

A Comparison of Outcomes in Conservative Versus Active Treatment of Patent Ductus Arteriosus in Two Neonatal Intensive Care Units

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Abstract

Objective: To determine whether the conservative management versus medical/surgical treatment of patent ductus arteriosus (PDA) in extremely low birth weight (ELBW) infants leads to improved morbidity, mortality, and length of stay (LOS).

Study Design: A cohort observational study was conducted on infants born October 31, 2017, through June 30, 2021, weighing ≤ 1000 grams with a confirmed PDA by echocardiogram. Median growth rate, LOS, ventilator days, need for oxygen at NICU discharge, major comorbidities, mortality, and the type of PDA treatment were collected. Subjects were divided into those who received only conservative management (Cohort 1) and those who received medical and/or surgical treatment to close the ductus (Cohort 2). Chi-square and Mann-Whitney U tests were used to compare baseline demographics and to determine any statistical significance in outcomes between the two cohorts.

Results: 225 patients met the inclusion criteria, with 79 (35%) in Cohort 1 and 146 (65%) in Cohort 2. Upon comparison, demographics were similar among the two groups. There were no significant differences in weight gain, LOS, or ventilator days, nor in need for oxygen at NICU discharge, rates of necrotizing enterocolitis, bronchopulmonary dysplasia, or mortality ($P > .05$).

Conclusion: The management of ELBW infants with a PDA proved varied, with more than half receiving a medical and/or surgical intervention. This study failed to demonstrate significant improvement in several important outcomes or common comorbidities in Cohort 2. This suggests that while treating a PDA may benefit an infant's day-to-day clinical course, it may not improve their outcomes at NICU discharge. Further research is needed to increase statistical power and obtain generalizable results.

Keywords

Ductus Arteriosus, Patent

Conservative Treatment

Infant, Extremely Low Birth Weight

Morbidity

Key Points

Should ELBW infants with a PDA be treated?

Many PDAs can be managed successfully with conservative treatment.

Medical or surgical closure of a PDA may not improve infant outcomes.

Introduction

Patent ductus arteriosus (PDA) is a prevalent heart defect in newborns, occurring at a rate of one in 2000 live births. It accounts for 5-10% of all congenital heart diseases in full-term infants. (1) Although the ductus arteriosus should functionally close within the first 72 hours of life, the incidence of closure is inversely related to birth weight and gestational age. (1-3) This makes it one of the most common problems encountered in the neonatal intensive care unit (NICU). At four days of life, it remains patent in 10% of infants born at 30-37 weeks, 80% of infants born at 25-28 weeks, and over 90% of infants born under 24 weeks. (3) A prolonged PDA can lead to left-to-right shunting, pulmonary over circulation, systemic hypoperfusion, cardiac remodeling, and eventual heart failure. (2-4) Large, hemodynamically significant PDAs are associated with prolonged mechanical ventilation, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia, cerebral palsy, retinopathy of prematurity (ROP), renal impairment, and mortality in preterm infants. (2-6)

“Therapy modalities include medical treatment with indomethacin, ibuprofen, and acetaminophen, and surgical or device closure. Although each of these methods has been shown to be effective in closing PDAs, large-scale studies have failed to demonstrate consistent long-term benefits compared to conservative, symptomatic management. (3,4,6,7)”

Therapy modalities include medical treatment with indomethacin, ibuprofen, and acetaminophen, and surgical or device closure. Although each of these methods has been shown to be effective in closing PDAs, large-scale studies have failed to demonstrate consistent long-term benefits compared to conservative, symptomatic management. (3,4,6,7) Overtreatment can lead to unnecessary exposure to indomethacin, ibuprofen, and acetaminophen; the use of these non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with acute renal injury, oliguria, NEC, thrombocytopenia, and decreased blood flow to the brain, kidneys, and gastrointestinal tract. (2,3,7,8) Surgical, transcatheter, or device closure of PDAs can lead to pneumothorax, pneumonia, sepsis, laryngeal/phrenic nerve injury, vocal cord paralysis, acute kidney injury, prolonged mechanical ventilation, and even BPD. (1-3,9)

Previous research on PDA management has focused on comparing the efficacy of a specific type of medical or surgical treatment with conservative management. Less commonly, studies

have compared the outcomes of broad medical (using any type of medicine) or surgical management (using any intervention) with conservative management such as ventilator adjustments, fluid restriction, and intermittent diuretics. (10,11) Few studies have compared the benefits of any intervention (medical or surgical) with conservative management. Our study compared the neonatal outcomes of extremely low birth weight infants (ELBW) receiving medical ad/or surgical treatment to conservative management to determine whether there is any clear benefit from treating PDA during the NICU stay.

