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ARTICLE

To Intubate or Not to Intubate? Transporting Infants on Prostaglandin E_1

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What's Known on This Subject

Apnea is a known adverse effect of PGE used for infants with congenital heart disease. Some physicians prophylactically intubate infants on PGE before transporting them to tertiary referral centers.

What This Study Adds

This is the first study to compare the clinical transport complications of unintubated and prophylactically intubated infants receiving PGE for congenital heart disease.

ABSTRACT

OBJECTIVES. The purpose of this work was to describe the pretransport and transport management of infants receiving prostaglandin E_1 infusion for congenital heart disease and to compare transport complications among unintubated and electively intubated infants.

METHODS. We conducted a retrospective chart review of 202 infants receiving prostaglandin E_1 during transport to our facility from 2000 to 2005. Prostaglandin E_1 adverse effects were described as likely or possible and transport complications as major or minor (requiring no intervention). Logistic regression was used to identify risk factors for major transport complications, and subgroup analysis compared risks among unintubated and prophylactically intubated infants.

RESULTS. Sixty-four percent of infants were intubated before transport: 34% emergently before prostaglandin E_1, 14% for prostaglandin E_1-related adverse effects, and 11% prophylactically. Likely prostaglandin E_1 adverse effects were noted in 38% of infants, including 18% with apnea. Major complications occurred during 42% of all of the transports, including 7 (10%) of 73 unintubated infants and 14 (61%) of 23 prophylactically intubated infants. After controlling for multiple factors, elective intubation was a significant predictor of major transport complications.

CONCLUSIONS. Despite high rates of prostaglandin E_1 adverse effects, elective intubation of infants for transport significantly increased the odds of a major transport complication. The risks of prophylactic intubation before the transport of otherwise stable infants on prostaglandin E_1 must be weighed carefully against possible benefits. *Pediatrics* 2009;123:e25–e30

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Key Words
PGE, transport, congenital heart disease, infants, apnea

Abbreviations
PGE_1—prostaglandin E_1
CHD—congenital heart defect
OR—odds ratio
CI—confidence interval

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In 1981 the Food and Drug Administration approved prostaglandin E_1 (PGE_1) for use in neonates with congenital heart defects (CHDs). PGE_1 dilates the ductus arteriosus, which can provide pulmonary or systemic blood flow to infants with ductal-dependent lesions.[1–6] As new surgical techniques improve the prognosis for a range of CHD, the early use of PGE_1 has become widespread before transport to regional medical centers for definitive care. PGE_1 infusion, however, has been associated with serious adverse effects, including apnea, hypotension, and fever.[7,8]

Concern for apnea and the technical difficulties securing a definitive airway during transport has lead to the common practice of elective intubation for infants receiving PGE_1 before transport.[9,10] Endotracheal intubation, however, carries its own risks and may add to the potential for adverse events during transport, such as endotracheal tube occlusion, displacement, and equipment failure.[10–15]

Few studies have examined the complications associated with interhospital transport of infants receiving PGE_1, and no standard of care for the preparation of these infants currently exists. We hypothesized that stable infants could safely be transported without endotracheal intubation. Therefore, we sought to describe the pretransport management of infants receiving PGE_1 infusions and to compare the transport complications of unintubated and electively intubated infants.

PATIENTS AND METHODS

We conducted a retrospective review of the medical charts of infants transported to Children's Hospital of Los Angeles with a diagnosis of CHD from January of 2000 to December of 2005. Subjects were included if they were transported

by the Children's Hospital Emergency Transport Team and received PGE_1 during transport. This study was approved by the institutional review board at Children's Hospital of Los Angeles.

