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Research Article

Use of Hypoxic Gas Admixture (Subambient) Prior to Norwood and its Impact on the Norwood Hospitalization

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Received: August 06, 2019; **Published:** September 26, 2019

Abstract

Introduction: The unique physiology of parallel circulation depends on balance between systemic blood flow and pulmonary blood flow to optimize systemic oxygen delivery [1-3]. Hypoxic gas delivery (subambient) is utilized by some institutions to control excessive pulmonary blood flow and for hypoxic conditioning of the systemic ventricle 24 - 48 hours prior to Norwood procedure. This study aimed to evaluate the impact of elective pre Norwood hypoxic gas delivery on hospital outcomes during Norwood admission.

Methods: A total of 549 patients were included in these analyses using data from Pediatric Heart Network Single Ventricle Reconstruction trial. Univariate analyses and regression analysis were conducted to compare outcomes between those who did and did not receive hypoxic admixture.

Results: Univariate analyses demonstrated no statistical difference between two groups in terms of APGARS, need for atrial septectomy, atrial balloon septostomy/stenting or pulmonary artery banding. Intubation prior to Norwood was more frequent in the hypoxic gas group 61.1% compared to 45.9% in non-hypoxic group (odds ratio 1.8, 95% CI 1.1 to 3.0, p-value < 0.01). No difference in peak lactate, need for ECMO, cardiopulmonary bypass time, cross-clamp, need for cardiac catheterization and cardiopulmonary resuscitation was found between two groups. Inpatient mortality was more frequent in the hypoxic gas group 25% compared to 15.1% in non-hypoxic gas group (odds ratio 1.8, 95% confidence interval 1.1 - 3.3, p = 0.03).

However, on regression analyses there were no statistical difference in mortality or other factors between two groups.

Conclusion: Hypoxic gas administration prior to Norwood does not improve Norwood admission characteristics. Univariate analysis demonstrated increased inpatient mortality in those receiving hypoxic gas although no significant association remained after regression analysis.

Keywords: *Hypoxic Gas; Subambient; Norwood*

Introduction

Functionally univentricular hearts are a unique subset of congenital heart disease with abnormal development of either left or right sided structures of the heart. The presence of parallel circulation (pulmonary artery saturation equal to that of the ascending aortic saturation) in the early weeks to months of requires a critical balance between systemic blood flow (Qs) and pulmonary blood flow (Qp) which is affected by pulmonary and systemic vascular resistance. Changes in Qp:Qs may impair systemic oxygen delivery, and thus it may be necessary to modulate Qp:Qs to optimize systemic oxygen delivery [1-3]. For those with excessive pulmonary blood flow prior to palliative surgical procedures, therapeutic maneuvers may be required to decrease pulmonary blood flow and augment systemic cardiac output. Respiratory manipulations utilized have included supplementing with carbon dioxide (inspired carbon dioxide fraction of 1% to 4%) or the delivery hypoxic gas admixture (FiO2 less than 21%) utilizing nitrogen. The aim of both of all such measures is to increase Qs and, subsequently, systemic oxygen delivery [4-9]. Although delivery of hypoxic gas has been demonstrated to decrease Qp:Qs, it has not shown to improve systemic oxygen delivery [10].

Nonetheless, hypoxic gas delivery, using nitrogen, is utilized at some institutions prior to initial surgical palliation to, anecdotally, achieve hypoxic conditioning of the systemic ventricle and pulmonary vasculature as well as to increase pulmonary vascular resistance. It is thought to prepare the systemic ventricle to lower oxygen saturations in post Norwood period. However, effects of such practice on hospital outcomes have not been studied yet.

Aim of the Study

This study aimed to evaluate the effects of elective hypoxic gas delivery on characteristics of the Norwood admission, including but not limited to, mortality, length of hospital stay, duration of mechanical ventilation, and need for extracorporeal membrane oxygenation (ECMO.

