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Long term developmental outcomes of pre-school age children following laser surgery for twin-to-twin transfusion syndrome

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ABSTRACT

Background: Laser therapy is now a well recognised treatment for twin-to-twin transfusion syndrome (TTTS). We investigated the early childhood neurodevelopmental outcome of children post laser treatment for TTTS in our centre.

Methods: Children of women who had laser therapy for TTTS between March 2006 and June 2008 were assessed at 30–69 months of age with WPPSI-III and a general health questionnaire. Major neurodevelopmental impairment (NDI) was reported as IQ < 70 or cerebral palsy (CP). Borderline cognitive impairment was defined by IQ 70–79.

Results: Amongst the 37 pregnancies treated, 62 infants were discharged home and the overall foetal survival rate was 84%. A total of 50 children (84%) from 31 pregnancies were assessed. Average age at assessment was 47 months. Two children with late treatment of congenital hypothyroidism were excluded. The majority of pregnancies were Quintero Stage III (74%). There was a significant trend for worse outcome with higher Quintero stage. The average gestational age at birth was 32 weeks. The majority (39, 78%) of children were found to be neurodevelopmentally normal; 9 (18%) had borderline cognitive development; and 2 (4%) had a major NDI, including one with cerebral palsy (2%).

Conclusions: There was a modest level of neurocognitive impairment post laser therapy for TTTS, mainly borderline cognitive development, lesser so major NDI. There was a low incidence of cerebral palsy. Routine developmental and neurological follow-up of these children is recommended.

1. Introduction

Twin to twin transfusion syndrome (TTTS), a condition in which uneven blood flow occurs through placental vascular anastamoses, affects 10–15% of monochorionic twin pregnancies [1]. This condition leads to blood passing from one twin to the other; with a risk of resultant oligohydramnios and severe growth retardation in the donor twin; and risk of polyhydramnios, bladder distension and cardiac dysfunction in the recipient twin. With no treatment the risk of perinatal death is more than 80% and foetal morbidity, both physical and neurological, as a result of the disease and/or preterm birth, is high [2].

Treatment of TTTS with fetoscopic laser coagulation therapy markedly improves perinatal outcome, resulting in higher perinatal survival rates and is now considered the treatment of choice for this condition [3,4]. Laser photocoagulation therapy of the communicating vessels aims to dichorionise the placenta, thereby stopping the blood exchange between the twins [5]. The overall perinatal survival rate post laser therapy is up to 77%, with between 76 and 87% survival for at least one foetus [6].

The main long term morbidity reported after laser treatment for TTTS is neurocognitive, with reported major neurodevelopmental impairment (NDI) rates up to 18% [7–12], inclusive of cerebral palsy rates up to 12%. Gestational age at delivery and Quintero stage at diagnosis, have been found in some studies to also be independently associated with neurologic morbidity [10,12–15].

The majority of studies performed to date on developmental outcomes post treatment with laser therapy for TTTS have been in children up to 2 years of age. In this study we looked at the long term developmental outcome of an older cohort of children, 2 and a half to 5 years post laser therapy for TTTS, to assess for NDI and to determine if there was a trend for improvement in NDI rates in an older cohort of children.

2. Methods

This study investigated the surviving children of women who had selective laser photocoagulation therapy for TTTS between March 2006 and December 2008 at the Royal Hospital for Women, Randwick, NSW, Australia. 45 women with TTTS were treated with laser therapy

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during this period. 37 of these women were living in Australia at the time of the follow-up study, and given the difficulties of coordinating the study internationally, 8 international women were excluded from the study, leaving a cohort of 37.

Diagnostic criteria and treatment methods for selective laser photocoagulation of communicating vessels are described in the primary study by Meriki et al. [16]. Laser therapy was performed between 16 and 25 weeks of gestation. Perinatal information (Quintero stage at presentation, gestational age (GA) at laser, GA at birth, birth weight, small for gestational age (SGA), perinatal outcome, intrauterine foetal demise (IUFD) and neonatal death (NND)) was obtained either from the original study data [16], medical records or via discussion with parents. SGA was defined as weight less than the 10th percentile [17]. Information on whether survivors were the donor or recipient was not obtained in the original data due to difficulty obtaining this information with certainty from outborn pregnancies retrospectively.

The children were assessed at an age of between 2 years and 6 months and 5 years and 9 months. Assessment consisted of *Wechsler Preschool and Primary Scale of Intelligence 3rd Edition* (WPPSI-III) [18], performed by experienced Clinical Psychologists, and a general health questionnaire, which was composed by ourselves. Further health information needing clarifying outside of this was obtained by parental phone discussion via single Medical Practitioner or via accessing medical reports or discussions with treating doctors.

The WPPSI-III provides verbal and performance intelligence quotient (IQ) scores as well as a Full Scale IQ score (FSIQ) [18]. The mean FSIQ is 100. Major cognitive impairment was defined as FSIQ < 70 on WPPSI-III, i.e. 2 standard deviations below the mean of 100. Borderline cognitive impairment was defined by a FSIQ of 70–79.