The Children's Hospital Emergency Transport Team is composed of staff physicians, registered nurses, respiratory therapists, and paramedics. All of the transport triage decisions are made by the physician, who determines the staffing needs and mode of transport for each call. Decisions regarding mode of transport are based on estimated travel time given distance, traffic, and weather conditions, as well as availability of fixed or rotor wing aircraft, rather than illness severity. Given the diversity of medical needs, no formal written protocols are used, and individual patient management strategies are at the discretion of the treating providers, although consultation with subspecialists (including cardiology and neonatology) is often sought before transport dispatch.

Demographic variables that were included in the analysis included gender, race/ethnicity (white, Hispanic, black, Asian, or other), estimated gestational age, and birth weight. Subjects were determined to have underlying pulmonary disease if they had airspace or pleural disease on chest radiograph or were described as having infant respiratory distress syndrome in the medical chart. Comorbid medical conditions such as sepsis, chromosomal abnormalities, and multiple congenital anomalies were also recorded. CHDs were categorized as 1- or 2-ventricle physiology based on the surgical repair planned or performed during the subsequent hospitalization.

PGE_1-related adverse effects and transport complications were the primary outcomes for this study. PGE_1 adverse effects were identified from previous studies[7,8] and included apnea, hypoventilation, hypotension, arrhythmias, vasodilation, and fever. These adverse effects were categorized as likely if they were directly attributed to PGE_1 in the medical chart or if they occurred within 12 hours of starting PGE_1 without alternate medical explanations. Adverse effects were categorized as possible if they met the same criteria, but alternate medical explanations were identified for the observed adverse effect (eg, apnea in a premature infant).

Transport complications were defined as an acute change in cardiovascular, respiratory, or neurologic status. These complications included the following: (1) cardiovascular: arrhythmias and hypotension (defined as less than the fifth percentile for age); (2) respiratory: apnea (>20 seconds for any age), hypoventilation (respiratory rate < 20 or P_{CO_2} > 70 if arterial blood gas was obtained), desaturation (>10% drop from baseline saturation), pneumothorax, and endotracheal tube occlusion/displacement; and (3) neurologic: seizure activity, agitation (subjectively determined by transport team), and temperature instability (a change in core temperature outside of the reference range defined as 35.6°C to 37.5°C, requiring external warming or cooling). Complications requiring more than tactile stimulation, sedation, or a change in ambient isolette temperature were classified as major. Those that resolved without intervention or with tactile stimulation or sedation were classified as minor. Fever (temperature > 38.0°C) and hypothermia (temperature <36.5°C) were also considered minor complications.

Characteristics of PGE_1 infusion included route of administration (peripheral intravenous, umbilical artery catheter, umbilical vein catheter, or other central line), dose (<0.05, 0.05, or >0.05 μg/kg per minute), and duration of infusion before transport (<3, 3–6, 6–12, or >12 hours). Data regarding pretransport airway management included whether patients were intubated, place of intubation (delivery room, nursery, NICU, emergency department, ambulance/helicopter/airplane, or cardiothoracic ICU at the receiving facility), indication for intubation (Apgar score, apnea, hypoxia/cyanosis, hypotension, acidosis, respiratory distress, "for transport," "starting PGE_1," or "other"), and time of intubation (before or after starting PGE_1). Patients were subsequently classified as "unintubated," "electively intubated" (physiologically stable infants intubated for transport or starting PGE_1), or "emergently intubated."

Data were analyzed by using SPSS 14.0 (SPSS Inc, Chicago, IL). We calculated descriptive statistics for patient characteristics, pretransport management, PGE_1 adverse effects, and transport complications. Bivariate analyses (χ^2 tests and Fisher's exact tests) and multivariate logistic regression were used to evaluate associations between major transport complications and patient characteristics, pretransport management variables, transport mode, and time. Variables were included in the multivariate regression if they had at least marginal bivariate significance in our data ($P < .10$) or had been identified as relevant in research published previously. Missing values varied for each item but in all of the cases were <5% and were not imputed. Percentages reported represent the valid percentage for each item. For all of the statistical tests, a 2-tailed P value of <.05 was considered statistically significant.