Methods

This study utilized data from the Pediatric Heart Network's Single Ventricle Reconstruction trial. This trial was conducted at 15 centers during from 2005 to 2009 with the primary aim being to determine whether or not transplant-free survival was better with placement of a right ventricle to pulmonary artery conduit at the time of the Norwood rather than with placement of a modified Blalock-Taussig shunt. Ultimately, 555 patients were randomized in the trial with 549 patients surviving to the Norwood [11]. A variety of demographic, laboratory, echocardiographic, clinical, and intraoperative factors were captured in this trial.

The aim of the current study was to determine whether or not using a hypoxic gas admixture with administration of nitrogen gas via a hood or endotracheal tube affects characteristics of the Norwood admission. The primary aim was to determine whether or not use of hypoxic gas admixture affects inpatient mortality during the Norwood admission. Secondary aims were to determine whether or not use of hypoxic gas admixture prior to Norwood affects duration of mechanical ventilation, duration of intensive care unit stay after Norwood, and need for ECMO.

Patients enrolled in the Single Ventricle Reconstruction trial were eligible for these analyses if they survived to Norwood. Those who did not were not eligible for inclusion in these analyses. Characteristics from before the Norwood, during the Norwood, and after the Norwood were compared between those who did and didn't receive hypoxic gas admixture.

Univariate analyses were conducted first to compare those who did and did not receive hypoxic gas admixture. Categorical variables were compared using chi-squared analyses and continuous variables were compared using a student t-test. These tests were utilized because of the fact that most data were normally distributed.

Next, regression analyses were conducted to determine the impact of hypoxic gas admixture on specific outcomes.

A linear regression analysis was conducted for duration of mechanical ventilation during the admission. In this regression analysis, duration of mechanical ventilation in days was the dependent variable with use of hypoxic gas admixture, need for cardiac catheterization prior to Norwood, peak lactate prior to Norwood, need for intubation prior to Norwood, need for ECMO at any time during the admission, and age at Norwood being entered as independent variables.

A logistic regression analysis was conducted for need for ECMO at any time during the admission. In this regression analysis, need for extracorporeal membrane oxygenation at any time during the admission was the dependent variable with use of hypoxic gas admixture, need for cardiac catheterization prior to Norwood, peak lactate prior to Norwood, need for intubation prior to Norwood, and age at Norwood being entered as independent variables.

A logistic regression was conducted for inpatient mortality. In this regression analysis, inpatient mortality was the dependent variable with use of hypoxic gas admixture, need for cardiac catheterization prior to Norwood, peak lactate prior to Norwood, need for intubation prior to Norwood, need for ECMO at any time during the admission, and age at Norwood being entered as independent variables.

A linear regression was conducted for age at discharge. In this regression analysis, age in days was the dependent variable with use of hypoxic gas admixture, need for cardiac catheterization prior to Norwood, peak lactate prior to Norwood, need for intubation prior to Norwood, need for ECMO at any time during the admission, and age at Norwood being entered as independent variables.

A linear regression was conducted for arterial saturation by pulse oximetry at time of discharge. In this regression analysis, arterial saturation by pulse oximetry was the dependent variable with use of hypoxic gas admixture, need for cardiac catheterization prior to Norwood, peak lactate prior to Norwood, need for intubation prior to Norwood, need for ECMO at any time during the admission, and age at Norwood being entered as independent variables.

Categorical data are presented as absolute number and percent while continuous data are presented as mean and standard deviation. All statistical analyses were conducted utilizing SPSS Version 23.0. A p-value of less than 0.05 was considered statistically significant. From here forward any mention of a significant difference refers to a difference that statistically significant unless otherwise specified.

Results

A total of 549 patients were included in these analyses.

Preoperative, univariate analyses

There were no statistically significant differences noted between APGAR score at 1 minute and 5 minutes. Need for atrial septectomy, atrial balloon septostomy, or atrial stenting also did not differ between the two groups. The need for pulmonary artery banding also did not differ between the two groups (Table 1).

