

Abstract

Background: Infants born with undiagnosed transposition of the great arteries continue to be born in district general hospitals despite the improvements made in antenatal scanning. Evidence indicates improved outcomes with early definitive treatment after birth, hence the recommendation of delivery in a tertiary centre. The role of specialist paediatric and neonatal transport teams, to advise, stabilise and transport the infants to a tertiary centre in a timely manner, is critical for those infants born in a district general hospital. This pilot study aims to compare outcomes between infants born in district general hospitals and those that were born in a tertiary maternity unit in South West England and South Wales. *Methods:* This was a secondary data analysis of data collected from the local Paediatric Intensive Care Audit Network and the local transport database. Infants born with a confirmed diagnosis of transposition on the great arteries that required an arterial switch operation as the definitive procedure between April 2012 and March 2018. *Results:* 45 infants with a confirmed diagnosis of transposition of the great arteries were included. Statistical analysis demonstrated there were no significant differences in the time to Balloon Atrial Septostomy ($p = 0.095$), time to arterial switch operation ($p = 0.461$), length of Paediatric Intensive Care Unit stay ($p = 0.353$) and hospital stay ($p = 0.095$) or mortality between the two groups. *Conclusions:* We found no significant differences in outcomes between infants delivered outside the specialist centre, who were transferred in by a specialist team.

Keywords: paediatric, neonatal, newborn, Balloon Atrial Septostomy, specialist retrieval, transport; Arterial Switch Operation

Introduction

Transposition of the great arteries is the most common cyanotic congenital heart defect that accounts for five percent of all congenital heart disease cases born.¹ The National Institute for Cardiovascular Outcomes Research found antenatal detection rates of congenital heart disease in infants is improving annually, with current rates at around 50% (NICOR 2016), with transposition of the great arteries detection rates ranging between 41-84% internationally.²⁻⁷ Within the United Kingdom following the British Congenital Cardiac Associations 'Fetal Cardiology Standards' (2012) it is recommended that infants with a diagnosis of transposition of the great arteries are born in a tertiary maternity centre.⁸ There are still 50% that are delivered outside a specialist centre. These infants then require stabilisation in a district general hospital and transfer to a specialist cardiac surgical centre.¹ In the United Kingdom, it is strongly recommended that these transfers are undertaken by specialist paediatric or neonatal intensive care teams.

These specialised paediatric transport teams have been established over the last 20 years across the United Kingdom to transfer critically ill children from the district general hospital into tertiary Paediatric Intensive Care Units (ICU)⁹ and are shown to improve the outcomes of critically ill children.¹⁰ With the move towards increasing centralisation of specialist services in the United Kingdom, such as paediatric cardiac surgical centres, the requirement for inter-hospital transport of infants with cardiac disease is only likely to increase.⁹ This pilot study is the first United Kingdom study to examine the impact of transport times in infants with transposition of the great arteries in relation to patient outcomes. We aimed to examine the outcomes of infants who were externally retrieved

from district general hospitals to those born in the tertiary maternity unit adjacent to the specialist paediatric ICU in the South West of England and South Wales.

Materials and Methods

A secondary data analysis was undertaken of all infants who had a confirmed diagnosis of transposition of the great arteries that were born in the South West of England and South Wales that were admitted to one regional paediatric ICU requiring an arterial switch operation as their definitive procedure, between April 2012 and March 2018. The data was extracted from the local Paediatric Intensive Care Audit Network database and the local specialist paediatric transport team database. The primary aim of this study was to compare the outcomes of infants who were externally retrieved from a district general hospital to those born in the tertiary maternity unit adjacent to the specialist paediatric ICU. Outcomes examined were: length of stay (days) in both paediatric ICU and hospital, paediatric ICU length of stay after balloon atrial septostomy, paediatric ICU length of stay after arterial switch operation and total length of hospital stay. Balloon atrial septostomy requirement was recorded and the age of the infant at balloon atrial septostomy and at arterial switch operation repair. The timing of diagnosis (antenatal or postnatal) was collected. Gestational age (weeks), age at presentation (days), weight on admission to paediatric ICU (kgs) and the type of transposition of the great arteries were all collected. Other key variables such as duration of invasive and non-invasive ventilatory support, inotrope requirement, and mortality was collected. The timing of the infants admission to paediatric ICU was calculated from either time of referral of the infant, for those born in a district general

hospital or from time of birth for those born in the tertiary maternity unit. The duration of the transport episode for the infants born in a district general hospital was calculated from the time of referral to the time of arrival on paediatric ICU, detailed by arrival of the team to the infant's bedside, stabilisation time and infants journey time. We also identified interventions required prior to the teams arrival and interventions undertaken by the transport team on arrival. In the infants born in the tertiary maternity unit we recorded the interventions that had been completed prior to arrival on the paediatric ICU. Interventions were: need for prostaglandin infusion, respiratory support requirements which included both invasive and non-invasive support, inotrope infusions and vascular access.

