Neonatal hematological and biochemical complications in TTTS and TAPS

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Chapter 5
Hypoalbuminemia in donors with twin-twin transfusion syndrome

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Abstract

Objective: To estimate the differences in albumin levels between donors and recipients with twin-twin transfusion syndrome (TTTS).

Methods: We performed a matched case control study including twin pairs with TTTS treated conservatively (conservative group) or with fetoscopic laser surgery (laser group) and analyzed the albumin levels at birth in donor and recipient twins.

Results: We included 18 twin pairs in the conservative group and 36 control twin pairs (laser group), matched for gestational age at birth. Median albumin levels in donor twins in the conservative group were significantly lower than in recipient twins, 25.0 versus 33.0 g/l, respectively ($p = 0.001$). In the laser group, albumin levels in donors and recipients were similar, 32.0 versus 32.0 g/l, respectively ($p = 0.633$). Hypoalbuminemia (albumin level < 20 g/l) occurred in 22% (4/18) of donor twins in the conservative group

Conclusions: Hypoalbuminemia occurs frequently in donor twins with TTTS treated conservatively. In TTTS treated with laser, donor twins have similar and normal albumin levels compared to recipients, confirming a successfully performed fetoscopic laser procedure.

Introduction

Twin-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twinning and is due to inter-twin blood transfusion via placental vascular anastomoses. TTTS affects 10% of monochorionic twin gestations and usually develops during the second trimester of pregnancy, leading to hypovolemia and oligohydramnios in the donor twin and hypervolemia and polyhydramnios in the recipient twin.[1;2] Several studies have reported significant inter-twin hematological differences, showing that the hemoglobin levels in donor twins are often significantly lower than in recipient twin.[3;4] Few small studies have reported on other inter-twin differences including biochemical variables and showed that conservatively treated donor twins may also have lower levels of albumin and total protein at birth.[3;5] Hypoalbuminemia in neonates is an independent risk factor for mortality and morbidity and has been associated with various adverse clinical conditions, including necrotizing enterocolitis, intracranial hemorrhage, sepsis, respiratory distress syndrome, chronic lung disease and edema.[6–10] Treatment with fetoscopic laser surgery ameliorates the clinical condition at birth, but it is unknown whether albumin levels are concomitantly higher.

Given the clinical importance of albumin in neonates and the high morbidity rates in TTTS, we analyzed the differences in albumin at birth between donors and recipients with TTTS treated with or without fetoscopic laser surgery.

Methods

We performed a retrospective analysis in all consecutive liveborn monochorionic twins with TTTS admitted to our neonatal nursery at the Leiden University Medical Center over a 10-year period, between August 2003 and August 2012. The Leiden University Center is a tertiary medical center and serves as the national referral center for fetoscopic laser treatment in TTTS pregnancies in the Netherlands.

Diagnosis of TTTS was reached using the standard ultrasound criteria.[11] TTTS was staged according to the classical staging system.[12] Included in the conservative group were all consecutive TTTS cases treated conservatively either with expectant management or with serial amnioreduction. Each twin pair in the conservative group was compared with 2 control twins pairs with TTTS treated with laser surgery (laser group), matched by gestational age at birth ±(1 week of gestation). We excluded TTTS cases with single or double intrauterine death, recurrent or reversal of TTTS after laser surgery, twin anemia-polycythemia sequence and triplet gestations (or higher order). The following obstetrical data were collected: TTTS stage, type of treatment for TTTS, mode of delivery, gestational age at birth, birth weight and inter-twin birth weight discordance. Birth weight discordance was assessed and calculated as follows: ((birth weight larger twin – birth weight smaller twin)/ birth weight larger twin) x 100. Birth weight discordance was defined as more than 20% difference in birth weight. The following neonatal data were collected: respiratory distress syndrome, necrotizing enterocolitis, patent ductus arteriosus, neonatal sepsis (defined as a clinically ill neonate with positive bacterial culture), and cerebral injury detected with cranial ultrasound (defined as any of the following: cystic periventricular leukomalacia or intraventricular hemorrhage grade 3–4) and neonatal mortality. Cranial ultrasound is routinely performed in all TTTS cases during the neonatal period according to our previously published protocol.[13] At birth, the following hematological and biochemical parameters

are routinely analyzed in all TTTS twins: levels of hemoglobin, albumin and total protein. Blood samples were obtained primarily from umbilical cord blood or from venous blood collected within 12 h after birth. In this study we defined hypoalbuminemia at birth as albumin level < 20 g/l and total protein was considered too low when < 40 g/l.[14–16] The primary outcome measure was albumin level at birth. We compared albumin differences between donors and recipients within the conservative group and within the laser group and between both groups. We hypothesized that albumin levels would be lower in donor twins in the conservative group.

Statistics

Data are reported as medians and interquartile range (IQR). Descriptive analyses on data of the conservative group and laser group were performed. Results of continuous variables within twin pairs were analyzed using paired Student's t test and categorical variables were compared using McNemar's test. Unpaired Student's t test was used to compare continuous variables between the conservative group and the laser group. For statistical analyses, two-sided tests were used and a p value ! 0.05 was considered to indicate statistical significance. Analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, Ill., USA).