Major neurodevelopmental impairment (NDI) was diagnosed based on major cognitive impairment (FSIQ < 70) or on the presence of CP. Borderline development was defined as borderline cognition scores on WPPSI-III (or equivalent test). Children that did not have a formal developmental assessment, in which we had only a health questionnaire, were assumed to have no NDI on the basis of parental reporting in the questionnaire. The health questionnaire was used as an adjunct tool for all children, though particularly in these cases where a formal developmental assessment was unable to be performed, to determine if significant medical conditions or NDI was present. Multiple questions alluded to the presence of NDI, including; the presence of medical conditions (specifying CP), history of hospitalisation or procedures, the use of regular medical services or allied health professionals, and the need for extra assistance at pre-school or utilisation of early intervention services.

Two sets of twins had been previously assessed with other standardised developmental tests (i.e. *Bayley Scales of Infant Development 3rd Edition* [19] and Griffiths Mental Development Scales [20]) the results of which we used for this study. Both sets of parents in these cases did not want further developmental tests done: one because of travel distance; the other because of her twin's autism which she felt made testing inappropriate.

Statistical analysis was performed through the use of GraphPad Instat3 (2012™). Fisher's exact test, Chi-square test and one-way analysis of variance (ANOVA) was used to compare variables where appropriate. A P value of <0.05 was considered statistically significant.

This study received ethics approval from the Human Research Ethics Committee of the South Eastern Sydney Illawarra Area Health Service Northern Hospital Network (HREC 08/052). All parents gave informed written consent.

3. Results

31 women participated in the study (n = 52 children); Table 1 shows the perinatal characteristics of these pregnancies and those that were unable to be assessed. In the assessed cases, the majority of pregnancies were Quintero Stage III (74%), and there was survival of both twins in 22 pregnancies (71%), with an overall foetal survival rate of 84%. The mean GA was 32 weeks and the mean birth weight was 1675 g. The majority of these characteristics were not significantly different to those in the non-assessed pregnancies; however there was a significantly higher number of higher Quintero stage pregnancies in the assessed group ($P = 0.044$).

Table 1
Comparison of clinical characteristics of assessed or non-assessed children.

	Assessed	Non-assessed	*P* value
Number of children	52	9	
Pregnancy characteristics			
Number of TTTS pregnancies	31	5[a]	
Quintero Stage II	7 (23%)	3 (60%)	
Quintero Stage III	23 (74%)	1 (20%)	0.044
Quintero Stage IV	1 (3%)	1 (20%)	
Gestational age at laser (weeks)	20.8 (2.3)	21.3 (2.6)	0.56
IUFD of one twin	9 (29%)	1 (20%)	1.0
Births			
Gestational age at birth (weeks)	32 (2.9)	30.6 (2.9)	0.19
Live births/foetuses[b]	52 (84%)	9 (90%)	1.0
Pregnancies with both live births	22 (71%)	4 (80%)	1.0
Birth weight (g)	1675 (585)	1715 (756)	0.86
SGA	20 (39%)	1 (11%)	0.15

Mean (SD) or n (%) is shown; IUFD, intrauterine foetal demise; SGA, small for gestational age.
[a] 5 non-assessed pregnancies: 4 were lost to follow-up after discharge. Birth data was not available in one case.
[b] Overall survival of foetuses including live births.

90% (n = 45) of children had a standardised developmental assessment performed. The majority, 32 children (64%), travelled and had their WPPSI-III assessment at the Royal Hospital for Women by our Growth and Development Clinic Psychologist who is very experienced in assessing high risk children on follow-up. Additionally, 13 children (26%) were developmentally assessed at other similar perinatal centres and developmental clinics and 6 of these 13 children had ongoing Paediatrician follow-up. Mean age at assessment was 48 months (range 30–69 months, SD 9.5 months). 41 children had a WPPSI-III assessment. 2 children had *Bayley Scales of Infant Development 3rd Edition* [19] and 2 children had Griffiths Mental Development Scales [20]; these tests were performed elsewhere and results were accessed for our study. In 6 children a complete WPPSI-III was not able to be obtained: In 2 sets of twins this was due to failure to complete sufficient tasks; another set of twins did not speak English, and were unable to cooperate with the test with parental translation. These aforementioned 6 children who had incomplete WPPSI-III were placed in neurodevelopmental outcome groups based on their health questionnaires and partial WPPSI-III scores if available. Health questionnaires were performed on all children. 5 children (10%) had health questionnaires alone, with no formal developmental assessment due to parental refusal of the assessment.

Fig. 1 shows the foetal and childhood developmental outcomes of the 37 pregnancies eligible for the study. The overall follow up rate was 84%. 6 women were not included in the study. 5 of these women were unable to be contacted and 1 refused participation. One set of twins were excluded from analysis (after WPPSI-III assessment) given a diagnosis and treatment of congenital hypothyroidism in late infancy was revealed in the health questionnaire and Paediatrician reports. Of the 30 included pregnancies (n = 50 children), 78% had a normal neurodevelopmental outcome, 18% had borderline development and 4% had a major NDI (i.e. abnormal group). 1 child (2%) had CP.

Table 2 shows potential perinatal risk factors for neurodevelopmental impairment. The majority of children from Quintero Stage II pregnancies had a normal neurodevelopmental outcome (92%) and no children in this group had a major NDI. All of the children with a major NDI were from Quintero Stage III pregnancies. There was not a statistically significant difference in outcome between the Quintero stages ($P = 0.25$; stages III and IV and borderline/abnormal groups combined for analysis given