CLINICAL SCIENCE

Does administering albumin to postoperative gastroschisis patients improve outcome?

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OBJECTIVES: Newborns who undergo surgery for gastroschisis correction may present with oliguria, anasarca, prolonged postoperative ileus, and infection. New postoperative therapeutic procedures were tested with the objective of improving postoperative outcome.

PATIENTS AND METHODS: One hundred thirty-six newborns participated in one of two phases. Newborns in the first phase received infusions of large volumes of crystalloid solution and integral enteral formula, and newborns in the second phase received crystalloid solutions in smaller volumes, with albumin solution infusion when necessary and the late introduction of a semi-elemental diet. The studied variables were serum sodium and albumin levels, the need for albumin solution expansion, the occurrence of anasarca, the length of time on parenteral nutrition, the length of time before initiating an enteral diet and reaching a full enteral diet, orotracheal intubation time, length of hospitalization, and survival rates.

RESULTS: Serum sodium levels were higher in newborns in the second phase. There was a correlation between low serum sodium levels and orotracheal intubation time; additionally, low serum albumin levels correlated with the length of time before the initiation of an oral diet and the time until a full enteral diet was reached. However, the discharge weights of newborns in the second phase were higher than in the first phase. The other studied variables, including survival rates (83.4% and 92.0%, respectively), were similar for both phases.

CONCLUSIONS: The administration of an albumin solution to newborns in the early postoperative period following gastroschisis repair increased their low serum sodium levels but did not improve the final outcome. The introduction of a semi-elemental diet promoted an increase in body weight at the time of discharge.

KEYWORDS: Gastroschisis; Gastroschisis repair; Hyponatremia; Morbidities; Neonates; Body wall defects.

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INTRODUCTION

In recent decades, the worldwide incidence of gastroschisis has increased (1-3). Despite survival rates higher than 90% (4,5), newborns (NBs) with gastroschisis demonstrate significant postoperative morbidity associated with long periods of hospitalization (6).

Surgical treatment for gastroschisis includes viscera reduction inside the cavity and abdominal wall closure in one- or two-stage procedures, always with at least a slight intra-abdominal tension (7). Patients in the early postoperative period tend to present with hydrosaline retention and fluid losses into the traumatic edema zone. These problems occur in association with increased intra-abdominal pressure due to reduced peritoneal cavity capacity and a consequent decrease in diuresis (8).

The classic treatment for NBs in the first two days after gastroschisis correction includes the administration of large volumes of hydration solutions and, if necessary, repeated expansion of the extracellular compartment with crystalloid solutions, which invariably leads to anasarca and diluted low serum levels. These results have deleterious consequences, specifically interstitial pulmonary edema and respiratory dysfunction (9). In a previous investigation involving a large number of patients with surgically repaired gastroschisis at three tertiary university centers, we demonstrated that the presence of hyponatremia and hypoalbuminemia in the postoperative period correlated with the number of days that the patient required a ventilator (10).

To avoid this vicious cycle, we proposed a different treatment in the current study. Instead of administering

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large volumes of crystalloid solution, a basal maintenance solution was administered in standard volumes, even if diuresis rates were low. In cases with more intense oliguria, albumin solution was administered in an attempt to maintain the intravascular compartment volume.

Another problem frequently found in NBs who have undergone gastroschisis repair is the prolonged postoperative ileus (11,12). The introduction of an enteral diet can be difficult because of repeated vomiting, abdominal distention, intestinal malabsorption of nutrients, and enterocolitis episodes. Special diets may reduce the risk of these complications (13), but this practice has not yet been proven in the medical literature.

The objectives of the present study were as follows: 1) to evaluate whether albumin solution administration improves the outcomes for NBs in the early postoperative period by decreasing the occurrence of hyponatremia and 2) to verify whether the introduction of a semi-elemental diet presents some advantage over natural diets.

