

Twin-twin transfusion syndrome: a review of treatment option

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Abstract. Objective: The twin-twin transfusion syndrome (TTTS) is a complication of monozygotic-mono-chorionic twinning and is a direct result of transplacental communication between the circulations of twins. When acute TTTS occurs in the second trimester, the perinatal mortality can be as high as 95% in the absence of treatment. For this reason, several aggressive, even desperate treatment modalities have been attempted including selective fetocide, umbilical cord ligation, maternal digoxin therapy. None have gained wide acceptance. Serial drainage amniocentesis or amnioreduction is actually the most widely used therapy. More recently, laser ablation under fetoscopic guidance of placental vessel has been reported in an attempt to improve survival. The objective of this review was to evaluate the impact of treatment modalities in TTTS. Study design: Reports of prospective and retrospective trials and other study designs in English identified from searches of MEDLINE, EMBASE, specialized databases, bibliographies of review articles. Study on twin pregnancies affected by TTTS between 1990 and 2003 that met our inclusion criteria were included. Results and conclusions: No single therapy is associated with a uniformly improved outcome for the involved twins and success is primarily related to gestational age and severity at diagnosis. Standard therapy has commonly been serial amnioreduction, which appears to improve the overall outcome. Intertwin septostomy similarly improves outcome but has no survival advantage over serial amnioreduction. Selective fetoscopic laser photocoagulation has emerged as an alternative treatment strategy in TTTS with at least comparable if not superior survival to serial amnioreduction. TTTS diagnosed before 26 weeks' gestation has significantly better survival rates and fewer neurological sequelae after laser therapy than amnioreduction.

Key words: Twin-twin transfusion syndrome, treatment, amnioreduction, fetoscopic laser ablation, fetal survival, review

Introduction

The twin-twin transfusion syndrome (TTTS) is a complication of monozygotic-mono-chorionic twinning and is a direct result of transplacental communication between the circulations of twins.

Characteristic ultrasound features of TTTS are progressive growth discordance, polyhydramnios (deepest vertical pool ≥ 8 cm) and distended bladder in the recipient; oligohydramnios (deepest vertical pool ≤ 1 cm) and collapsed bladder in the donor, with the do-

nor being enveloped by the intertwin membrane exhibiting the "stuck twin" sign.

It is estimated that up to 98% of mono-chorionic placentas have anastomoses between the circulatory bed and in approximately 15% of monozygotic twins manifest TTTS, which accounts for 17% of perinatal death (1). Partly as a result of an inadequate understanding of the pathophysiology of the syndrome, there is a lack of consensus in clinical management. This syndrome has a very high perinatal mortality and as a result various treatment strategies have been at-

tempted ranging from amniocentesis to selective fetocide. The prognosis is poor in cases diagnosed in the second trimester and when untreated, perinatal mortality approaches 100% (2). For this reason, several aggressive, even desperate treatment modalities have been attempted including selective fetocide, umbilical cord ligation, maternal digoxin therapy. None have gained wide acceptance. Serial drainage amniocentesis or amnioreduction is actually the most widely used therapy. Recently, laser ablation under fetoscopic guidance of placental vessel has been reported in an attempt to improve survival.

The objective of this review was to evaluate the impact of treatment modalities in TTTS.

Literature searched: we searched MEDLINE, EMBASE and the Cochrane Collaboration.

Table 1 presents inclusion/exclusion criteria for articles chosen for review.

Amnioreduction

Feingold et al (3) described two cases where 3500 and 4750 mL were removed, resulting in prolongation of the pregnancies by 14 and 11 days, respectively. Although two of the four fetuses died, these investigators concluded that decompression amniocentesis "can offer some hope in an otherwise hopeless situation".

Thereafter in a review of the available literature comprising 252 fetuses from 26 reports, Moise (4) re-

ported an overall perinatal survival rate after serial amnioreduction in TTTS of 49%. However, many of these cases were reported in the 1930s and 1940s when amniocentesis was performed without ultrasound assistance with drainage of only small quantities of amniotic fluid. Uncontrolled series employing modern aggressive amnioreduction in which amniotic fluid volume is reduced to normal have been associated with perinatal survival rate from 37 to 83%, and risk of neurological damage of 17-33% (table 2). As shown in table 2 fetal survival is correlated principally to gestational age at delivery and appears also higher in those cases where aggressive therapeutic amniocentesis was conducted. On careful review of published series, it is not uncommon to find patients in whom the classical fetuses of TTTS resolve after a single amniocentesis or after the last of a series if amniocentesis, with no subsequent need for therapy. Several authors have also observed rapid reaccumulation of amniotic fluid volume in the donor twin's sac immediately after amnioreduction. Procedure related complications occur with serial amnioreduction in the order of around 10%. This is mostly fetal death within 48 hours of the procedure or spontaneous abortion. Abruption placenta has been reported.