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Methods

A cohort observational study was conducted from October 31, 2017, through June 30, 2021. Data was collected from Banner – University Medical Center Phoenix and Banner Children’s at Desert Medical Center, level III NICUs in the Phoenix, Arizona, area. Admissions were screened by creating a report using the BabySteps® application (Pediatrix Medical Group Inc., Sunrise, FL). This report included infants with a birthweight ≤ 1000 g diagnosed with a PDA of any size after an echocardiogram. Study inclusion criteria also specified that the infant was inborn. Infants were excluded based on comorbidities such as chromosomal, renal, and significant cardiac anomalies (other than a PDA) or other comorbidities at the discretion of the Principal Investigator. The Banner Health Institutional Research Board provided human protection oversight, and the study can be found on Clinicaltrials.gov as NCT04379843.

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Once an infant was found eligible to be included, the electronic health record system, Cerner Millennium (Oracle Corporation, Austin, TX), was used to collect data, including demographics, birth information, and outcomes during hospitalization. The length of stay (LOS) was recorded, as well as the average weight gain (calculated by dividing the total weight gain during admission by the LOS). The days the infant required respiratory support of continuous positive airway pressure or higher were included as ventilator days. Mortality after the first 48 hours of life, the diagnosis of BPD or NEC, and supplemental oxygen usage at discharge were collected. Management of the PDA was categorized as either conservative (symptomatic care), medical (use of ibuprofen, indomethacin, acetaminophen), or interventional/surgical management (via invasive catheter closure or ligation). The subjects were further divided into conservative management (Cohort 1) and medical and surgical management (Cohort 2).

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Baseline differences were calculated to determine whether the two cohorts’ demographic and clinical characteristics were similar. Chi-square tests were used to evaluate the sex, racial, and ethnic breakdowns, and the Mann-Whitney U test was used to evaluate differences between the median birth weight and gestational age (GA). Clinical outcomes were similarly compared between the cohorts. Mortality after 48 hours of life, the need for oxygen at NICU discharge, and the presence of BPD or NEC were compared using Chi-square tests. Mann-Whitney U tests were used to compare LOS, average weight gain, and the number of ventilator days.

Results:

During the study period, there were 466 infants admitted to the 2 study sites weighing ≤ 1000 g at birth. Of these, 265 patients were diagnosed with a PDA. Forty infants were excluded from the study for the following reasons: born in the community or at another hospital ($n = 19$), congenital anomalies ($n = 12$), hemodynamically significant heart defect other than a PDA ($n = 2$), serious comorbidities ($n = 4$), and those still hospitalized at the end of the data collection period ($n = 3$). This left 225 patients that met inclusion criteria between the 2 NICUs, over half of which (53%) were male. The overall racial stratification was: 77% White, 11% Black, 7% American Indian, < 1% Asian, and 5% Other/Unknown. Twenty-nine percent of the infants were identified as having a Hispanic ethnicity. A large portion (71%) of the 160 infants were delivered

Table 1. Demographics

| | Total Population N = 225 | Cohort 1 n = 79 | Cohort 2 n = 146 | Cohort 1 versus Cohort 2 P-value |
|--|---|----------------------------|-----------------------------|---|
| Sex (male)^a | 0.53 | 0.61 | 0.50 | .025 |
| Cesarean section delivery^a | 0.71 | 0.81 | 0.66 | .016 |
| Birth weight (grams)^b | 760 (725-780) | 765 (685-800) | 750 (723-782) | .509 |
| Gestational age (weeks)^b | 25.3 (25.0-25.6) | 25.6 (25.0-26.3) | 25.1 (25.0-25.4) | .163 |
| Race^a | | | | .459 |
| White | 0.77 | 0.77 | 0.77 | |
| Black | 0.11 | 0.13 | 0.10 | |
| Asian | 0.01 | 0.00 | 0.01 | |
| American Indian | 0.06 | 0.08 | 0.06 | |
| Other/Unknown | 0.05 | 0.02 | 0.06 | |
| Ethnicity^a | | | | .506 |
| Hispanic or Latino | 0.29 | 0.27 | 0.31 | |
| ^a Mean, ^b Median (Confidence Interval 95%) | | | | |

via cesarean section. The infants had a median gestational age of 25.3 weeks and a median birth weight of 760 g. A classification of demographics by cohort can be seen in Table 1.