MATERIALS AND METHODS

The data for this study were obtained by reviewing the records for all NBs with gastroschisis who were treated between January 2000 and June 2010 at the Neonatal Intensive Care Unit of the Child Institute of the University of Sao Paulo School of Medicine. This prospective study protocol was approved by the institution's ethical committee. The study was divided into two phases.

Phase 1 (January 2000 to December 2003): Postoperative treatment consisted of an infusion of 120 to 150 mL/kg/day of crystalloid solutions (containing 37.5 mEq Na^+/L, 20 mEq K^+/L and 9 mEq Ca^{++}/L) followed by 20 mL/kg/30 min of normal saline, repeated up to three times whenever the NBs presented with oliguria (defined as urinary output <0.8 mL/kg/h) in the first two days of the postoperative period. Colloid solution (containing normal saline and 10% albumin) in volumes of 20 mL/kg/30 min was administered only if there was no increased diuresis. Enteral nutrition was introduced as soon as the flow of fluids through the orogastric tube indicated restoration of intestinal transit. A whole-milk formula appropriate for each NB's gestational age was used.

Phase 2 (January 2004 to June 2010): Postoperative treatment consisted of an infusion of 80 to 100 mL/kg/day of crystalloid solutions and 20 mL/kg of albumin solution when oliguria occurred (i.e., diuresis less than 0.8 mL/kg/h). The orogastric tube was removed when appropriate, and after one or two days without vomiting or abdominal distension, a semi-elemental diet (Pregomin®) was introduced followed by a gradual transition to a full enteral formula.

In both phases, the aim of the selected surgical treatment was always primary closure of the defect. A staged reduction with silo was used only if the total reduction of visceral contents would impair hemodynamic and respiratory function.

The following data were evaluated: gestational age, weight (at birth and at hospital discharge), APGAR score (at 1 and 10 minutes), type of gastroschisis (simple or complicated; associated with atresia, necrosis and/or intestinal perforation), and type of surgical treatment. We evaluated whether the NBs received a colloid infusion in the early postoperative period and the average serum sodium and albumin levels in the first 72 hours of life. Furthermore, the occurrence of anasarca and the length of orotracheal intubation (OTI) were verified.

Because we usually opted for a mild sedation, the ventilator support method of choice for both groups was synchronized intermittent mandatory ventilation.

Hyponatremia was defined as sodium serum levels <135 mEq/L, and hypoalbuminemia was defined as albumin serum levels <3 g/dL. No patient received loop diuretics during the study period. No severity score was used.

To examine the nutritional support, we evaluated the necessary parenteral nutrition (PN) time, time until the initiation of the enteral diet, and time until reaching the full enteral diet. We also recorded the occurrence of enterocolitis, the length of hospitalization, and mortality.

Initially, we used the Shapiro-Wilk test to investigate the framing of the numeric variables in the Gaussian model of distribution. Mann-Whitney's U test was used to compare the median values for colloid solution administration with enteral diet, PN time, length of hospitalization, serum sodium levels, and serum albumin levels. The chi-squared test was used to compare the percentages of newborns who presented anasarca. Simple linear regression tests were used to analyze the relationship between length of hospitalization, gestational age, birth weight, low serum sodium levels, low serum albumin levels, PN time, and OTI time. A multiple linear regression model was fitted to assess the association between each outcome (serum albumin levels, serum sodium levels, and the need for albumin solution infusion) and the independent variables. The adjusted analysis was conducted following a previously formulated hierarchical model in three levels: 1) gestational age; 2) birth weight; and 3) hospitalization time, OTI time, time to first enteral feeding, and time of full enteral feeding. In this model, the variables were controlled for factors in the same level and in the superior levels. P-values ≤ 0.20 were adopted in the univariate analysis as necessary to determine which variables to include in the multiple analyses or when there was a ß modification of more than 10% for any variable already in the model. The variables were then entered using the forward method. The significance level was set at $p<0.05$. Moreover, homoscedasticity was assessed graphically in all regression models. The Stata statistical software package, Version 10.0 (Stata Corp., College Station, TX, USA) was used for all statistical calculations.