Mari et al (5) in 2001 illustrates results of the International Amnioreduction Registry, where 223 sets of twins affected by TTTS were enrolled and treated with amnioreduction; the survival rate 4 weeks after birth was 60% and the author concluded that the survival rate was significantly related to gestational age at diagnosis, presence of end-diastolic blood flow in the umbilical artery velocity waveforms, presence of hydrops, mean volume of amniotic fluid removed per week, higher birth weight and gestational age at delivery.

Fetoscopic laser ablation

DeLia et al (15) evaluated the feasibility of fetoscopically directed occlusion of placental vasculature using a neodymium-YAG laser in four ewes. Theoretically it has the advantage of solving the underlying mechanism that causes unbalanced twin-twin transfusion.

Since this first report, a total of 71 patients have been described by two groups of investigators (16, 17).

Table 1. Treatment of TTTS: inclusion/exclusion criteria for efficacy studies

Category	Criteria
Study population	Humans Pregnant female
Condition	Signs of TTTS
Study setting	Inpatient and outpatient setting
Time period	1990 and later
Geographic site of study	Exclude locations based on language of publication
Publication language	English
Admissible evidence	Randomised and quasi-randomised studies; prospective and retrospective cohort studies, case-control, meta-analyses, review articles.

Table 2. Amnioreduction: summary of published cases

Authors	No of patients	Gestational at diagnosis (weeks)	No of procedure (mean)	Amniotic volume removed at each amnioreduction (ml)	Gestation at delivery (mean; weeks)	Survival (% fetuses)
Urig et al (6) 1990	5	21-25	1-7 (4)	1000-5000	27.3	60
Mahoney et al (7) 1990	8	16-28	2-6 (3.5)	300-5500	31.4	69
Radestad et al (8) 1990	18	21-32	1-4 (2)	125-5000	30.1	53
Elliot et al (9) 1991	17	16-28	1-10 (4)	225-5000	33.2	79
Saunders et al (2) 1992	19	17-25	1-6 (3)	500-6700	28.3	37
Pinette et al (10) 1993	9	20-26	1-9 (3.5)	300-8500	32.6	83
Reisner et al (11) 1993	27	16-30	1-6 (3.5)	250-5500	31.5	74
Dennis et al (12) 1997	11	15-26	1-12 (5.5)	-	30.4	82
Dickinson et al (13) 2000	92	19-25	1-23 (2)	1050-2450	29	62.5
Mari et al (14) 2000	33	14.5-33	1-15 (2)	-	30.5	70
Mari et al (5) 2001	223	14-27.5	1-31 (2)	140-5875	29	60

In each series, 53% of the fetuses survived to delivery. These initial results do not compare favourably with amnioreduction, a less invasive and more readily available therapy. As shown in table 3 later published series have however shown a 55-82% survival rate but with a 4.2% neurological handicap rate (18). These authors argue that irrespective of the depth of the individual anastomoses, their afferent and efferent branches are superficial and can be seen on the placenta surface. Systematic coagulation of all these vessel should include the branches of these anastomoses and currently this remains the only method that can prevent transfusion between the placentas.

Better neurological outcome observed in those patients who underwent laser ablation confirmed in a retrospective cohort outcome study di Sutcliffe, who observed an overall cerebral palsy rate of 9%: 0% in the singleton survivors group and 13.3% in the twin survivor group (19).

Maternal morbidity may be much higher than with amniocentesis related procedures and bleeding of the placental vessels is consistently reported (20).

Amniotic septostomy

Disruption of the dividing membrane would cause fluid to move along a hydrostatic pressure gradient from the sac with polyhydramnios into the sac with oligohydramnios with equalization of the pressure in the two sacs. Septostomy may be a relative safe procedure which does not require special equipment. The major risk associated with amniotic septostomy is cord entanglement, since it leads to a monoamniotic pregnancy with a single sac.

This technique was initially described following an iatrogenic error during amnioreduction where the amnion separating the twins was inadvertently punctured at the time of amniocentesis (25). In one of the larger studies published by the same author (26) on 12 patients, survival rate as high as 83% was achieved but no results regarding neurological outcome are available. Less encouraging are the results obtained by Adegbite (27) in 13 pregnancies treated by amniotic septostomy in combination with amnioreduction who reported a survival rate of 46%.

Table 3. Fetoscopic laser ablation: summary of published cases

Authors	No of patients	Gestational age at diagnosis	Mean gestation at treatment	Survival (%)	At least one Survivor (%)
Martinez (21) et al 2003	110	16-25	20.7	68.6	88.2
Hecher (22) et al 2000	200	16-25	20.7	68	81
Thilaganathan (23) et al 2000	10	17-23	20.3	55	70
Zikulnig (24) et al 1999	121	17-26	20.7	64	81
De Lia (17) et al 1995	26	18-24	20.8	52	-

Digoxin

Digoxin crosses the placenta readily in the absence of hydrops and therapeutic levels have been achieved in the fetus following maternal administration.