Intubation prior to Norwood was more frequent in the group receiving hypoxic gas with 61.1% in the hypoxic gas group being intubated prior to Norwood compared to 45.9% in the group not receiving hypoxic gas (odds ratio 1.8, 95% confidence interval 1.1 to 3.0, p-value < 0.01) (Table 1).

Peak lactate and need for ECMO prior to Norwood did not differ between the two groups (Table 1).

	No hypoxic gas (N = 477)	Hypoxic gas (N = 72)	Odds ratio (95% odds ratio)	p-value
APGAR score at 1 minute	7.0 ± 3	7.0 ± 3.3	--	0.96
APGAR score at 5 minutes	7.9 ± 3.4	7.8 ± 3.1	--	0.81
Atrial septectomy	3 (0.6)	0 (0.0)	--	0.50
Atrial balloon septostomy	0 (0.0	(0.0)	--	--
Atrial stent	0 (0.0)	0 (0.0)	--	--
Pulmonary artery banding	3 (0.6)	0 (0.0)	--	0.50
Intubation	219 (45.9)	44 (61.1)	1.8 (1.1 to 3.0)	0.01
Peak lactate	3.5 ± 2.8	3.8 ± 3.3	--	0.43
Extracorporeal membrane oxygenation	1 (0.2)	0 (0.0)	--	0.69

Table 1: *Prenorwood.*

Intraoperative, univariate analyses

The mean age at Norwood did not differ between the two groups. Cardiopulmonary bypass time and cross-clamp time also did not differ. Need for ECMO leaving the operating room also did not differ between the two groups (Table 2).

	No hypoxic gas (N = 477)	Hypoxic gas (N = 72)	Odds ratio (95% odds ratio)	p-value
Age at Norwood (days)	6.7 ± 4.2	7.1 ± 2.6	--	0.30
Bypass time (minutes)	143.3 ± 54.0	147.9 ± 54.8	--	0.49
Cross-clamp time (minutes)	56.4 ± 22.8	53.0 ± 26.8	--	0.24
Left operating room on extracorporeal membrane oxygenation	28 (5.9)	7 (9.7)	1.7 (0.7 to 4.1)	0.21

Table 2: *Norwood.*

Postoperative, univariate analyses

Delayed sternal closure was more frequent in those having received hypoxic gas with 94.4% of those who received hypoxic gas having delayed sternal closure compared to 75.1% of those who did not receive hypoxic gas (odds ratio 5.6, 95% confidence interval 2.0 to 15.8, $p < 0.01$) (Table 3).

Need for cardiac catheterization, cardiopulmonary resuscitation, and ECMO also did not differ between the two groups (Table 3).

	No hypoxic gas (N = 477)	Hypoxic gas (N = 72)	Odds ratio (95% odds ratio)	p-value
Delayed sternal closure	358 (75.1)	68 (94.4)	5.6 (2.0 to 15.8)	< 0.01
Duration of mechanical ventilation (days)	15.3 ± 28.1	14.1 ± 32.2	--	0.73
Days in intensive care unit	26.5 ± 13.2	20.9 ± 16.6	--	0.19
Age at ICU discharge (days)	31.0 ± 22.3	26.5 ± 23.2	--	0.27
Discharged with supplemental oxygen	45 (9.4)	9 (12.5)	1.3 (0.6 to 2.9)	0.41
Oxygen saturation at time of discharge (%)	81.8 ± 9.3	79.0 ± 14.5	--	0.07
Cardiac catheterization	36 (7.6)	3 (4.2)	0.5 (0.1 to 1.8)	0.30
Cardiopulmonary resuscitation	83 (17.4)	14 (19.4)	1.1 (0.6 to 2.1)	0.67
Extracorporeal membrane oxygenation	48 (10.1)	9 (11.1)	1.1 (0.5 to 2.4)	0.78
Inpatient mortality	72 (15.1)	18 (25.0)	1.8 (1.1 to 3.3)	0.03

Table 3: *Postnorwood.*

Duration of mechanical ventilation, length of stay in the intensive care unit, and age at discharge did not differ between the two groups. The proportion of patients requiring supplemental oxygen at the time discharge and arterial saturation by pulse oximetry did not differ between the two groups, either.