RESULTS

The characteristics of the study population are described in Table 1. The mean gestational age was 38 weeks (range: 24–40 weeks), and the median birth weight was 3100 g (range: 725–4636 g). The most common cardiac defect was hypoplastic left heart syndrome (25%), followed by transposition of the great arteries (19%) and coarctation of the aorta (15%).

Table 2 describes the pretransport management of subjects. PGE_1 was started by the referring facility in

TABLE 1 **Characteristics of the Study Population**

Characteristic	No. (%)
Male ($N = 202$)	129 (64)
Race/ethnicity ($N = 199$)	
Hispanic	119 (60)
White	41 (21)
Asian	21 (11)
Black	9 (5)
Single ventricle lesion ($N = 202$)	86 (43)
Underlying pulmonary disease ($N = 184$)	22 (12)
Comorbid medical conditions ($N = 189$)[a]	78 (41)

[a] Conditions include sepsis, chromosomal abnormalities, and multiple congenital anomalies.

TABLE 2 **Characteristics of PGE_1 Administration and Airway Management**

PGE_1 Characteristics ($N = 196$)	No. (%)
Route of administration	
PIV	138 (70)
UVC	44 (22)
UAC	5 (3)
Central venous line	4 (2)
Dose ($N = 197$)	
<0.05 μg/kg per min	54 (28)
0.05 μg/kg per min	99 (50)
>0.05 μg/kg per min	44 (22)
Relation to transport ($N = 196$)	
<3 h before transport	50 (26)
3–6 h before transport	41 (21)
6–12 h before transport	44 (22)
>12 h before transport	61 (31)
Airway management ($N = 199$)	
Type of intubation	
Unintubated	73 (37)
Emergent	103 (52)
Elective	23 (12)

PIV indicates peripheral catheter; UVC, umbilical venous catheter; UAC, umbilical artery catheter.

95% of cases at a median dose of 0.05 μg/kg per minute (range: 0.01–0.42 μg/kg per minute). Infusion occurred through a peripheral intravenous route in 70% of subjects and through an umbilical venous catheter route in 22%. A total of 129 infants (64%) were intubated before transport: 69 (34%) emergently before PGE_1, 28 (14%) emergently after starting PGE_1, and 23 (11%) electively. In 6 patients, the relationship between intubation and PGE_1 was unclear, and for another 3 it was uncertain whether the intubation was emergent or elective.

Adverse Effects of PGE_1

Probable PGE_1 adverse effects were noted in 74 subjects (38%), with an additional 16 (8%) classified as possible. Of probable and possible adverse effects combined, apnea was the most common (18%), followed by hypotension (13%) and fever (11%). Excluding fever, 32% of possible PGE_1 adverse effects occurred during transport, including 4 cases of apnea (2%). PGE_1 adverse effects and their relation to transport are described in Table 3. Two predictors of PGE_1 adverse effects were significant in multivariate analysis: comorbid medical conditions (odds ratio [OR]: 2.16 [95% confidence interval (CI): 1.07–4.33]) and PGE_1 dose (OR: 0.32 for dose <0.05 μg/kg per minute vs 0.05 μg/kg per minute [95% CI: 0.14–0.71]). Predictors of PGE_1 adverse effects during transport (excluding fever) included single-ventricle physiology (OR: 3.70 [95% CI: 1.13–12.19]) and duration of PGE_1 infusion before transport (OR: 0.39 for each additional 3 hours after starting PGE_1 [95% CI: 0.22–0.69]).

Transport Complications

Complications occurred in 133 transports (66%). Major complications occurred during 84 transports (42%), with a total of 92 events in 75 patients (some transports and patients had multiple complications). These were roughly divided between respiratory (54%) and cardiovascular (46%) complications. Four intubated infants required airway interventions during transport: 3 were reintubated (1 for apnea and absent chest rise with bag valve mask and 2 for unintended extubation), and 1 had the endotracheal tube repositioned for asymmetric breath sounds. Table 4 lists the major transport complications and their management according to intubation status. Minor complications consisted of hypothermia in 55 patients (28%) and fever in 29 (14%). In addition, 3 cases of apnea and 2 of hypoventilation resolved with tactile stimulation, and 1 episode of agitation was treated with sedation.

