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# N-terminal Pro-brain Natriuretic Peptide Levels in Monochorionic Diamniotic Twins with Twin-to-twin Transfusion Syndrome Treated by Fetoscopic Laser Photocoagulation

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**Key words:** Monochorionic diamniotic twin, N-terminal pro-brain natriuretic peptide, NT-proBNP, Fetoscopic laser photocoagulation, Twin-to-twin transfusion syndrome

**Twin-to-twin transfusion syndrome (TTTS) affects 15% of monochorionic diamniotic (MD) twin pregnancies, and is associated with adverse perinatal outcome. Recently, fetoscopic laser photocoagulation (FLP) has been widely accepted as the most definitive therapy to treat TTTS. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a powerful diagnostic marker of cardiac dysfunction in neonates, and is elevated in MD twins with TTTS. However, there are no reports assessing the effect of FLP on neonatal cardiac overload in TTTS by measuring the serum NT-proBNP levels at birth. Here, we aimed to compare serum NT-proBNP levels at birth in MD twins with TTTS treated with FLP or not. Twelve MD twin pairs with TTTS admitted to our center between October 2007 and September 2012 were enrolled in this study. The MD twin pairs were separated into two groups: seven twins (12 newborn infants) with FLP (FLP group) and five twins (nine newborn infants) without FLP (non-FLP group). Gestational age, birthweight, and Apgar scores were significantly higher in the FLP group than that in the non-FLP group. Serum NT-proBNP levels at birth were significantly lower in the FLP group than in the non-FLP group [1425 pg/ml (range, 466–9560) vs. 29900 pg/ml (range, 7300–77900), respectively; p=0.0003]. The serum NT-proBNP levels of larger and smaller co-twins were significantly correlated with each other (r=0.750; p=0.026). In conclusion, serum NT-proBNP levels at birth are lower in MD twins with TTTS after FLP treatment than in those without FLP.**

## INTRODUCTION

Approximately 15% of monochorionic diamniotic (MD) twin pregnancies are complicated by twin-to-twin transfusion syndrome (TTTS) (7, 16). Despite the recent advances in perinatal management, TTTS remains an important cause of neonatal death and handicap in infants (13, 16). TTTS is thought to arise from an imbalance in intertwin blood supply across the vascular anastomoses in placentas, and leads to hypervolemia, polyuria,

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and polyhydramnios in the recipient, and hypovolemia, oliguria, and oligohydramnios in the donor (13).

Fetoscopic laser photocoagulation (FLP) of the placental vascular anastomoses offers a promising treatment option by interrupting the placental anastomoses (8, 23). Acute improvements in recipient myocardial performance were reported to occur within 2 weeks after successful FLP (10). Although the effects of FLP on several perinatal outcomes have been reported in multiple publications, most were focused on obstetric outcomes, such as pregnancy complications and survival rates (1, 21). There is relatively little information about the impact of FLP on neonatal outcomes, especially hemodynamic and endocrinological effects at birth.

Brain natriuretic peptide (BNP) or its precursor, N-terminal pro-BNP (NT-proBNP), which is accepted as a more stable and reliable factor for measurement than BNP itself (5), is a convenient and objective diagnostic marker of cardiac dysfunction in neonates, as well as in adults and children (25, 26). NT-proBNP is derived from the fetus itself and does not reflect transplacental exchange of maternal NT-proBNP, although theoretically the factor is small enough to pass from mother to child (11). It is reported that high BNP levels in umbilical cord blood and amniotic fluid are predictive of cardiac dysfunction and hypotension soon after birth in singleton neonates (15).

To date, several studies have revealed that the NT-proBNP levels in amniotic fluid are elevated in twins with TTTS and are correlated with cardiac workload (3, 9), but there are no reports assessing the effect of FLP on neonatal cardiac overload in TTTS by measuring the serum NT-proBNP levels at birth. Thus, the purpose of this study was to compare serum NT-proBNP levels at birth in MD twins with TTTS treated with FLP or not.

## METHODS

### Study design and patient groups

This observational study was approved by the Ethical Committee of Hyogo Prefectural Kobe Children's Hospital with informed consent waived, because of the retrospective nature of the data collection.