Results

A total of 216 live-born twin pairs with TTTS were admitted to our neonatal nursery during the 10-year study period. 25 (12%) TTTS twin pairs were treated conservatively and included in the conservative group. Seven eligible twin pairs in the conservative group were excluded because of incomplete biochemical data at birth. Twelve TTTS pregnancies (66%) were treated with serial amnioreduction and the other six pregnancies (34%) were managed expectantly because of asymptomatic stage 1 TTTS. We were able to match each twin pair in the conservative group (n = 18) with 2 control TTTS twin pairs (n = 36) treated with laser surgery. Baseline characteristics of both groups are shown in table 1.

TABLE 1 Baseline characteristics in the TTTS group treated conservatively (conservative group) and TTTS group treated with laser surgery (laser group)

	Conservative group (n^a = 36)	Laser group (n^a = 72)
TTTS stage at diagnosis - n (%)		
Stage 1	14 (39)	10 (14)
Stage 2	10 (28)	18 (25)
Stage 3	8 (22)	42 (58)
Stage 4	4 (11)	2 (3)
Treated with serial amnioreduction - n (%)	24 (67)	
Gestational age at diagnosis - weeks[b]	27.0 (24.25 – 29.0)	19.5 (17.25 – 23.75)
Gestational age at birth - weeks[b]	30 (29 – 32)	30 (29 – 32)
Birth weight difference - %[b,c]	15.9 (10.9 – 27.5)	15.9 (5.9 – 26.4)
Caesarean delivery - n (%)	24 (67)	35 (49)
Female - n (%)	24 (67)	46 (64)

[a]Refers to the number of fetuses vs. neonates
[b]Value given as median (interquartile range (IQR))
[c]Birth weight difference was calculated as follows: ((birth weight larger twin – birth weight smaller twin)/ birth weight larger twin) x 100

In the conservative group, median albumin levels in donor twins were significantly lower than in recipient twins, 25.0 versus 33.0 g/l, respectively (p = 0.001) (table 2). Hypoalbuminemia occurred in 22% (4/18) of donor twins. A co-twin (recipient) of 1 of these 4 donor twins had also an albumin level < 20 g/l. In 1 of the donors with severe hypoalbuminemia, skin edema was present. This patient had an albumin level of 17 g/l at birth and received two albumin transfusions, while his twin brother had an albumin level of 36 g/l at birth. Total protein levels < 40 g/l were detected in 50% (9/18) of the donors and 16.6% (3/18) of the recipient twins in the conservative group (p = 0.031). Hemoglobin levels at birth were also significantly lower in donors compared to recipients.

We found no relationship between albumin levels and TTTS stage in the conservatively managed cases.

TABLE 2 Hematological and biochemical differences at birth between donors and recipients

	Conservative group			Laser group		
	Donors (n = 18)	**Recipients (n = 18)**	**p-value**	**Donors (n = 36)**	**Recipients (n = 36)**	**p-value**
Hemoglobin – g/dL[a]	13.6 (11.6-15.7)	16.1 (13.8-20.2)	0.018	16.7 (15.1-18.7)	16.8 (15.2-17.7)	0.640
Albumin – g/L[a]	25.0 (19.5-30.8)	33.0 (28.0-38.0)	0.001	32.0 (30.0-35.0)	32.0 (30.0-34.0)	0.633
Albumin < 25 g/L – n (%)	9 (50)	1 (5.6)	0.008	0 (0)	0 (0)	1.000
Albumin < 20 g/L – n (%)	4 (22)	1 (5.6)	0.250	0 (0)	0 (0)	1.000
Total protein – g/L[a]	40.0 (31.0-48.0)	48.0 (45.0-58.3)	0.002	48.0 (44.3-52.8)	48.0 (44.0-52.5)	0.721
Total protein < 40 g/L – n (%)	9 (50)	3 (16.6)	0.031	4 (11.2)	1 (2.8)	0.250
Inter-twin hemoglobin difference – g/dL[a]		3.6 (1.6-6.0)		1.2 (0.5-2.1)		0.007
Inter-twin albumin difference – g/L[a]		5.0 (2.0-15.3)		2.0 (1.0-4.8)		0.009
Inter-twin total protein difference – g/L[a]		6.5 (2.0-23.8)		3.5 (1.0-6.0)		0.011

[a]*Data given as median (IQR)*

In the laser group, albumin levels in donors and recipients were similar, 32.0 versus 32.0 g/l, respectively (p = 0.633). No differences in levels of hemoglobin, total protein were noted between donors and recipients.

No differences were found in neonatal morbidity or mortality between donors and recipients in the conservative group and laser group (table 3). In the conservative group, neonatal sepsis occurred more frequently in donor twins compared to recipient twins 38.8% (7/18) versus 16.6% (3/18), but the difference did not reach statistical significance.