Bivariate predictors of major transport complications included intubation status (unintubated: 10%; electively intubated: 61%; emergently intubated: 52%; $P < .01$), PGE_1 dose (<0.05 μg/kg per minute: 17%; 0.05 μg/kg per minute: 44%; >0.05 μg/kg per minute: 45%; $P < .01$), estimated gestational age (<32 weeks: 83%; 32–35 weeks: 45%; 36–39 weeks: 23%; and >40 weeks: 47%; $P < .01$), mode of transport (ground: 35%; helicopter: 52%; fixed wing: 19%; $P = .03$), comorbid medical conditions (49% with and 30% without; $P < .01$), and underlying pulmonary disease (55% with and 33% without; $P = .04$). Results of the multivariate analysis are presented in Table 5.

Subgroup Analysis

Subjects who were electively intubated for transport did not differ significantly from those who were not intubated with regard to race, gender, birth weight, type of CHD, or comorbid medical conditions. Compared with unintubated subjects, those who were electively intubated received a higher dose of PGE_1 (35% vs 12% received >0.05 μg/kg per minute; $P = .05$) and were transported by helicopter more often (50% vs 10%; $P < .01$). After controlling for these differences in a multi-

TABLE 3 **PGE_1 Adverse Effects in Relation to Transport ($N = 193$)**

Variable	Before Transport		During Transport		After Transport		Total (%)
	Likely, *n* (%)	Possible, *n* (%)	Likely, *n* (%)	Possible, *n* (%)	Likely, *n* (%)	Possible, *n* (%)	
Apnea	22 (11.0)	2 (1.0)	4 (2.0)	0 (0.0)	6 (3.0)	0 (0.0)	34 (18.0)
Hypoventilation	0 (0.0)	1 (0.5)	6 (3.0)	0 (0.0)	0 (0.0)	1 (0.5)	8 (4.0)
Hypotension	3 (1.5)	3 (1.5)	10 (5.0)	8 (4.0)	0 (0.0)	1 (0.5)	25 (13.0)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)
Fever	0 (0.0)	0 (0.0)	22 (11.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (11.0)

TABLE 4 **Major Transport Complications and Their Management**

Complication	Unintubated		Electively Intubated		Emergently Intubated		Total *N*
	N[a]	Intervention (*n*)	*N*[b]	Intervention (*n*)	*N*[c]	Intervention (*n*)	
Any	9		14		69		92
Cardiovascular	4	—	6	—	32	—	42
Arrhythmia	1	Weaned PGE_1 (1)	0	—	2	Weaned PGE_1 (1); CPR (1)	3
Hypotension	3	Volume (2); weaned PGE_1 (1)	6	Volume (3); inotrope (2); weaned PGE_1 (1)	30	Volume (15); inotrope (14); weaned PGE (1)	39
Respiratory	5		8		37		50
Apnea	2	BVM (2)	1 (4.3)	BVM (1)	2 (1.9)	BVM (1); intubate (1)	5
Hypoventilation	1	Weaned PGE_1 (1)	2	Increased vent (2)	6	Increased vent (6)	9
Desaturation	2	BVM (2)	5	Vent change (4); BVM (1)	26	Increased vent (14); BVM (6); CPR (1)	33
ETT displaced	0	NA	0	NA	3	—	3

NA indicates not applicable; —, no data; ETT, endotracheal tube; BVM, bag-valve-mask; CPR, cardiopulmonary resuscitation.

[a] Data show the number of complications occurring in 7 of 73 unintubated patients (some patients had multiple events).

[b] Data show the number of complications occurring in 14 of 23 electively intubated patients.