RESULTS

One hundred thirty-six NBs were included in this study: 36 NBs in the first phase and 100 NBs in the second phase.

The comparisons of perinatal data and surgical treatment between the two phases are presented in Table 1.

Comparisons and correlations of serum sodium levels, serum albumin levels, anasarca and the need for albumin solution infusion

Table 2 shows the data for serum sodium levels, serum albumin levels, and OTI time in the two study phases and the results of the statistical comparisons.

Albumin solution administration was necessary in 47.2% (17/36) and 56.0% (56/100) of NBs in the study's first and second phases, respectively ($p = 0.47$).

Table 1 - Gestational age (GA), APGAR scores at 1 and 10 minutes, birth weight (mean ± sd), occurrence of complicated gastroschisis and silo usage in both phases of the study.

Variable	Phase 1	Phase 2	*P*-value
GA (weeks)	36 1/7 ± 2	36 6/7 ± 1	0.22
APGAR 1 min.	7.8 ± 1.7	7.0 ± 2.3	0.16
APGAR 10 min.	9.3 ± 0.7	9.0 ± 0.7	0.53
Birth weight (g)	2334.8 ± 478.3	2415.8 ± 463.2	0.30
Silo	16.6%	13.6%	0.97
Complicated gastroschisis	23.3%	10.0%	0.13

In the first phase, four newborns responded well to treatment with normal saline boluses, increasing their urinary output with no need for colloid solution administration. Their mean OTI time was 2.5 days, and their mean natremia level was 123.5 mEq/L.

The percentage of newborns who presented with anasarca was 19.4% in the first phase and 8% in the second phrase ($p = 0.117$).

In all cases, there was no statistical correlation between serum albumin levels and gestational age, birth weight, and OTI time or hospitalization time. However, there was a strong correlation between low serum albumin level and the time to both the initiation of enteral feeding and a full enteral diet ($p<0.001$) (Table 3).

There were no correlations between serum sodium levels and gestational age, hospitalization time, birth weight, or time to first and full enteral feedings. There was, however, a correlation between low serum sodium levels and increased OTI time ($p = 0.04$). The need for colloid solution infusion did not correlate with any of the studied variables (Table 3).

Comparisons regarding nutritional support

The nutritional data, including the fasting time before beginning the enteral diet, the length of time before the patient received a full enteral diet, the duration of PN administration, the length of hospitalization, and weight at discharge, and the results of the statistical comparisons are summarized in Table 4.

The time until the first and full enteral feeding, the length of time for PN and the length of hospitalization were similar during both phases. However, the discharge weights of the NBs in the second phase were higher than those of the NBs in the first phase ($p = 0.03$). It is important to note that no patient presented with peripheral edema at the time of discharge.

Finally, episodes of necrotizing enteritis occurred in two NBs in the first phase and in none of the NBs in the second phase ($p = 0.11$).

Table 2 - Serum sodium levels, serum albumin levels, and OTI time in the two phases of the study (mean ± sd).

Variable	Phase 1	Phase 2	*p*-value
Serum sodium levels (mEq/L)	123.4 ± 8.6	128.6 ± 6.4	0.006
Serum albumin levels (g/dL)	2.5 ± 0.5	2.0 ± 0.5	0.02
OTI (days)	4.3 ± 6.5	5.5 ± 9.4	0.98

Table 3 - Results of the multiple linear regression analysis evaluating the association between independent variables and patient outcomes.