TABLE 3 Clinical differences between donors and recipients

	Conservative group			Laser group		
	Donors (n = 18)	**Recipients (n = 18)**	**p-value**	**Donors (n = 36)**	**Recipients (n = 36)**	**p-value**
Birth weight – g[a]	1231 (925-1688)	1459 (1265-1819)	0.002	1293 (1008-1697)	1550 (1247-1783)	0.007
RDS – n (%)	10 (56)	10 (56)	1.000	13 (36)	14 (38)	1.000
NEC– n (%)	1 (5.6)	1 (5.6)	1.000	2 (5.6)	2 (5.6)	1.000
PDA– n (%)	1 (5.6)	1 (5.6)	1.000	0 (0)	1 (2.8)	1.000
Cerebral injury – n (%)[b]	1 (2.8)	3 (16.6)	0.500	1 (5.6)	5 (13.8)	0.125
Sepsis – n (%)[c]	7 (38.8)	3 (16.6)	0.344	5 (13.8)	4 (11.2)	1.000
Mortality– n (%)	0 (0.0)	0 (0.0)	1.000	1 (2.8)	1 (2.8)	1.000

RDS = Respiratory distress syndrome, NEC = necrotizing enterocolitis, PDA = patent ductus ateriosus,
a Value given as median (IQR)
b Cerebral injury is defined as any of the following: cystic periventricular leukomalacia or intraventricular hemorrhage grade 3-4
c Sepsis is defined as blood-culture proven clinical sepsis

Discussion

This study shows that donor twins with TTTS treated conservatively have significantly lower levels of albumin and total protein compared to recipient twins and compared TTTS twins treated with fetoscopic laser surgery. In addition, lower hemoglobin levels were only found in donors of the conservative group. Our findings may suggest that patent placental vascular anastomoses allow not only significant loss of hemoglobin from donors to recipients, but also result in loss of albumin. Once placental anastomoses are completely coagulated with laser surgery, levels of albumin or total protein in donors are restored and no inter-twin differences are detected.

Interestingly, albumin levels in recipients in the conservative group were only slightly increased compared to the lasered cases (33 vs. 32 g/l, respectively). Albumin levels in recipient twins could be lower than expected due to hemodilution following (cardiac) overload. Alternatively, our finding could suggest that the inter-twin difference in albumin levels depend on more factors than simply a loss of albumin from donors to recipients. Hypothetically, hypoalbuminemia in donor twins may also result from a decreased production in the liver.
The pathophysiology of TTTS is still not completely understood. The validity of the traditional theory of TTTS being based solely on unbalanced blood shunting from the donor to

the recipient has frequently been questioned [17]. In contrast with twin anemia-polycythemia sequence, which is primarily a transfusion process, the pathophysiology of TTTS seems to be based on several factors including hormonal dysregulation and circulatory imbalance. Nevertheless, the inter-twin transfusion process probably also plays an important role in the development of TTTS.

Inter-twin hematological differences in TTTS have frequently been reported in various studies [3,4]. However, only two small studies have reported on other inter-twin differences including biochemical variables [3,5]. In a small study with cordocentesis in 8 TTTS cases, Berry et al. [3] found significant inter-twin albumin difference between donors and recipients with a median difference of 12.1 g/l, which is higher compared to the inter-twin albumin difference of 8.11 g/l found in our study. In another small study with cordocentesis in 6 TTTS cases, Okamura et al. [5] found normal albumin levels in all twins. Although albumin levels were lower in donor twins, the difference did not reach statistical significance, probably due to the small sample size. Different results between the studies are probably due to differences in methodology, sample sizes, time of measurements (intrauterine vs. postnatal) and cohort-differences.

Albumin has several important physiological properties, including protein binding and transport, maintenance of colloid osmotic pressure, free radical scavenging, platelet function inhibition, antithrombosis and -alterations of vascular permeability [6]. Albumin is -produced in the liver, but not stored [18]. It is immediately excreted into the hepatic lymph system or the sinusoids and circulates from the vascular space across the capillary wall into the interstitium and returns to the vascular space via the lymphatic system [6,18]. This circulation half-life of albumin is approximately 16-18 h and degradation half-life is 17-20 days [6]. Hypothetically, the loss of albumin and total protein, and possibly other important nutrients, may also play a role in the deterioration of the intrauterine clinical condition of the donor twin in TTTS and may prevent adequate growth. In this study we did not detect an increased risk of neonatal morbidities or mortality in donor twins, but our study was not designed to detect such differences.

Our results should be interpreted with care due to the retrospective nature of the study. In addition, a selection towards milder TTTS cases was present in the conservative group, which is inherent with the conservative treatment. Most severe TTTS cases in our country are treated primarily with laser surgery. This means that our research might not be truly representative for most twins with TTTS. Nevertheless, our results show that 50% (9/18) of the donors in the conservative group has an albumin level <25 g/l, while this never occurred in the laser group. Albumin levels appear thus to restore after fetoscopic laser surgery, which could partly explain the catch-up growth detected in donor twins after laser surgery [19].

In conclusion, significant albumin differences are found between donors and recipients with TTTS treated conservatively but not after laser surgery. Our data do not support that hypoalbuminemia per se is associated with an increased risk of neonatal morbidity and mortality in donor twins, but larger studies are required to detect differences in neonatal outcome.

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