Inpatient mortality was more frequent in those who received hypoxic gas with 25% of those having received hypoxic gas experiencing mortality compared to 15.1% of those not having received hypoxic gas (odds ratio 1.8, 95% confidence interval 1.1 to 3.3, $p = 0.03$).

Regression analyses

The use of hypoxic gas was not independently associated with the duration of mechanical ventilation (beta coefficient = -2.9, p = 0.39). ECMO at any time during the admission and older age at the time of Norwood did significantly increase the duration of mechanical ventilation.

The use of hypoxic gas was not independently associated with the need for ECMO at any time during the admission (beta coefficient = 0.3, p = 0.22). None of the other independent variables were independently associated either.

The use of hypoxic gas was not independently associated with inpatient mortality (beta coefficient = 0.5, p = 0.08). The need for ECMO at any time during the admission and need for cardiac catheterization prior to Norwood were independently associated with increased inpatient mortality.

The use of hypoxic gas was not independently associated with age at intensive care unit discharge (beta coefficient = -6.9, p = 0.07). Need for ECMO at any time during the admission, peak lactate prior to Norwood, and age at Norwood were all independently associated with increased age at intensive care unit discharge.

The use of hypoxic gas was not independently associated with arterial oxygen saturation by pulse oximetry (beta coefficient -2.9, p-0.06). None of the other independent variables were independently associated either.

Discussion

This set of analyses from the Single Ventricular Reconstruction trial demonstrates that hypoxic gas administration by use of inhaled nitrogen prior to the Norwood does not improve Norwood admission characteristics. By univariate analysis, use of hypoxic gas was actually associated with increased mortality. No independent association between hypoxic gas administration and inpatient mortality remained after regression analysis.

The use of hypoxic gas has decreased significantly over the past several years. Hypoxic gas was utilized to help decrease the ratio of pulmonary to systemic blood flow prior to the Norwood in those with parallel circulation. While the ratio of pulmonary to systemic blood flow does decrease with hypoxic gas administration, systemic oxygen delivery has not been demonstrated to improve [10]. Our group has demonstrated this in a previous study, utilizing renal near infrared spectroscopy and lactate as markers of systemic oxygen delivery. Other studies have also demonstrated no benefit of hypoxic gas administration on systemic oxygen delivery.

In the modern era, modulation of systemic vascular resistance with afterload reduction and augmentation of total blood flow (pulmonary and systemic blood flow) is utilized when pulmonary overcirculation is present. Such strategies do improve systemic oxygen delivery and it is systemic oxygen delivery that needs to be maintained [12,13]. If systemic oxygen delivery is maintained at an adequate level then pulmonary overcirculation is not of consequence. In this scenario pulmonary edema from such pulmonary overcirculation can simply be diuresed until the Norwood.

Some continue to administer hypoxic gas administration by introducing nitrogen gas. Anecdotally some feel that this allows for conditioning of the pulmonary vasculature and the body to the lower arterial saturations that will ensue after the Norwood. This phenomenon has never been demonstrated. This analysis shows that those who receive hypoxic gas prior to Norwood have the same clinical outcomes as those who do not, thus any sort of conditioning that may even occur seems to be of no meaningful consequence.