Of the 124 twin pairs (242 newborn infants and six intrauterine fetal deaths) who were born at Kobe Children's Hospital between October 2007 and September 2012, 12 MD twin pairs (21 newborn infants) with TTTS were enrolled. The median gestational age was 31 weeks (range, 24–37 weeks), and median birthweight was 1,262 g (range, 492–2,564 g). Patients with congenital or chromosomal anomalies, and patients whose serum NT-proBNP levels were not measured due to sample insufficiency, were excluded.

TTTS was defined as the presence of polyhydramnios in the recipient (maximum vertical pocket $\geq$8 cm) and oligohydramnios in donor (maximum vertical pocket $\leq$2 cm), according to Quintero's diagnostic criteria (18). Inclusion criteria for FLP were TTTS Quintero stages 1 through 4 and a gestational age between 16 and 26 weeks. Exclusion criteria were a major fetal anomaly, ruptured membranes, uncontrolled uterine contractions, and a maternal condition mandating delivery. All TTTS patients who met the above criteria were offered FLP, according to Japanese guidelines (21). FLP of placental vascular anastomoses was performed in a similar manner at our designated referral institute in accordance with previously described methods (19).

Fetal condition was monitored conventionally by ultrasonography in combination with fetal heart rate monitoring or fetal biophysical profiling. All twin infants were delivered by cesarean section. Indications for delivery were at the discretion of the attending physicians, and mainly depended on fetal deterioration. Abnormal Doppler waveforms, including

reversed flow in the ductus venosus and reversed flow in the uterine artery, were taken into consideration as indications for delivery in some cases.

Serum NT-proBNP has been measured at birth in order to determine intrauterine cardiac load in MD twins in our center, since its diagnostic use for cardiac failure was approved in 2007.

Twelve twin pairs with TTTS were separated into two groups; seven twins (12 newborn infants) with FLP treatment (FLP group) and five twins (nine newborn infants) without FLP treatment (non-FLP group). One intrauterine fetal death and one donor twin in the FLP group, and one recipient twin in the non-FLP group were excluded because NT-proBNP levels at birth were unavailable. Clinical and laboratory data, including birthweight discordancy between donor and recipient twin (discordant rate), the degree of TTTS severity determined by ultrasonographic findings (the Quintero staging) (18), and serum NT-proBNP levels at birth were compared between the two groups.

**Clinical data of the patients**

Clinical data collected from patient records included gestational age, birth weight, Apgar scores (1 and 5 min), sex, maternal age, and the presence or absence of assisted reproductive technology, pregnancy-induced hypertension (maternal systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg during pregnancy), premature rupture of the membranes (rupture of the membranes more than 24 h before delivery), small for gestational age (birth weight less than the 10th percentile of median birth weight at the same gestational age in Japanese newborns (17)), discordant rate [(birth weight of the larger twin - birth weight of the smaller twin) / birth weight of the larger twin × 100.], and the Quintero staging.

**Sample collection and measurements of serum NT-proBNP levels**

Blood samples were collected within 2 hours of birth. They were promptly ice-cooled and centrifuged. Their serum samples were stored at -20°C until assay. Serum NT-proBNP was measured by electro-chemiluminescence immunoassay on the EClusys 2010 analyzer (Roche Diagnostics K.K., Tokyo, Japan).

**Statistical analysis**

Data are expressed as the median (range) or number (%). Statistical analyses were performed using the Mann-Whitney nonparametric rank test, Chi-square test, or Fisher's exact test as appropriate. Correlation analysis was performed to compare serum NT-proBNP levels at birth between larger and smaller MD co-twins. The correlation coefficient (r) was also calculated. Differences and correlations were deemed statistically significant at $p<0.05$.

## RESULTS

**Clinical background of the FLP and non-FLP groups**

Clinical characteristics in the FLP group and the non-FLP group are shown in Table I. Sex, maternal age, discordant rate, and Quintero staging were similar in both groups. There were no significant differences in the incidence of small for gestational age, assisted reproductive technology, pregnancy-induced hypertension, premature rupture of membranes, uncontrolled uterine contractions, and abnormal cardiotocogram findings. Gestational age, birth weight, and Apgar scores were significantly higher in the FLP group than in the non-FLP group.