This treatment was suggested by DeLia et al (28), who treated the mother with digoxin when signs of cardiac failure persisted in recipient twin. Signs of cardiac decompensation resolved and both twins survived. To date this therapy, used in conjunction with amnioreduction or laser thermocoagulation has been anecdotally reported (29, 30). Fetal heart and blood dynamics however suggest that it does not work and it therefore has been abandoned.

Cord occlusion

Selective fetocide, with deliberate ending of one twin's life, has been suggest as an extreme mode of

treatment. Benirschke and Driscoll (31) first suggested ligation of one umbilical cord, but their attempt was unsuccessful. Wittmann (32) et al reported fetocide of the donor at 25 weeks' gestation with subsequent successful delivery of the recipient at 37 weeks. It therefore appears that selective fetocide may solve some of the problems associated with the syndrome but must be performed in a way that does not permit transfer of blood from one twin to the other. Therefore it is essential that all vascular communications between the pump and perfused fetuses be occluded simultaneously and completely to prevent a significant portion of the pump fetus's blood volume becoming trapped in the perfused fetus. In addition, timing of the procedure may have a significant effect on outcome. Prophylactic cord occlusion has to be carried out before development of congestive heart failure.

Ligation of the perfused fetus's umbilical cord has been reported in serial cases (table 4).

Table 4. Cord occlusion: summary of published cases (TTT: twin-twin transfusion; TRAP: twin reversed arterial perfusion)

Authors	No of patients	Type of patients	Mean of gestational age (weeks)	Type of procedure	Result
McCurdy (33) et al	1	TTT	18	Endoscope (5 mm)	Died within 24 hours
Quintero (34) 1994	1	TTT	19	Endoscope (1.9 mm)	Delivery at 36 weeks
Foley (35) et al	1	TRAP	21	Foley cordostat grasping	Delivery at 35 weeks
Lemery (36) et al	1	TTT	27	Single puncture ultrasound-guided	Delivery at 29 weeks
Ville (37) et al	4	TRAP	17 20 26 28	YAG-laser via fetoscopy	Successfully Successfully Failed Failed
Porecco (38) et al	1	TRAP	24	Percutaneous intravascular injection of a thrombogenic material under ultrasound guidance (PIITM)	Failed
Holzgreve (39) et al	1	TRAP	21	PIITM	Successfully
Sepulveda (40) et al	1	TRAP	23	PIITM	Delivered 11 days after
Quinterno (41) et al 1996	13	10 TRAP/ 2 TTT/1 fetal abnormality in 1 twin	21	Cord ligation	Survival 63%
Deprest (42) et al	4	3 TRAP/1 TTT	20.5	Cord ligation	Survival rate 50%
Nicolini ⁴³ et al	17	9TTT/2TRAP/6 fetal abnormalities	18-27 (range)	Bipolar diathermy	Survival rate 76%
Taylor (44) et al	14	TTT	21	Bipolar diathermy	Survival rate 93%
Gallot (45) et al	11	TTT	20	Cord ligation using a suture Cord coagulation (bipolar forceps) Cord compression	Survival rate 72%

The numbers of women treated by this methods is very small, as the procedure is usually only performed where demise of the co-twin is certain. The numbers are therefore too small to provide valid neurological outcomes for the surviving twin in these pregnancies and the survival rate by definition can at best be only 50%. Selective feticide has also relative risks associated with the technique used. Among the techniques applied from a retrospective observational study conducted by Gallot (45) to 11 patients, bipolar coagulation appears to be the easiest technique, but the choice of procedure depends on local conditions.

Comment

No single therapy is associated with a uniformly improved outcome for the involved twins and success is primarily related to gestational age and severity at diagnosis.

Standard therapy has commonly been serial amnioreduction, which appears to improve the overall outcome. Intertwin septostomy similarly improves the outcome but has no survival advantage over serial amnioreduction. Survivor of TTTS treated by serial amnioreduction have an 18% to 26% incidence of sonographically detectable brain abnormalities. Selective fetoscopic laser photocoagulation has emerged as an alternative treatment strategy in TTTS with at least comparable if not superior survival to serial amnioreduction. In particular TTTS diagnosed before 26 weeks' gestation has significantly better survival rates and fewer neurological sequelae after laser therapy than amnioreduction. TTTS diagnosed after 26 weeks can best be treated by amnioreduction or delivery. Contrary to previous claims, fetoscopic laser therapy has a outgrown its experimental status. Although improvements in technique and technology are likely, laser placental ablation has a firm scientific and clinical basis.

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