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Oral Digoxin In Treatment Of Early Diagnosed Cases Of Twin To Twin Transfusion Syndrome, Is It Useful?

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ABSTRACT

Twin-to-twin transfusion syndrome is the major complication of monochorionic twin pregnancy and one of the most challenging problems of obstetrics. Even though invasive intrauterine techniques for the treatment of twin-to-twin transfusion syndrome [TTTS] such as laser photocoagulation are established, they are not always feasible due to lack of necessary equipment in low resource facilities like our hospital. The aim of the study was to evaluate the use of oral digoxin as a treatment for early diagnosed cases of TTTS [18-27 weeks gestation]. Nine diagnosed cases with TTTS from July 2017 till July 2018 received daily digoxin till delivery with follow up regarding digoxin levels in blood, twin fetal weight, umbilical artery systolic:diastolic ratio [S/D], amniotic fluid volume through assessment of deepest vertical pocket [DVP] and fetal outcome assessment was done. There was significant improvement in cases regarding weight discordance with normal S/D of UA and amniotic fluid volume throughout pregnancy with fair fetal outcome at birth in 6 of the cases. These results showed that early diagnosed cases of TTTS can get benefit from the use of daily oral digoxin..

Keywords: Twin-to-twin-transfusion syndrome; Digoxin, oligohydramnios; polyhydramnios; preterm labor; monozygotic twins.

SOMMARIO

La sindrome da trasfusione gemello-gemello è la principale complicazione della gravidanza gemellare monocoriale e uno dei problemi più difficili dell'ostetricia. Anche se sono state stabilite tecniche invasive intrauterine per il trattamento della sindrome da trasfusione gemello-gemello come la fotocoagulazione laser, non sono sempre fattibili a causa della mancanza di attrezzature necessarie in strutture a basso costo come il nostro ospedale. Lo scopo dello studio era di valutare l'uso della digossina orale come trattamento per i casi di diagnosi precoce di sindrome da trasfusione gemello-gemello [18-27 settimane di gestazione]. Nove casi diagnosticati con sindrome trasfusionale da gemello a gemello da luglio 2017 a luglio 2018 hanno ricevuto digossina giornaliera fino al parto con follow up riguardante i livelli di digossina nel sangue, peso fetale gemellare, sistolica dell'arteria ombelicale: rapporto diastolico [S / D], volume del liquido amniotico attraverso la valutazione della tasca verticale più profonda [DVP] e la valutazione del risultato fetale è stata fatta. C'è stato un miglioramento significativo nei casi riguardanti la discordanza di peso con normale S / D di UA e il volume di liquido amniotico durante la gravidanza con esito fetale giusto alla nascita in 6 dei casi. Questi risultati hanno mostrato che i casi di diagnosi precoce della sindrome trasfusionale da gemello a gemello possono trarre beneficio dall'uso della digossina orale quotidiana.

INTRODUCTION

Monochorionic (MC) twin pregnancies represent 20–25% of all twin pregnancies with a continuously increasing incidence.(1) Twin-to-twin transfusion syndrome [TTTS] occurs in approximately 10% of all monochorionic twins. TTTS has been estimated to affect 1 to 3 in 10,000 births.(2) It has an 80% to100% mortality rate if severe and left untreated(3).

The diagnosis of TTTS is based upon ultrasound evidence of monochorionicity with discordance in fetal growth, amniotic fluids, twin oligohydramnios, and polyhydramnios sequence(4).

The twin-to-twin transfusion syndrome (TTTS) occurs due to imbalanced blood flow through vascular communications in the placenta, such that one twin is compromised and the other is

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favored[5].

Laser photocoagulation is the main established treatment for TTTS[6-12].

MATERNAL DIGOXIN

Digoxin's primary mechanism of action is through inhibition of sodium-potassium adenosine triphosphatase (ATPase)[13]. Digoxin also has neurohormonal effects and causes improved baroreceptor sensitivity, decreases norepinephrine concentration, and decreases activation of the renin-angiotensin system [RAS][14-15]. Digoxin delays the onset of recipient heart failure and hydrops and it also reduces donor RAS production. Digoxin administration improved recipient cardiovascular function, causing an improved or reversed recipient hydrops[16-18]. Treatment of the recipient twin without compromise of the donor may become feasible, using agents that cross the placenta and are nontoxic to the developing fetus.