Physiological and clinical parameters on arrival to paediatric ICU were recorded. These were arterial oxygen saturations (SaO₂), Fraction of Inspired Oxygen (FiO₂) requirements, systolic blood pressure, base excess, serum lactate and paediatric index of mortality 2 score.

Data was analysed using Microsoft Excel and IBM SPSS Statistics for Mac version 24.0 (Armonk, New York: IBM Corp). Normally distributed data was analysed using parametric tests and is presented as mean and standard deviation and non-normally distributed data is presented as median and IQR. To compare groups an independent t-test was used for comparing the means between two groups of normally distributed variables or Mann-Whitney or Kruskal-Wallis test for the non-normal distribution. Differences between categorical variables were compared using chi-square. A p value of <0.05 was considered significant and two tailed tests were used.

This study used anonymised patient data already collected by Paediatric Intensive Care Audit Network, which has ethical approval to collect data in the United Kingdom (PICANet Ref Number is PIAG-4-07-(c)/2002). The local transport database was accessed with permission of the service lead. Ethical approval was obtained from the University of the West of England, (Reference number HAS.18.06.181)

Results

Forty-five infants had a confirmed diagnosis of transposition of the great arteries between April 2012 to March 2018. Fifty-six percent (25/45) of infants were diagnosed antenatally. The majority (92% 23/25) of these infants were born at the tertiary maternity unit, whilst the majority (90% 18/20) of the postnatally diagnosed infants were born in a district general hospital (Table 1). There were no significant differences in the total length of hospital stay between the two groups. The retrieved infants had a median stay of 17 days (IQR 13.5-22.5) compared with the infants born in the tertiary maternity unit of 18.5 days (IQR 15-24.5) ($p = 0.095$ 95%CI -9.237-0.689). Eighty-three percent (34/41) of the infants transferred by either the paediatric or neonatal team required a balloon atrial septostomy prior to the arterial switch operation. Infants born in the tertiary maternity unit had a balloon atrial septostomy earlier than the retrieved infants with a median age of one day (IQR 0-1) compared to 2.5 days (IQR 1-7.75), but this was not significant ($p = 0.095$). Infants admitted from the tertiary maternity unit had a similar length of stay on paediatric ICU after balloon atrial septostomy, compared with the retrieved infants, median 2 days (IQR 1-2) versus 3 days (IQR 2-3) ($p = 0.162$ 95%CI -0.473-2.330). Length of stay following the arterial switch operation repair was not significantly different

between the two groups with those born in the tertiary maternity unit staying for a median of 5 days (IQR 3-8) versus 4 days (IQR 4-5) ($p = 0.353$). There were no significant differences in age at arterial switch operation repair with the infants born in the tertiary maternity unit having the procedure at a median of day 8 (IQR 6-11) and the retrieved infants on day 10 (IQR 8-11) ($p = 0.461$) (Table 2).

Most infants (91% 41/45) were transferred to paediatric ICU by either the specialised paediatric ICU transport team (33% 15/45) or the local neonatal team (58% 26/45) with 4/45 (9%) being transferred by another team. In the district general hospital born infants, the median time from referral to paediatric ICU arrival was 440 minutes (IQR 343.5-470) and from referral to the transport teams arrival to the infants bedside was a median of 180 minutes (IQR 122.5-215), with a median stabilisation time of 95 minutes (IQR 92.5-140). Transit times from the district general hospital to the paediatric ICU was median of 92 minutes (IQR 56-114). The specialist transport team has a median transit time of 73.5 minutes (IQR 53-112).(Table 3). The geographical area for the service is approximately 15000 miles with a median distance to the referring district general hospitals being 51 miles (IQR 42-95)

In the retrieved infants, most (93% 14/15) infants required a prostaglandin infusion, 11/15 (73%) required invasive ventilation, one (7%) required Continuous Positive Airway Pressure and two (14%) High Flow Nasal Cannula. Inotropic support was required in 53% (8/15) infants, with various inotropes being used; Dopamine, with doses between 5-20mcg/kg/min in all eight infants with two also requiring Dobutamine infusion at 5mcg/kg/min, two needing Noradrenaline infusions and one necessitated both Noradrenaline and

Adrenaline infusions. All of the infants had vascular access secured prior to the specialised transport teams arrival. In the infants born in the tertiary maternity unit, most (92% 24/26) required a prostaglandin infusion, 9/26 (35%) required invasive ventilation, 5/26 (19%) required Continuous Positive Airway Pressure and one (4%) High Flow Nasal Cannula. Inotropic support was required in 2/26 (8%), with Dopamine used. The dose was 5mcg/kg/min in one case and 10mcg/kg/min in the other. All of the infants in this group had vascular access secured prior to admission to Paediatric ICU (Table 4).