The average LOS for the total population was 113.5 days, with 66.8 ventilator days and a mean average weight gain of 24.2 g/day. Nineteen infants (8.4%) died between 48 hours of life and discharge. There was a diagnosis of NEC in 20 infants (8.9%), 190 (84.4%) developed BPD, and 104 (46.2%) required supple-

mental oxygen upon discharge. It should be noted that some subjects were transferred or had died before a diagnosis of BPD, or the need for oxygen at NICU discharge could be assessed.

Of the infants who met inclusion criteria, 79 (35%) were in Cohort 1, having received conservative management for their PDA. Cohort 2 consisted of 146 infants (65%) that received medical or surgical management. The cohorts were similar in racial and ethnic distribution ($P \geq .05$), median birth weight, and GA at birth.

Table 1. Demographics

| | Cohort 1 n = 79 | Cohort 2 n = 146 | P-value |
|---|----------------------------|-----------------------------|----------------|
| Length of Stay (days)^b | 111 (97.9-124.4) | 115 (109.7-124.0) | .329 |
| Weight gain (grams/day)^b | 24.1 (23.0-25.1) | 24.3 (23.5-25.6) | .368 |
| Ventilator days^{b*} | 59 (54-75) | 71 (65-74) | .126 |
| Bronchopulmonary dysplasia^{a*} | 0.80 | 0.87 | .205 |
| Necrotizing enterocolitis^a | 0.11 | 0.08 | .436 |
| Oxygen at hospital discharge^a | 0.44 | 0.47 | .663 |
| Mortality after 48 hours^a | 0.13 | 0.06 | .095 |

^aMean, ^bMedian (Confidence Interval 95%)
^{*}Ventilator days = duration of respiratory support of nasal continuous airway pressure or above
^{*}Bronchopulmonary dysplasia = any oxygen support at 36 weeks postmenstrual age

Interestingly, male infants were more likely to receive conservative management than females (63% versus 48%, $P = .025$). In addition, infants who were delivered by Cesarean section were more likely to receive conservative management than those born vaginally (81% versus 66%, $P = .016$) (Table 1). The outcomes at NICU discharge between the cohorts were comparable in terms of mortality, LOS, the number of ventilator days, average weight gain, need for oxygen at NICU discharge, and rates of BPD and NEC ($P > .05$) (Table 2).

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Discussion:

Untreated large PDAs cause left-to-right shunting leading to pulmonary over-circulation and systemic under-circulation. (2) Over time, this can lead to pulmonary edema, suboptimal gas exchange, ineffective ventilation, pulmonary hemorrhage, and eventual BPD. (2-5) The undue strain on the right side of the heart can lead to eventual congestive heart failure in severe cases. (1,3) Ongoing left-to-right shunting leads to ductal steal, where the body receives persistent under circulation and low diastolic blood pressure. (1) This disruption in blood flow leads to dysfunction in oxygen-sensitive organs like the brain, eyes, kidneys, and gastrointestinal tract. As a result, infants with a prolonged, hemodynamically significant PDA are more at risk for IVH, ROP, NEC, oliguria, acute kidney injuries, and death. (1-6) One study of very premature infants (birth weight ≤ 1500 g and GA ≤ 29 weeks) by Dr. Noori et al. (12) found that infants whose PDA failed to close had an eightfold increase in mortality. Our study did not track the incidence of IVH, ROP, or renal dysfunction; however, a number of the infants, regardless of management, had NEC, BPD, need for oxygen at NICU discharge, and mortality, which is known risk factors of PDA.

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Scores of studies over many decades have shown that pharmaceuticals can be helpful in the closure of PDAs. A recent meta-analysis by Marconi et al. (13) analyzed 64 randomized controlled trials and 24 observational studies, totaling nearly 15 000 research subjects. They found that infants who received indomethacin (odds ratio [OR] 0.17, credible interval [CrI] 0.11-0.24), ibuprofen (OR 0.19, CrI 0.12-0.28), and acetaminophen (OR 0.15, CrI 0.09-0.26) were more likely to have their PDAs close when compared to a placebo. (13) Surgical treatment can also be successful by ligating the ductus arteriosus or a mixture of dividing the ductus and closing it with sutures or clips. (1) Yet, the surgery itself is not without risks. A 25-year cohort study by Foster et al. (14) showed that 44% of ELBW infants who underwent a PDA ligation had at least one short-term complication from the repair. In an additional study of almost 200 infants who underwent surgical closure of their PDA, the majority did not exhibit the expected outcome of a rapid improvement in cardiorespiratory status and went on to develop BPD. (15) In recent years, less invasive transcatheter device closure has become more common with promising results. (2)