SUBJECTS

This prospective cohort study was conducted on 9 pregnant women in Shatby maternity University hospital, Alexandria, Egypt, from July 1st 2017 to July 1st 2018.

All participants were informed about the nature of the study and informed consent was taken from each of them.

INCLUSION CRITERIA

Twin pregnant women where TTTS confirmed on ultrasound basis by:

1. Confirmation of monochorionicity.
2. Oligohydramnios in one sac and polyhydramnios in the other.
3. Growth discordance more than 20 % between both fetuses.

EXCLUSION CRITERIA:

1. Higher order multiple pregnancy.
2. Dichorionic twin pregnancy.
3. Singleton pregnancy.
4. Contraindications to digoxin.

METHODS

Data collected included maternal age, last menstrual period, obstetric and medical history. Initial ultrasound and Doppler examination were performed for diagnosis of the TTTS using Voluson P8 ultrasound machine; General Electric [GE]®.

All patients received oral digoxin daily till delivery, aiming to reach therapeutic serum level of digoxin which was measured at the first follow up interval using cobas c 6000 analyzer (Roche Diagnostics).

Digoxin dose was increased up to two or three tablets per day until therapeutic levels (0.8- 2 ng/ml)[19] were reached and maintained in the maternal circulation. Patients were monitored closely for the development of any symptoms or signs of digoxin toxicity

Follow up ultrasound and Doppler were performed for all patients every two weeks till delivery to assess the donor and recipient fetal weight , weight discordance percentage, amount of liquor, the urinary bladder shadow and the umbilical artery resistance through assessing the S/D ratio.

Data collected on pregnancy outcome were based on gestational age at delivery, route of delivery and fetal condition, including neonatal birth weight, neonatal hemoglobin level, neonatal jaundice and the need for blood exchange transfusion.

Statistical analysis of the data [20]

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp)[21].

Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

The procedures followed were in accordance with, and approved by, the ethical standards of the Committee on human experimentation of the Faculty of medicine, University of Alexandria, Egypt.

RESULTS

The minimum gestational age at diagnosis was 18 weeks with mean 21.59 ± 3.37 weeks while the maximum gestational age at delivery was 36 weeks with mean 31.02 ± 3.43

One case was diagnosed at the age of 27 weeks+4days and intrauterine fetal death [IUFD] of both twin occurred at the age of 29 weeks.

Table (I):
Analysis of the studied twins after the use of maternal digoxin regarding the perinatal outcome whether: IUFD, live birth, abortion or still birth (n=18):

Fetus A [donor]and fetus B [recipient]	Before treatment		After treatment		χ2	FEp
	No.	%	No.	%	8.690*	0.008*
Live birth	18	100%	11	61.1		
IUFD, still birth and Abortion	0	0.0	7	38.9		

χ2: Chi square test FE: Fisher Exact
*: Statistically significant at p ≤ 0.05

The study started by observing 9 pregnant females with TTTS (9 donor fetuses and 9 recipient fetuses). One recipient fetus turned IUFD at 29 weeks gestation. Termination of pregnancy occurred with 2 cases due to preterm labor pains; the first case at the gestational age of 25 weeks+3days while the other case was at the age of 27 weeks

Table (II):
Comparison of the studied cases according to weight discordance (%) at diagnosis ant at termination of pregnancy (n=8):

	Weight discordance at diagnosis (%)	Weight discordance at birth (%)	Z	P
Min. – Max. Mean ± SD. Median	24.22 – 50.8 37.74 ± 10.47 39.20	1.8 – 51.50 26.45 ± 15.12 23.05	2.100*	0.036*

Z, p: Z and p values for Wilcoxon signed ranks test for comparing between at diagnosis and final weight
*: Statistically significant at p ≤ 0.05

Regarding the weight discordance between the donor twin and recipient twin, the mean discordance percentage at diagnosis was 39.51 ± 11.14% with significant improvement at birth; 25.5 ± 14.6%.