Clinical parameters of the infants are presented in Table 5. There were clinically significant differences in FiO₂ on arrival to paediatric ICU between the two groups. Infants born in a district general hospital had a higher median FiO₂ of 0.6 (IQR 0.25-0.89) at paediatric ICU arrival compared to those born in the tertiary maternity unit with a FiO₂ of 0.21 (IQR 0.21-0.3) ($p=0.045$ 95%CI .00428- .38536). Despite the differing FiO₂ levels, the infants SaO₂ levels were similar with a median value of 70% (IQR 62-80) in the retrieved infants and 78% (IQR 71-85) in the infants born in the tertiary maternity unit. There was a difference in the rate of invasive ventilation required: 11/15 (73%) in the retrieved group compared with 8/26 (31%) of the infants born in the tertiary maternity unit ($p = 0.447$). Serum lactate was no different at infant arrival to paediatric ICU was a median 3.1(IQR 1.6-9.4) for the infants retrieved, compared to 2.7 for tertiary maternity unit (IQR 1.5-3.3) ($p=0.077$ 95%CI -.44772 – 7.72541). There was no different in paediatric index of mortality score between the groups, the tertiary maternity unit has a median paediatric index of mortality score of 5.37 (IQR 2.2-10.4) and the retrieved group a median of

7.5 (1.9-10.7) p value (p= 0.467). Two infants died across the cohort, one in each group (5%).

Discussion

This pilot study is the first United Kingdom study to examine the impact of transport times in infants with transposition of the great arteries in relation to patient outcomes. Other international studies have specifically compared outcomes of infants with antenatal versus postnatal diagnosis of transposition of the great arteries.^{7,11-15} Studies from Australia¹⁶⁻¹⁷ considered the impact of transfer distance and use of a specialist transport team and the impact on infant physiological stability. Both studies identified that transfers of infants over long distances, with a postnatal diagnosis of transposition of the great arteries, can be undertaken safely when performed by specialised teams and appears to have no adverse effects on outcomes. Due to the vastly larger distances, the majority of their transfers took place via air, either fixed wing or rotor. This is different to the United Kingdom picture as the majority of transfers take place in a road ambulance with data indicating that only 2% of transfers involve air transfers.¹⁸ In the United Kingdom, transport services can cover a geographical area that require journey times of over 180 minutes for the critically ill children. However, these studies did not compare the impact of a specialist transport team and the differences to clinical outcomes such as the overall hospital length of stay, time to balloon atrial septostomy or arterial switch operation in infants with transposition of the great arteries.

We did not find any significant differences in outcomes in these infants who were retrieved. This implies that retrieval by specialist transport teams does not delay time to paediatric ICU admission, and more importantly, does not worsen

outcomes. In 1993, Macrae¹⁹ recommended that all children requiring intensive care management should be moved to a paediatric ICU by dedicated paediatric ICU staff skilled in transport. However, at that time there was no established policy, which meant that most of the moves were undertaken by a doctor and nurse team from the district general hospital, most of whom will not have been skilled in intensive care. Many studies in the early 1990s¹⁹⁻²² reported high levels of morbidity and adverse events occurring when high risk transfers were carried out by non-specialised teams compared to paediatric transport teams. In 1997 'A Framework for the Future' was published which identifies standards for paediatric intensive care including provision of transport services.²³ A study published in 2010¹⁰ showed an improvement in survival rates for children transferred by a specialist paediatric team. Since 2010 across the United Kingdom, specialist paediatric transport teams operate to a set national standard, which is set by the Paediatric Intensive Care Society.²⁴ Emergency and unplanned admission to paediatric ICU equal approximately 12,000 per year of which approximately 6,000 are carried out by specialist transport teams.²⁵