Outcomes	*p*-value*
Serum albumin level	
Gestational age (per 1-week increase)	0.382
Birth weight (per 100-g increase)	0.812
OTI time (per 1-day increase)	0.278
Time to the initiation of an enteral diet (per 1-day increase)	<0.001
Time to full enteral diet (per 1-day increase)	<0.001
Hospitalization time (per 1-day increase)	0.382
Serum sodium level	
Gestational age (per 1-week increase)	0.533
Birth weight (per 100-g increase)	0.514
OTI time (per 1-day increase)	0.041
Time to the initiation of an enteral diet (per 1-day increase)	0.392
Time to full enteral diet (per 1-day increase)	0.319
Hospitalization time (per 1-day increase)	0.389
Need for colloid infusion	
Gestational age (per 1-week increase)	0.312
Birth weight (per 100-g increase)	0.928
OTI time (per 1-day increase)	0.300
Time to the initiation of an enteral diet (per 1-day increase)	0.630
Time to full enteral diet (per 1-day increase)	0.613
Hospitalization time (per 1-day increase)	0.439

*variables with $p>0.2$ were excluded from the model.

The survival rate in Phase 1 was 83.4%; in Phase 2, it was 92% ($p = 0.25$).

DISCUSSION

This study aimed to clarify the epidemiological, surgical, and postsurgical data for newborns with gastroschisis. Initially, we investigated the therapeutic changes related to extracellular volume expansion and the use of colloid solutions and their impact on fluid and electrolyte balance and the final outcomes for NBs with gastroschisis. The NBs in the two phases of the study (i.e., from 2000 to 2003 and from 2004 to 2010) had similar gestational ages and birth weights, which allowed statistical comparisons between the two groups.

However, although the serum albumin levels were higher in the patients from Phase 1, the serum sodium levels were significantly lower in this phase, which may reflect the excessive use of crystalloid solution infusion during this phase. Such extreme crystalloid administration was also ineffective because 47.2% of the NBs in this group remained oliguric and required albumin solution expansion to improve diuresis. A similar proportion of patients from Phase 2 received colloid solution infusion without previous crystalloid administration.

Table 4 - Initiation time for an enteral diet or a full diet, length of time for parenteral nutrition, weight at discharge, and hospitalization time in the two phases of the study (mean ± sd).

Variable	Phase 1	Phase 2	*p*-value
Initiation of an enteral diet (days)	17.9 ± 12.8	21.6 ± 12.9	0.06
Full enteral diet (days)	29.9 ± 27.1	30.8 ± 17.2	0.18
PN time (days)	27.3 ± 28.6	29.2 ± 17.6	0.06
Weight at discharge (g)	2561.3 ± 510.7	2814.5 ± 515.8	0.03
Hospitalization time (days)	35.2 ± 34.8	34.9 ± 19.5	0.16

The joint analysis of the data on serum sodium and albumin levels from the two time periods did not show any correlation between these data and the NBs' initial birth weights. However, in both phases of the study, low serum sodium and albumin levels were observed. In experimental studies of chicken embryos and rabbit fetuses with iatrogenic gastroschisis, low sodium and chloride serum levels, low amino acid uptake and glucose deficits were observed along with the minor expression of a series of genes involved in enterocyte nutrient absorption (14,15). Finally, Carroll et al. observed that human fetuses with gastroschisis present with lower total serum protein levels and higher quantities of protein in the amniotic fluid, which should reflect protein losses and intrauterine growth deficits (16).

Thus, after the surgical correction of gastroschisis, the NBs should present with large exudative losses (e.g., water, sodium, and proteins) to the so-called ''third space'' or the inflamed bowel walls. The low serum albumin levels lead to decreased coloidosmotic plasma pressure, with fluid leakage to the extravascular areas, decreased intravascular volume, and decreased renal perfusion. In addition, the increased intra-abdominal pressure from the closed-wall defect contributes to decreased renal perfusion, which is responsible for oliguria. Thus, NBs with gastroschisis would have increased antidiuretic hormone secretion to promote free water retention and blood-volume reestablishment. The infusion of crystalloid solutions, however, cannot increase the blood volume because the infused liquid continues to leak into the interstitial space due to the previous low albumin levels; as a result, the serum sodium concentration remains low. Consequently, edema in the pulmonary interstice occurs, with defects in gaseous exchange and ventilatory mechanics. This effect explains the correlation between low serum levels and increased OTI time because both of these values are probably related to the excessive infusion of crystalloid solutions ($p = 0.04$). Furthermore, newborns in the first phase received sodium at levels much higher than normal maintenance, which increased their tendency to present with anasarca. Finally, despite the therapeutic administration of albumin solutions in the second phase of the study, the serum albumin levels decreased ($p = 0.02$), although the serum sodium levels may have increased ($p = 0.006$). The albumin levels may have initially decreased when albumin was administered, probably because the intravascular space had been expanded. The Phase 2 patients did indeed have a tendency to be less edematous than the newborns in Phase 1, which explains why the low sodium levels in the second phase did not correlate with longer OTI times.