**Table I.** Clinical background of the FLP and non-FLP groups

| | | FLP n=12 | Non-FLP n=9 | p-value |
|---|---|---|---|---|
| Gestational age (weeks) | | 33.5 (31–37) | 26 (24–29) | <0.001 |
| Birth weight (g) | | 2038 (896.0–2564) | 802.0 (492.0–1262) | <0.001 |
| Apgar score | 1 min | 8 (6–9) | 6 (4-8) | <0.01 |
| | 5 min | 9 (7–9) | 7 (5-9) | <0.05 |
| Male (%) | | 4/12 (33%) | 6/9 (67%) | 0.13 |
| Maternal age (years) | | 29.5(24–37) | 31(26–35) | 0.66 |
| Small for gestational age (%) | | 5/12 (42%) | 4/9 (44%) | 0.90 |
| Assisted reproductive technology (%) | | 1/7 (14%) | 0/5 (0%) | 0.38 |
| Pregnancy induced hypertension (%) | | 0/7 (0%) | 1/5 (20%) | 0.22 |
| Premature rupture of the membranes (%) | | 2/7 (29%) | 0/5 (0%) | 0.19 |
| Uncontrolled uterine contractions (%) | | 1/7 (14%) | 0/5 (0%) | 0.38 |
| Abnormal cardiotocogram findings (%) | | 1/7 (14%) | 1/5 (20%) | 0.79 |
| Discordant rate (%) | | 14.5 (1.3–45.9) | 21.6 (7.8–39.7) | 0.76 |
| Quintero staging | | 3 (1–4) | 2 (1–3) | 0.46 |

**Comparison of serum NT-proBNP levels between the FLP and the non-FLP group**

Serum NT-proBNP levels at birth in the FLP group were significantly lower than in the non-FLP group [1425 pg/ml (range, 466–9560 pg/ml) vs. 29900 pg/ml (range, 7300–77900 pg/ml), p=0.0003] (Figure 1).

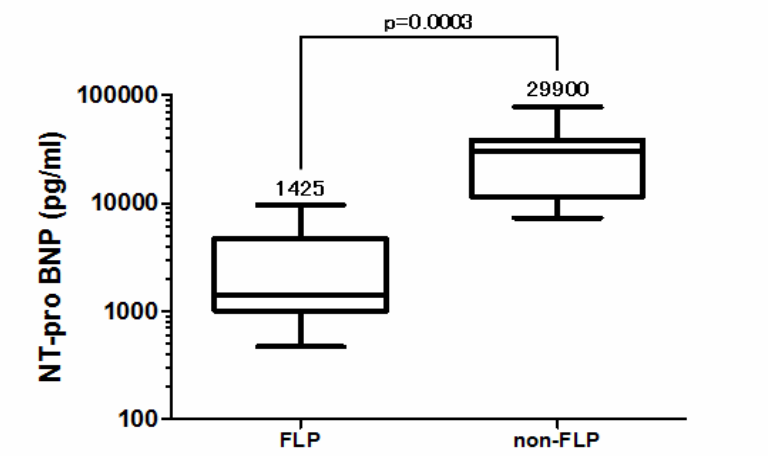



**Figure 1.** Comparison of serum NT-proBNP levels between the FLP and the non-FLP group.

**Correlation of serum NT-proBNP levels between larger and smaller co-twins**

As shown in Figure 2, the serum NT-proBNP levels between larger and smaller co-twins were significantly correlated (r=0.750; p=0.026).

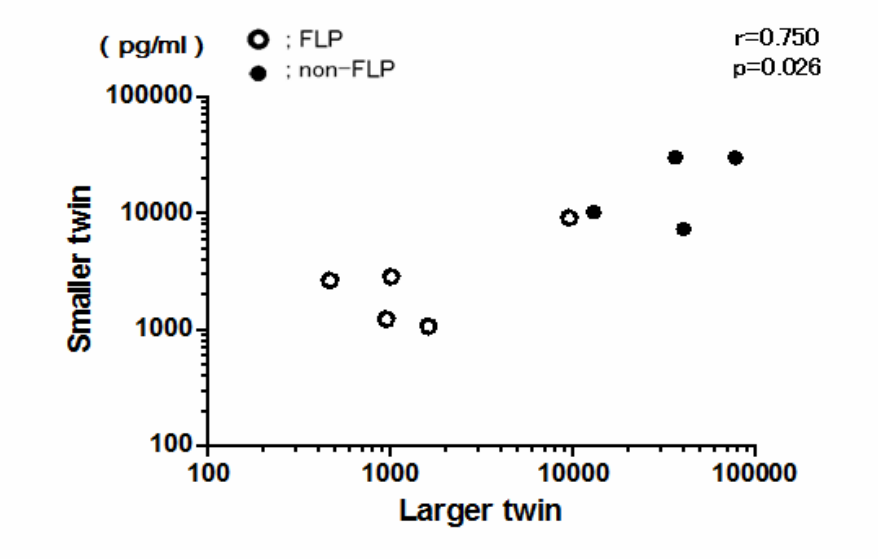



**Figure 2.** Correlation of serum NT-proBNP levels between larger and smaller co-twins.

## DISCUSSION

The present study has demonstrated for the first time that serum NT-proBNP levels at birth were significantly lower in MD twins with TTTS treated with FLP than in those not treated with FLP, even though there were no differences in the discordant rate and the Quintero staging between the groups.