Fifty six percent (25/45) of the infants in this study had an antenatal diagnosis of which 92% (23/25) were born at the tertiary maternity unit. This is consistent with findings of previous studies that showed that the detection rate for infants with transposition of the great arteries is between 41-84%.²⁻⁷ We found specialist management was undertaken in the district general hospitals for the retrieved infants with 94% (14/15) on a prostaglandin infusion and 11/15 (73%) were intubated and ventilated for safe transfer. This is supported by other studies which found that between 31% and 77% of infants with CHD required

a prostaglandin infusion and were intubated and ventilated for transfer.²⁶⁻²⁸ Intravenous prostaglandin is a potent vasodilator that is routinely used to reopen or maintain the patency of the ductus arteriosus.²⁷ Prostaglandin has well known side effects of causing apnoea's especially in high doses (>15ng/kg/min) however Browning et al²⁸ suggests that infants on low dose prostaglandin (<15ng/kg/min) can safely be transferred self-ventilating, so long as the transfer is completed by specialist teams. This may reduce risks further as the infants are not exposed to additional risks associated with invasive ventilation.

An interesting finding was that infants transferred in were on higher FiO₂ levels despite the same oxygen saturations. Clearly, for transposition of the great arteries, administering more oxygen is unlikely to improve arterial oxygen saturation of the infant until there is a communication formed with a balloon atrial septostomy. This is due to the systemic and pulmonary circuits running parallel and therefore the problem of inadequate mixing. Within this study the infants were transferred to paediatric ICU by either a paediatric or neonatal team. In preterm infants, the accepted management is to give as little oxygen as possible to achieve the desired SpO₂ level as they have higher risk factors with hyperoxia, such as retinopathy of prematurity, periventricular leukomalacia and bronchopulmonary dysplasia.²⁹ We do not fully understand the reason for this finding in this pilot study and further exploration of this finding is warranted. The use of oxygen is recommended in transposition of the great arteries infants to try and reduce hypoxia as much as possible, with the aim of maintaining arterial oxygen saturations between 75-85% and help stabilise the infants haemodynamic status and improve cardiac output.

The paediatric index of mortality score predicts the risk of mortality for a cohort of critically ill children at the point of paediatric ICU delivery.³⁰ Our study found no difference in paediatric index of mortality, and this is supported by the mortality outcome of four percent; Kirzner³¹ identifies that centres around the world are now reporting survival rates of >95% in children that have had the arterial switch operation.

There are a number of limitations in this pilot study that require acknowledgement. The study was completed with the data of a single paediatric ICU and one specialist paediatric transport team with a low number of infants. This study reviewed clinical parameters on admission to paediatric ICU, but not during paediatric ICU admission. However, despite the limitations this is the first United Kingdom study to examine the impact of specialist intensive care transport teams on transfer and outcomes of infants with transposition of the great arteries and its findings as this may not be generalisable to the other specialist transport teams. Further larger scale work across the United Kingdom is now required to fully establish generalisability of findings.

Conclusion

Ideally, all infants with transposition of the great arteries would be diagnosed antenatally, to facilitate delivery in a tertiary maternity unit. However, there will continue to be a percentage of infants born with undiagnosed CHD in district general hospitals, who will require stabilisation and transfer to a regional specialist centre and paediatric ICU and this study demonstrates that the use of specialist transport teams to carry out transfer of infants with transposition of the great arteries appears to be safe practice. This study has demonstrated that

the outcomes between infants born with a transposition of the great arteries diagnosis are not significantly different between the two groups. This indicates that the use of a specialised paediatric transport team in the process from referral to admission to paediatric ICU is a useful resource to have access to. With the advice and support offered by the transport team the infants can have the same timely access to the definitive procedures required for the treatment and management of transposition of the great arteries.

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Conflict of Interest

None to declare

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Table 1. Demographics of infants

		Total N = 45 (%)	Born in DGH N = 19 (%)	Born in a Tertiary Maternity Unit N = 26 (%)	P value
<u>Gender</u>					
Male		32 (71)	11 (58)	21 (80)	0.113
Female		13 (29)	8(42)	5(20)	
<u>Diagnosis</u>					
Antenatal		26 (55)	2 (10)	24 (92)	0.308
Postnatal		19 (45)	17 (90)	2 (10)	
Gestational age (weeks)	Median	39	40	38	0.023
	(IQR)	(38-40)	(39-40)	(38-39)	
Age at presentation (days)	Median	0	1.5	0	0.013
	(IQR)	(0-1)	(1-6)	(0-0)	
Weight on admission to PICU (kg)	Median	3.3	3.3	3.3	0.893
	(IQR)	(3.1-3.5)	(03.3-3.5)	(3.1-3.5)	
<u>TGA type</u>					
IVS		26 (57.7)	12 (65)	14 (52)	0.221
Complex		19 (42.3)	7 (35)	12 (48)	