Table (III):
Descriptive analysis of the studied cases according to deepest vertical pocket of amniotic fluid (DVP):

	At diagnosis	Final DVP	Z	P
Fetus A [donor] Min. – Max. Mean ± SD. Median	1.0 – 3.0 2.17 ± 0.75 2.0	3.0 – 8.0 4.92 ± 2.15 4.50	2.207*	0.027*
Fetus B [recipient] Min. – Max. Mean ± SD. Median	6.0 – 9.0 7.50 ± 1.05 7.50	4.20 – 8.0 6.53 ± 1.31 7.0	1.219	0.223

Z, p: Z and p values for Wilcoxon signed ranks test for comparing between at diagnosis and final DVP
*: Statistically significant at p ≤ 0.05

Comparing the deepest vertical pocket at time of diagnosis to that at the time of delivery, for the donor twin, it showed significant improvement with Digoxin therapy. For the recipient twin, there was no worsening of the condition.

Table (IV):
Descriptive analysis of the studied cases according to umbilical artery S/D (n=6)

UA S/D	At diagnosis	Final FU	Z	P
Fetus A [donor] Min. – Max. Mean ± SD. Median	6.0 – 7.0 6.58 ± 0.38 6.50	3.0 – 4.0 3.33 ± 0.42 3.13	2.207*	0.027*
Fetus B [recipient] Min. – Max. Mean ± SD. Median	5.70 – 6.30 6.01 ± 0.19 6.0	2.7 – 4.50 3.48 ± 0.67 3.35	2.201*	0.028*

Z, p: Z and p values for Wilcoxon signed ranks test for comparing between at diagnosis and final FU
*: Statistically significant at p ≤ 0.05

Regarding the fetal Doppler, umbilical artery [UA] S/D remained within the normal values for both the donor and the recipient twin throughout the follow up intervals.

One recipient twin presented with ascites at the age of 24 weeks gestation with umbilical artery S/D 5.5 which resolved at the age of 26 weeks gestation.

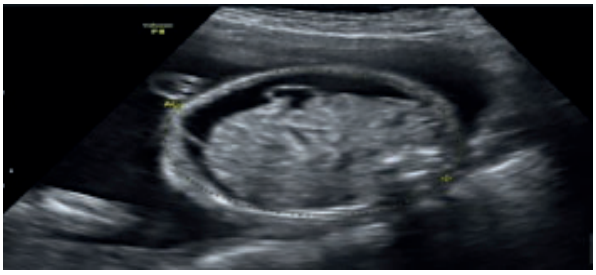

Figure 1: *Abdominal ascites seen at the gestational age of 24 weeks in a recipient twin*

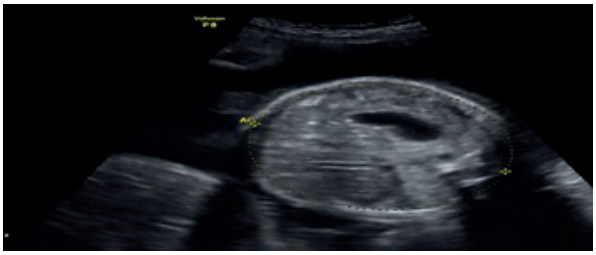

Figure 2: *Resolution of abdominal ascites after treatment*

Table (V):
Descriptive analysis of the studied cases according to birth weight

Birth weight (grams)	Min. – Max.	Mean ± SD.	Median
Fetus A (n = 8) (Donor)	450.0 – 1950.0	1293.5 ± 587.9	1510.0
Fetus B (n = 7) (Recipient)	700.0 – 3300.0	1695.71 ± 926.95	1800.0
Discordance % (n = 5)	17.40 – 51.50	25.52 ± 14.61	19.10

#: IUFD case was excluded

Regarding the birth weight, mean birth weight for the donor twin is 1293.5 ± 587.9 gm while the mean for the recipient twin is 1695.71 ± 926.95 gm with mean weight discordance 25.52 ± 14.61 gm

Table (VI):
Descriptive analysis of the studied cases according to hemoglobin

hemoglobin (gm/dl)	Min. – Max.	Mean ± SD.	Median
Neonate A [donor] (n=6)	13.0 – 16.5	14.42 ± 1.36	14.5
Neonate B [recipient] (n=5)	15.0 – 23.0	18.8 ± 3.56	18

The mean fetal hemoglobin level for the donor twin at birth is 14.42 ± 1.36, while the mean hemoglobin level for the recipient twin is 18.8 ± 3.56gm/dl

DISCUSSION

Until a few decades ago, the only available antenatal treatment option was serial amnioreduction to treat polyhydramnios and reduce the risk of preterm delivery. However, amnioreduction is not a causal treatment and only a temporary solution.[22]

Technical advances in ultrasound, endoscopy, video recording, and medical lasers formed the basis for diagnosis and in utero therapy of placental disorders.[23]

The outcomes of this condition have been significantly improved after the introduction of fetoscopic laser ablation. However, there is still a significant fetal loss rate and morbidity associated with this condition.[24]Another problem is the high cost which makes it unavailable in many settings including El Shatby Maternity University hospital, Alexandria, Egypt.