While these analyses are helpful as they represent one of the few studies to demonstrate the effect of hypoxic gas administration prior to Norwood on Norwood admission characteristics. The data come from the Single Ventricle Reconstruction trial which stopped enrollment in 2009. Thus, this data does come from an earlier era. The benefit of this is that it provides a reasonable number of patients who received hypoxic gas and the impact of such a therapy should not change despite era. Admission characteristics, however, are slightly different. For example, inpatient mortality is higher in the study cohort than is generally seen in the current era. Intensive care unit stay and duration of mechanical ventilation are also greater in the study cohort than generally seen in the current era.

It is also not clear why some patients received hypoxic gas while others did not. It is possible that some institutions routinely utilized hypoxic gas while other institutions may have utilized in patients with greater degree of pulmonary overcirculation. The former seems more likely in this cohort as peak lactate prior to Norwood did not differ between the two groups. It also must be noted that a small subset of patients may in fact benefit from the use of hypoxic gas although this study did not identify any such group. Yet, the current study cannot entirely eliminate this as a possibility.

Conclusion

Hypoxic gas administration using nitrogen gas prior to Norwood does not improve Norwood admission characteristics such as duration of mechanical ventilation and length of intensive care unit stay. Univariate analysis demonstrated increased inpatient mortality in those having received hypoxic gas but this association no longer remained present after regression analysis. There appears to be no particular benefit of hypoxic gas administration prior to Norwood although utility in a specific subset of patients with parallel circulation cannot be entirely precluded from this study.

Bibliography

1. Roeleveld PP., *et al*. "Hypoplastic left heart syndrome: from fetus to fontan". *Cardiology in the Young* 28.11 (2018): 1275-1288.

2. Austin EH., *et al*. "Balancing the circulation in hypoplastic left heart syndrome". *Journal of Cardiovascular Surgery* 35.6 (1994): 137-139.

3. Barnea O., *et al*. "Balancing the circulation: theoretic optimization of pulmonary/systemic flow ratio in hypoplastic left heart syndrome". *Journal of the American College of Cardiology* 24.5 (1994): 1376-1381.

4. Mora GA., *et al*. "Experimental model of single ventricle. Influence of carbon dioxide on pulmonary vascular dynamics". *Circulation* 90.5 (1994): II43- II46.

5. Ramamoorthy C., *et al*. "Effects of inspired hypoxic and hypercapnic gas mixtures on cerebral oxygen saturation in neonates with univentricular heart defects". *Anesthesiology* 96.2 (2002): 283-288.

6. Tabbutt S., *et al*. "Impact of inspired gas mixtures on preoperative infants with hypoplastic left heart syndrome during controlled ventilation". *Circulation* 104.12 (2001): I159- I164.

7. Shime N., *et al*. "Hypoxic gas therapy using nitrogen in the preoperative management of neonates with hypoplastic left heart syndrome". *Pediatric Critical Care Medicine* 1.1 (2000): 38-41.

8. Bailey LL and SR Gundry. "Hypoplastic left heart syndrome". *Pediatric Clinics of North America* 37.1 (1990): 137-150.

9. Feinstein JA., *et al*. "Hypoplastic left heart syndrome: current considerations and expectations". *Journal of the American College of Cardiology* 59.1 (2012): S1-S42.

10. Thomas L., *et al*. "Acute effects of hypoxic gas admixtures on pulmonary blood flow and regional oxygenation in children awaiting Norwood patients". *Congenital Heart Disease* (2019).

11. Ohye RG., *et al*. "Comparison of shunt types in the Norwood procedure for single-ventricle lesions". *New England Journal of Medicine* 362.21 (2010): 1980-1992.

12. Hoffman GM., *et al*. "Alteration of the critical arteriovenous oxygen saturation relationship by sustained afterload reduction after the Norwood procedure". *Journal of Thoracic and Cardiovascular Surgery* 127.3 (2004): 738-745.

13. Nakazawa M., *et al*. "Afterload reduction treatment for large ventricular septal defects. Dependence of haemodynamic effects of hydralazine on pretreatment systemic blood flow". *British Heart Journal* 49.5 (1983): 461-465.

Volume 6 Issue 10 October 2019