Abbreviations: DGH = District General Hospital, TGA = Transposition of the Great Arteries, IVS = Intact Ventricular Septum Complex = VSD, Coarctation of Aorta or Left Ventricular Outflow Tract Obstruction alongside the TGA

Table 2 – Interventions in PICU and Length of Stay

		Total N = 41 (%)	Retrieved Infants N = 15 (%)	Tertiary Maternity Unit Infants N = 26 (%)	P value
Required BAS		34 (83%)	10 (66.6%)	24 (92%)	0.076
Age at BAS (days)	Median (IQR)	1 (0-2)	2.5 (1-8)	1 (0-1)	0.095
LOS in PICU post BAS (days)	Median (IQR)	2 (1-3)	3 (2-3)	2 (1-2)	0.162
Age at ASO (days)	Median (IQR)	9 (7-11)	10 (8.5-11.5)	8 (6-11)	0.461
LOS in PICU post ASO (days)	Median (IQR)	5 (3-7)	4 (4-5)	5 (3-8)	0.353
Days Ventilated post ASO (days)	Median (IQR)	3 (2-5)	3 (2-5)	3 (2-5)	0.634
Days on Inotropic support post ASO (days)	Median (IQR)	3 (2-4.5)	4 (3-6.5)	2 (2-4)	0.802
Total LOS in hospital (days)	Median (IQR)	18 (15-23)	17 (13.5-22.5)	18.5 (15-24.5)	0.095

Abbreviations: BAS = Balloon Atrial Septostomy, LOS = Length of Stay, PICU = Paediatric Intensive Care Unit, ASO = Arterial Switch Operation

Table 3 – Transport times and distances

		Total N = 41	Retrieved infants N = 15	Tertiary maternity unit N = 26
Distance from PICU (miles)	Median	0.3	76.4	0.3
	(IQR)	(0.3-42.8)	(42.8-120)	(0.3-0.3)
Time to patient bedside from referral call (minutes)	Median		180	
	(IQR)		(122.5-215)	
Stabilisation time (minutes)	Median		95	
	(IQR)		(92.5- 140)	
Patient journey time (minutes)	Median		92	
	(IQR)		(56-114)	
Time to PICU admission from referral (minutes)	Median		440	
	(IQR)		(343.5-470)	
Time to PICU admission from time of Birth (minutes)	Median			443.5
	(IQR)			(292-623)

Abbreviations: PICU = Paediatric Intensive Care Unit

Table 4 – Interventions

	Total N = 41 (%)	Retrieved infants N = 15 (%)	Tertiary maternity unit N = 26 (%)
PGE1 Infusion	38 (93)	14 (93)	24 (92)
Respiratory support	28 (68)	14 (93)	14 (54)
High flow	3	2	1
CPAP	6	1	5
Invasive Ventilation	19	11	8
Inotrope support	10 (24)	8 (53)	2 (8)
Vascular access	41 (100)	15 (100)	26 (100)
Peripheral cannula	19	11	8
Central Access	16	7	9
Intra-osseous Access	2	2	0
Unspecified	9	0	9
Arterial access	Yes 12 (29)	6 (40)	6 (23)

Abbreviations: PGE1 = Prostaglandin, CPAP = Continuous Positive Airway Pressure

Table 5 - Clinical parameters on arrival to the Paediatric Intensive Care Unit

		Total N = 41 (%)	Retrieved infants N = 15 (%)	Tertiary maternity unit N = 26 (%)	P value
Prostaglandin Infusion		38 (82)	14 (93)	24 (92)	0.159
Fraction of Inspired Oxygen	Median (IQR)	0.21 (0.21-0.6)	0.6 (0.25-0.89)	0.21 (0.21-0.3)	0.045
Oxygen saturation (%)	Median (IQR)	75 (65-81)	70 (62-80)	78 (71-85)	0.153
Invasive Ventilation		19 (46)	11 (73)	8 (31)	0.447
Systolic blood pressure (MmHg)	Median (IQR)	70 (58-81)	72 (66-81)	64 (57-80)	0.258
Base excess	Median (IQR)	-3.8 (-5.9--1.8)	-2.6 (-7.1 - 0)	-3.8 (-5.3 - -3.1)	0.981
Serum Lactate	Median (IQR)	2.7 (1.5-3.5)	3.1 (1.6-9.4)	2.7 (1.5-3.3)	0.077
Paediatric Index of Mortality 2 Score	Median (IQR)	6.3 (2.0-10.6)	7.5 (1.9-10.7)	5.4 (2.2-10.4)	0.467
Mortality		2 (5)	1 (7)	1 (4)	