The use of digoxin for TTTS has a long history. Digoxin was first suggested for hydropic fetus with severe TTTS before any effective ablative therapies were available[25].

The current study showed reversal of recipient fetal hydrops with the use of digoxin without compromise to the donor twin. This is similar to the van den Wijngaard et al[25] mathematical simulation models study which showed that digoxin administration in TTTS with a hydropic recipient, simulated an improved recipient cardiovascular function, causing an improved or reversed recipient hydrops.

This is also comparable to the TTTS case described by De Lia et al[26] in which a pregnancy complicated by twin transfusion syndrome was presented and when signs of cardiac failure persisted in the recipient twin, maternal digoxin therapy was instituted at 27 weeks' gestation

which lead to resolution of the signs of failure and the twins were delivered electively by cesarean section at 34 weeks.

This result is also similar to Arabin et al[27] case report in which a TTTS pregnant case presented at 16 weeks gestational age with one twin severely hydropic with normal amniotic fluid while the co-twin had anhydramnios. Laser treatment was performed. However, signs of severe cardiac decompensation in the recipient remained unchanged. After treatment with digoxin resolution of the hydrops was achieved and at 37 weeks 2 healthy boys were delivered.

In this study the mean postnatal hemoglobin level for the donor fetus was 14.42 ± 1.36 while that for the recipient fetus was 18.8 ± 3.56 gm/dl with median intertwin hemoglobin difference 5 gm/dl (2.0 - 7.0 gm/dl). In comparison to L.Verbeek et al[28] study which studied the hematological parameters at birth that showed mean Hb level for donor 13.9 ± 3.5 and for the recipient 18.4 ± 3.6 for the TTTS that was treated conservatively with median intertwin hemoglobin difference 3.6 (1.6–6.0) gm/dl. In contrast, in TTTS treated with laser coagulation surgery, no significant difference in hemoglobin levels was found with mean Hb level for the donor 16.8 ± 2.9 gm/dl and for the recipient 17.1 ± 2.5 gm/dl. Treatment with Digoxin therefore might be associated with lower donor hemoglobin levels, yet still within normal range for neonates

In this study one case developed IUFD of the recipient twin at the age of 28 weeks gestation and the donor fetus was born at the age of 32 weeks with fetal weight 1950 gm and fetal Hb level 15 gm/dl with good neurological performance. This shoes better outcome compared to Roman et al[29] study in which a case with TTTS was diagnosed with IUFD of one twin at the age of 20 weeks with evidence of fetal hydrops in the surviving twin and the administration of maternal digoxin and amniocentesis resulted in the delivery of 1186 gm fetus at the age of 30 weeks.

In this study, the average duration of pregnancy was 31 weeks, the average birth weight for the recipients was 1695.71 gm and the average birth weight for the donors was 1293.5 gm. Four recipients and three donors died in the peripartum period. This again shows better outcome compared to study performed by Pfeiffer et al[30] which was carried on 12 TTTS cases, the average duration of pregnancy was 30 + 4 weeks (Range 26 + 6 to 35 + 6 weeks).

The average birth weight of the recipients reached 1377g (range 2485 ± 870 g), that of the donors 999 g (range 1930 ± 520 g). In comparison to Sago et al[31] study regarding fetoscopic laser surgery for treatment of TTTS, the mean gestational age at the time of surgery was 21.2 weeks. The mean gestational age at delivery was 32.9 weeks

CONCLUSION

Even though invasive intrauterine techniques for the treatment of TTTS such as laser photocoagulation are established, they are not always feasible. In conservative treatment of TTTS oral digoxin therapy can be used as it showed fair results regarding fetal outcome for both the donor and recipient twin.

The use of oral digoxin is recommended to be started in early diagnosed cases for the best outcome.

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