[c] Data show the number of complications occurring in 52 of 103 emergently intubated patients.

TABLE 5 **Multivariate Analysis of Major Transport Complications**

Variable	OR	95% CI
Medical comorbidity	2.22	1.02–4.08
PGE_1 dose		
<0.05 μg/kg per min	(1)	
0.05 μg/kg per min	4.80	1.60–14.40
>0.05 μg/kg per min	3.72	1.10–12.63
Intubation type		
Unintubated	(1)	
Emergent	15.68	3.85–63.83
Elective	7.44	2.82–19.68
CHD physiology		
Single ventricle	1.42	0.66–3.07
Transport mode		
Ground	(1)	
Helicopter	1.17	0.49–2.78
Fixed wing	0.20	0.02–2.59
Transport time		
<30 min	(1)	
30–60 min	0.89	0.36–2.19
60–90 min	0.58	0.18–1.89
>90 min	3.73	0.44–31.39
Gender, EGA	NS	

EGA indicates estimated gestational age; NS, not significant.

variate subset regression, however, elective intubation remained a significant predictor of major transport complications (OR: 20.56 [95% CI: 3.34–113.09]).

DISCUSSION

In 1976, Olley et al[3] reported the successful presurgical palliation of infants with CHDs using prostaglandin infusion. The Food and Drug Administration approved alprostadil (PGE_1) for use in infants with CHD in 1981, and shortly thereafter, Lewis et al[16] published the results of a large multicenter trial demonstrating the efficacy of PGE_1 in maintaining ductal patency in infants with CHD. In a separate analysis of the same sample, Lewis et al[7] described the adverse effects of therapy with PGE_1 and found cardiovascular and respiratory adverse effects in 32% and 31% of the sample, respectively, including apnea in 12%. Infants weighing <2 kg were at increased risk for respiratory depression, although potential confounding with prematurity was not addressed.[7]

This and other early trials commonly used intra-arterial infusions of PGE_1 at the manufacturer-recommended dose of 0.1 μg/kg per minute, and because successful surgical techniques for the palliation of hypoplastic left heart syndrome did not exist, infants with this condition were excluded.[4,8,17,18] Although our sample included 25% with hypoplastic left heart syndrome, used a lower mean dose of PGE_1, and had <5% with intra-arterial infusions, the overall incidence of adverse effects was similar. Probable adverse effects of PGE_1 were noted in 38% of subjects, with an 18% incidence of apnea overall. Overall, we found that comorbid medical conditions and higher PGE_1 dose were associated with possible PGE_1 adverse effects, whereas birth weight and gestational age were not independently associated with increased risk.

Although several studies have described the transport of infants with CHD,[9,10,15,19–21] we are unaware of any that have evaluated the incidence of PGE_1 adverse effects during transport. Apnea possibly related to PGE_1 occurred before transport in 24 (71%) of 34 patients, with 4 episodes during transport (2%). Three of these cases were managed with bag-valve-mask ventilation, and 1 required reintubation. We found infants with single-ventricle physiology and a shorter interval between initiation of PGE_1 infusion and transport to be associated with an increased risk for adverse effects during transport.

The fear of PGE_1-related apnea and potential challenges of securing a definitive airway during transport have lead to a variety of pretransport stabilization practices. No standard of care, particularly with regard to pretransport airway management, currently exists. In their review of the transport issues of infants on PGE_1, Grubbs and Kraft summarize one approach, stating "the possibility of sudden onset apnea requires team members to be prepared to perform an emergency intubation . . . therefore, it is preferable in most instances for infants to be intubated before transport."[22]

However, Yeager et al[10] voiced the counterargument that, "elective intubation exposes the infant to the potential for mechanical malfunction such as ventilator failure or tube plugging," and found that some transport teams did not routinely elect to intubate patients if they were otherwise stable.