Although there have been many studies on intrauterine cardiac function in MD twins with TTTS treated by FLP (1, 3, 10), no study has assessed the cardiac load at birth by measuring NT-proBNP levels of the newborns. Fetal echocardiography is the most frequently used modality to evaluate the cardiac overload in TTTS patients (4, 10, 20), but the accuracy of assessment may depend on the examiner's experience, fetal movement and position, and intrinsic cardiac movement, as well as the maternal status (2). Although increased ventricular wall thickness, which indicates ventricular hypertrophy, is a widely accepted echocardiographic feature in cardiac overload in TTTS patients (4), a paradoxical increase in left and right ventricular thickness after FLP was reported with evidence of improved cardiac overload (10). Therefore, we adopted serum NT-proBNP as a more convenient biomarker of cardiac overload in TTTS patients than echocardiography in the present study.

It has been widely accepted that FLP is the most definitive therapeutic modality to treat TTTS (22, 23). Significant improvements in the survival rates and rates of long-term neurologic complications in patients of TTTS treated by FLP have been reported (22, 23). Habli et al., in a retrospective study of 65 patients with TTTS, reported acute improvements in recipient myocardial performance index (10). Baschat et al., in a retrospective study of 45 patients with TTTS, noted that fetoscopic laser occlusion corrected intertwin differences in

umbilical venous volume flow (1). Van Mieghem et al. have shown that BNP levels are elevated in the amniotic fluid of recipient twins in TTTS. BNP levels in amniotic fluids are stage dependent and are associated with impaired fetal cardiac function as assessed by ultrasound (24). Our results are consistent with those in previous reports, suggesting attenuated cardiac overload at birth in the FLP group.

We demonstrated in the present study that serum NT-proBNP levels at birth in the FLP group were significantly lower than those in the non-FLP group. A possible reason for the decreased NT-proBNP levels in the FLP group is that FLP reduced intrauterine cardiac overload in the recipient twins and prevented progression to congestive heart failure. We previously reported that cord blood BNP levels were not increased even in MD twins with large birth weight discordances, without congestive heart failure due to developed TTTS (7). We also found that there was a significant correlation in NT-proBNP levels between larger (recipient) and smaller (donor) MD twins with TTTS. In addition, the levels of NT-proBNP were similar between larger and smaller twins (data not shown). The finding of increased serum BNP levels in both larger and smaller twins in the non-FLP group may be partly explained by volume overload in the recipient and cardiac afterload and pressure overload by activation of renin–angiotensin system in the donor (14).

The limitation of this study is the relatively small number of TTTS patients with or without FLP, because this was a retrospective observational study at a single center. Further studies using larger sets of twin patients are required. Additionally, there were significant differences in clinical backgrounds, including gestational age, birth weight, and Apgar scores between the groups. In an observational study, high natriuretic peptide levels in umbilical cord blood associated with prematurity, uteral contraction and antenatal stress were reported (12). In the present study, newborns in the non-FLP group were significantly more premature than those in the FLP group, although there were no differences in the incidence of uncontrolled uterine contractions and abnormal cardiotocogram findings between the groups. However, Fortunato et al. in a observational study of 109 uncomplicated pregnancies, reported that the upper reference limits for NT-proBNP in umbilical cord blood were 5402 pg/mL in fetuses in the second trimester (20–25 weeks of gestation), and 1690 pg/mL in healthy neonates (6). In the present study, NT-proBNP levels in the non-FLP groups were significantly higher than the upper limits in Fortunato's study, suggesting intrauterine cardiac overload in these patients.

## CONCLUSION

This preliminary study has shown for the first time that serum NT-proBNP levels at birth are lower in MD twins with TTTS after FLP treatment than those without FLP. These results suggest that FLP for MD twins with TTTS could attenuate cardiac overload in the perinatal period.

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