Although medical and surgical treatments have shown to be successful in closing PDAs, consistent, long-term beneficial effects are few when compared to conservative management. (3,4,6,7) This is especially true for infants > 1000 g, as up to 97% of PDAs will close with conservative treatment by discharge from the NICU. (16) Given this, in recent years, neonatologists' treatment has trended towards less active management, which often involves fluid restriction, diuretics, ventilation adjustments, and “watchful waiting” until the PDA closes or at least becomes less hemodynamically significant. (1,2,16,17) Bixler et al. (17) reviewed all infants born at 23-30 weeks GA with a PDA from indomethacin decreased from 32 to 18%, and PDA ligation decreased from 8.4 to 2.9%. (17) Over time, neonatologists have recognized that a conservative approach avoids the invasiveness, side effects, and expenses of medical and/or surgical management, with potentially the same results in managing PDA-related morbidities and mortality.

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A reduction in active treatment was similarly found by Hagadorn et al. (18), who studied nearly 14,000 very low birthweight (VLBW) infants with PDA at 19 children's hospitals across the United States. Between 2005-2014, the use of NSAIDs or surgery to treat PDAs decreased by 11% per year. Although this was temporally associated with improved survival, there was also an increased incidence of BPD, periventricular leukomalacia, ROP, and acute renal failure. Ultimately, the increase in conservative PDA management did not lead to significant changes in preterm outcomes or mortality. (18) This mirrors the findings from our study, where infants who received active treatment failed to demonstrate significant improvements in known complications of PDA. Our data also failed to show improvements in the ventilator days, average weight gain, length of hospital stay, and need for oxygen at NICU discharge. In some categories, such as the length of hospital stay, ventilator days, incidence of BPD, and need for oxygen at discharge, the infants in Cohort 1 had improved outcomes, although none of these differences achieved statistical significance.

“Our results align with much of the existing literature that suggests conservative management may be a safe option and could provide advantages over other treatments. (10,17,19-21) During a review of over 800 000 infants at 280 NICUs across the United States, Bixler et al. (17) found that a less invasive approach was associated with a lower incidence of mortality, IVH, NEC, and severe NEC ($P < .001$), with the incidence of BPD being the only outcome that did not change.”

Our results align with much of the existing literature that suggests conservative management may be a safe option and could provide advantages over other treatments. (10,17,19-21) During a review of over 800 000 infants at 280 NICUs across the United States, Bixler et al. (17) found that a less invasive approach was associated with a lower incidence of mortality, IVH, NEC, and severe NEC ($P < .001$), with the incidence of BPD being the only outcome that did not change. A meta-analysis by Hundscheid et al. (10) compared the effects of conservative management with any medical or surgical treatment. It was composed of 12 cohort studies and four randomized controlled studies and included infants born < 32 weeks GA, or < 1500 g. In the cohort studies totaling nearly 42 000 infants, those who received conservative management had a higher risk of mortality (relative risk [RR] 1.34, 95% CI 1.12-1.62). However, they had a lower risk of BPD (RR 0.55, 95% CI 0.46-0.65), NEC (RR 0.85, 95% CI 0.77-0.93), IVH (RR 0.88, 95% CI 0.83-0.95), and ROP (RR 0.47, 95% CI 0.28-0.79). In the four randomized controlled trials with 720 patients, there was no significant difference in outcomes of mortality, BPD, NEC, IVH, or ROP between the groups who received active versus conserva-

tive PDA treatment. (10)

A study by Park et al. (21) analyzed treatment data on all South Korean infants with a PDA between 2015-2018, totaling over 12,000 patients. Infants who received active PDA treatment (whether pharmaceutical or surgical) had no significant differences in the incidence of mortality or IVH. Conversely, infants who received active PDA treatment had a higher incidence of BPD (OR 2.23, 95% CI 1.83-2.71), NEC (OR 2.35, 95% CI 1.75-3.51), sepsis (OR 2.65, 95% CI 2.17-3.25), and ROP (OR 1.47, 95% CI 1.17-1.86). (21) Clyman et al. (19) compared outcomes of pharmaceutical treatment versus conservative management of PDA in infants < 28 weeks GA across 17 international NICUs (the United Kingdom, the United States of America, Sweden, and Turkey). There was no difference between the two groups in the presence of a PDA at discharge or the need for surgical ligation. Similar to the findings in our study, the incidence of mortality, BPD, and NEC were comparable between the two groups. Infants who received pharmaceutical treatment and were born at 26-28 weeks GA achieved full enteral feeds later and had higher incidences of mortality and late-onset non-coagulase-negative *Staphylococcus* bacteremia. (19) Letshwiti et al. (20) studied VLBW infants who were fluid-restricted and received increased positive end-expiratory pressure as the first-line intervention (conservative treatment) to 2 other cohorts who received ibuprofen for a hemodynamically significant or clinically symptomatic PDA. The infants in the conservative treatment group had significantly decreased BPD compared to the other two groups and no changes in other measured short-term outcomes. (20)

