 23-24주에서 평균 2.36 g/dL 만삭에 3.43 g/dL으로 재태 기간이 증가함에 따라 증가하였으며, 임상 증상에 따른 혈중 알부민치는 재태 기간 30-36주의 미숙아중 신생아 호흡 곤란 증후군, 뇌실 내 출혈, 미숙아 망막증, 무호흡이 있었던 군과 대조군 사이에 의미있는 차이를 보였으며 특히 신생아 호흡 곤란 증후군, 뇌실 내 출혈, 미숙아 망막증, 무호흡증이 있었던 경우 알부민치가 감소함에 따라 이들 질환의 발생 위험률이 증가함을 보였다.

결 론 : 신생아에서 저알부민혈증은 반드시 재태 기간을 고려하여 정의되어야 하며, 출생 직후 알부민치는 30-36주 사이의 미숙아에서 신생아 호흡 곤란 증후군, 뇌실 내 출혈, 미숙아 망막증, 무호흡 등 각각의 증상이 나타난 군에서 증상이 없었던 군보다 의미있게 낮았으며, 저알부민혈증이 이들 질환의 발병과

관계가 있는 것으로 사료된다.

References

1) Margason MP, Soni N. Serum albumin : touchstone or totem? Anaesthesia 1998;53:789-803.
2) Greenough A. Use and misuse of albumin infusions in neonatal care. Eur J Pediatr 1998;157:699-702.
3) Jardin LA, Jenkinns-Manning S, Davis MW. albumin infusion for low serum albumin in pretrm newborn infants. In : The Cochrane Library, Issue1, 2004. Chichester, UK : John Wiley & Sons, Ltd.
4) Moison RM, Haasnoot AA, Van Zoeren-Grobben D, Berger HM. Plasma proteins in acute and chronic lung disease of the newborn. Free Radic Biol Med 1998;25:321-8.
5) Watts CL, Bruce MC. Comparison of secretory component for immunoglobulin A with albumin as reference proteins in tracheal aspirate from preterm infants. J Pediatr 1995; 127:113-22.
6) Vanek V. The use of serum albumin as a prognostic or nutritional maker and the pros and cons of IV albumin therapy. Nutr Clin Prac 1998;13:110-22.
7) Greenough A, Emery E, Hird MF, Gamsu HR. Randomised controlled trial of albumin infusion in ill preterm infants. Eur J Pediatr 1993;152:157-59.
8) Reading RF, Ellis R, Fleetwood A. Plasma albumin and total protein in preterm babies from birth to eight weeks. Early Human development 1990;22:81-7
9) Cartlidge PHT, Rutter N. Serum albumin concentrations and oedema in the newborn. Arch Dis Child 1986;61:657-60.
10) Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin epidemiol 1997;50:673-703.
11) Ebbesen F, Nyboe J. Postnatal changes in the ability of plasma albumin to bind bilirubin. Acta Paediatr Scan 1983; 72:665-70.
12) Lackmann GM, Hesse L, Tollmer U. Reduced iron-associated antioxidant in premature newborn suffering intracranial hemorrhage. Free Radic Biol Med 1996;20:407-9.
13) Atkinson SD, Tuggle DW, Tunell WP. Hypoalbuminemia may predispose infants to necrotizing enterocolitis. J Pediatr Surg 1989;24:674-6.
14) Greenough A, Morley C, Roberton NRC. In : Roberton NRC, editors. Textbook of Neonatology. 2nd ed. London : Churchill Livingston 1992:385-504.
15) Greenough A, Emery E, Hird MF, Gamsu HR. Randomized entrolled trial of albumin infusion in ill infants. Eur J Pediatr 1993;152:157-9.
16) Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients : systemic reviews of randomized controlled trials. Cochrane Injuries Group Albumin Reviewers. BMJ 1998;317:235-40.