Several groups have described the potential for physiologic deterioration during transport, and scoring systems have been developed to help quantify the adverse impact of transport on critically ill infants and children.[23,24] Few studies, however, have examined the specific transport risks of infants with CHD. Hellstrom-Westas et al[21] published a descriptive study of the long-distance transport experience in Sweden during a 4-year period. In 286 transports, they reported 2 cases of blocked endotracheal tube, 3 additional "technical equipment failures," and 1 death. Only 16% of their sample, however, was intubated during transport, and less than one third (32%) received PGE_1 en route.

More recently, Yeager et al[10] reported the pretransport and post-transport characteristics and outcomes of neonates admitted to a regional cardiac ICU in New England. The authors used physiologic parameters of temperature, pH, and oxygen saturation before and after transport to characterize the stability of transported neonates with CHD. The authors describe a 17% incidence of transport-related physiologic deterioration; however, no analysis of infants receiving PGE_1 is reported, and no mention of airway management or specific interventions is made. Although our study identified a 42% rate of major transport complications, it is difficult to make direct comparisons given the differing operational definitions between studies.

The only published study to address the transport airway management of infants receiving PGE_1 was a 10-year retrospective review of the Australian transport experience by Browning Carmo et al.[15] The authors of that study reported that 78 of 300 infants receiving PGE_1 during transport were unintubated (26%), whereas 125 (42%) were electively intubated. Of the unintubated transported infants, only 2 developed apnea. In our study, 73 infants (36%) were unintubated during transport, and 23 (11%) were electively intubated for transport. None of the unintubated infants required intubation during transport for apnea.

We are unaware of any other studies that attempt to compare the transport complications of unintubated and electively intubated infants receiving PGE_1. In our subgroup analysis, we found only 2 differences between these groups: infants who were electively intubated for transport received higher doses of PGE_1 than their unintubated counterparts and were more likely to be transported by helicopter. We controlled for these differences in our subgroup analysis and found that elective intubation remained the strongest independent predictor of major transport complications.

Although higher doses of PGE_1 were associated with more complications in our study, the effect of mode of transport on complications is less clear. Mode of transport was not independently associated with transport complications in multivariate analysis, and complication rates for helicopter transport were intermediate between ground and fixed-wing transport. The mode of transport was determined at triage by the team physician and was based on distance, traffic, and weather conditions rather than illness severity. Interestingly, transport time was not correlated with either transport mode or major complications.

There are several important limitations to our study. As with previous studies, ours was a retrospective cohort study limiting our ability to draw conclusions between cause and effect. Although we used conservative definitions for elective intubation and attempted to control for potential confounders between groups, only randomization could address whether elective intubation or unintubated transport is safer. We felt that the lack of published data made a randomized, prospective study unethical; however, with the combined results of this and the report of Browning Carmo et al,[15] prospective evaluation might be considered in the future. Although our overall sample size was large, only 11% were electively intubated, which limits the power of comparisons between groups.

Finally, our operational definition of transport complications was based on the need for interventions, rather than standardized physiologic parameters or scoring systems. Although we felt that the information obtained in this way was more meaningful when planning for appropriate staffing and equipment needs for transport, the inclusion of desaturation as a transport complication must be interpreted cautiously. All of the infants in this study received prostaglandin for congenital heart disease, which includes cyanotic lesions associated with varying degrees of desaturation, and for some lesions (eg, mixing defects and hypoplastic left heart syndrome) an oxygen saturation in the 70s or 80s is expected or even preferred. In general, a >10% decrease from baseline oxygen saturation was treated with an increase in FIO_2; however, the decision to intervene was left to the discretion of the treating transport staff and was not standardized in this retrospective review.

CONCLUSIONS

Despite high rates of PGE_1 adverse effects, elective intubation of infants for transport significantly increased the odds of a major transport complication. The risks of prophylactic intubation before the transport of otherwise stable infants on PGE_1 must be weighed carefully against possible benefits.

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