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There is increasing evidence that conservative management may be equally effective and perhaps somewhat safer than pharmaceutical or surgical treatments. However, it would not be justified to argue that active treatment does not have a place in managing PDAs. In isolated cases, infants with a particularly large PDA and an unstable clinical course may benefit from medical, trans-catheter, or surgical treatment. Isayama et al. (22) highlight the need to identify which infants may most benefit from intervention definitively. Their 2020 review of over 39 000 infants showed a significant U-shaped relationship between the observed/expected PDA treatment ratio and adverse outcomes. This suggests a fine line between PDA treatment’s potential advantages and harms, where the benefits may only exceed the risks when a PDA is hemodynamically significant. (22) In addition, Elhoff et al. (23) found that delaying indomethacin treatment in favor of conservative management makes it less likely to be successful. Perhaps treatment options must be used more judiciously and selectively, not eliminated.

A common limitation of this study and others is the possibility of confounding variables affecting the outcomes. Infants who received active PDA treatment may have had, on average, a more

unstable, traumatic clinical course than those who received conservative management. This would make them more likely to experience BPD, IVH, NEC, ROP, and death, whether their PDA was treated with pharmaceuticals or surgery. Yet, due to active PDA management, some of these patients may have experienced less severe comorbidities than they otherwise would have.

Other limitations include that it was confined to 2 NICUs in Arizona, which may not represent the national and international neonatal population. Our study was limited to ELBW infants, so the results cannot be justifiably extrapolated to the remainder of the NICU population with PDAs. Furthermore, our study only included 225 research subjects, which limits the statistical power of this study. Male infants and those delivered via Cesarean section were significantly more likely to receive conservative management, which may bias the results of our study. Infants were not further divided into subgroups by GA or PDA size to analyze possible differences that may have been present. We defined BPD in our study solely by the presence of supplemental oxygen at 36 weeks postmenstrual age; newer definitions that may more accurately categorize BPD are now available. (24)

Further research across multiple medical centers and states, with careful clinical course controls, needs to be conducted to minimize bias and determine which PDAs would genuinely benefit from medical or surgical treatment to improve an infant’s NICU course and post hospital outcomes.

“Unless an infant is clearly symptomatic from a PDA, conservative management should be strongly considered to limit unnecessary therapies and their undesirable side effects. Our study showed no benefits in the outcomes at NICU discharge for ELBW infants whose PDAs were treated with medication and surgery versus conservative management.”

Conclusion

Unless an infant is clearly symptomatic from a PDA, conservative management should be strongly considered to limit unnecessary therapies and their undesirable side effects. Our study showed no benefits in the outcomes at NICU discharge for ELBW infants whose PDAs were treated with medication and surgery versus conservative management. There was no statistically significant difference in mortality, LOS, ventilator days, average weight gain, BPD incidence, NEC, or need for oxygen at NICU discharge. These results suggest that while large, clinically significant PDAs may benefit from medical and surgical treatment, many can be managed conservatively with little to no impact on outcomes by hospital discharge.

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Which Infants are More Vulnerable to Respiratory Syncytial Virus?

RSV is a respiratory virus with cold-like symptoms that causes 90,000 hospitalizations and 4,500 deaths per year in children 5 and younger. It's 10 times more deadly than the flu. For premature babies with fragile immune systems and underdeveloped lungs, RSV proves especially dangerous.

But risk factors associated with RSV don't touch all infants equally.*

*Source: Respirator Syncytial Virus and African Americans

| Caucasian Babies | Risk Factor | African American Babies |
|------------------|--|-------------------------|
| 11.6% |  Prematurity | 18.3% |
| 58.1% |  Breastfeeding | 50.2% |
| 7.3% |  Low Birth Weight | 11.8% |
| 60.1% |  Siblings | 71.6% |
| 1% |  Crowded Living Conditions | 3% |



AFRICAN AMERICAN BABIES bear the brunt of RSV. Yet the American Academy of Pediatrics' restrictive new guidelines limit their access to RSV preventative treatment, increasing these babies' risk.



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