The low serum albumin levels did not correlate with longer OTI times, although a correlation with the time to first and full enteral feeding was observed. Additionally, the need for albumin solution expansion did not correlate with any of the studied variables. These facts suggest that the low albumin levels combined with hemodynamic alterations and oliguria (requiring the administration of exogenous albumin), which are significant morbidity factors, did not influence the time of postoperative ileus. In fact, the mechanisms of the intestinal dysfunction observed in gastroschisis patients are not fully known. Intestinal dysfunction can be explained by changes and immaturity of the enteric nervous plexus and by exposure of the intestine to the amniotic fluid, as described in experimental investigations in rabbits (12, 17).

The results of the present study agree with several studies of adult patients undergoing abdominal surgery or after trauma. These studies found that maintaining albumin concentrations above 3.5 g/dL with exogenous albumin did not alter the length of postoperative ileus or hospital stay and did not improve pulmonary function or final mortality (18). There are few studies of albumin treatment in pediatric surgical patients. In an interesting study by Kenny et al. (19), hypoalbuminemia occurred in 27% of postoperative neonates, and the mortality of the hypoalbuminemic infants was greater but was unrelated to the albumin level or albumin treatment. Finally, two randomized controlled studies comparing isotonic saline to 5% albumin in hypotensive term and preterm neonates showed that these two solutions are equally effective in treating hypotension and that patients treated with albumin had greater fluid retention (20,21). It is possible that the increased fluid retention was responsible for the decreased serum albumin levels observed in our Phase 2 patients. Another explanation would be the extravasation of albumin into the interstitial space.

Another interesting difference between the two study periods is the higher body weights found in the second phase, even though no weight differences were observed between the two phases at the beginning of the enteral diet. Moreover, there was a tendency toward more episodes of necrotizing enterocolitis in the first group than in the second group. Such data suggest a possible benefit of initially introducing a semi-elemental diet and then gradually transitioning to integral formulas. This result agrees with a previous report suggesting that the early introduction of minimal enteral feeding and the controlled increase of nutritional elements after bowel reintegration significantly improves the NBs' outcomes after the surgical repair of gastroschisis (13).

The comparisons regarding nutritional support demonstrated that no differences occurred between the two phases of the study, even though the albumin solution administration in the second phase of the study may have exacerbated the low serum sodium levels and decreased the serum albumin levels (Table 2). In both phases of the study, the time to initiation of the enteral diet, time to reach the full enteral diet, time on PN, and length of hospitalization did not vary. These results are in accord with the conclusion of a previous study of 163 gastroschisis patients that demonstrated that hyponatremia and hypoalbuminemia could not have influenced intestinal function because these alterations were not correlated with the number of days on PN (10).

In conclusion, the present study suggests that the administration of albumin solution to NBs in the early postoperative period of gastroschisis repair improved the decreased serum sodium levels but did not improve the final outcomes. In addition, the introduction of a semi-elemental diet was responsible for increased body weight at hospital discharge.

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AUTHOR CONTRIBUTIONS

Tannuri ACA, Tannuri U, and Leal AJG performed medical and surgical care of the patients and wrote the manuscript. Silva LM examined the medical records and statistical analyses. Moraes ACF performed the final revision of the statistical analyses.

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