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Changing patterns of patent ductus arteriosus surgical ligation in the United States

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Abstract

Optimal management of patent ductus arteriosus (PDA) is unclear. One treatment, surgical ligation, is associated with adverse outcomes. We reviewed data from the Kids' Inpatient Database (2000–2012) to determine if PDA ligation rates: (1) changed over time, (2) varied geographically, or (3) influenced surgical complication rates. In 2012, 47,900 infants ≥ 1500 g birth weight were born in the United States, including 2,800 undergoing PDA ligation (5.9%). Ligation was more likely in infants ≥ 1000 g (85.9% vs. 46.2%), and associated with necrotizing enterocolitis (59.2% vs. 37.5%), BPD (54.6% vs. 15.2%), severe intraventricular hemorrhage (16.4% vs. 5.3%), and hospital transfer (37.6% vs. 16.4%). Ligation rates peaked in 2006 at 87.4 per 1000 hospital births, dropping to 58.8 in 2012, and were consistently higher in Western states. Infants undergoing ligation were more likely to experience comorbidities. Rates of ligation-associated vocal cord paralysis increased over time (1.2–3.9%); however, mortality decreased (12.4–6.5%). Thus, PDA ligation has become less frequent, although infants being ligated are smaller and more medically complex. Despite increase in some complications, mortality rates improved perhaps reflecting advances in care.

Keywords

Patent ductus arteriosus; surgical ligation; kids' inpatient database; vocal cord paralysis; geographic variation

Introduction

Closure of the ductus arteriosus (DA) is a normal physiological process among most term newborns. However, failure of postnatal closure, termed persistent patency of the DA (PDA), complicates the course of nearly 2 out of 3 preterm extremely low birth weight infants (ELBW),^{1,2} making it one of the most common congenital cardiac disorders in this

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1053/j.semperi.2018.05.008>.

population.^{3–5} The DA of infants 430 weeks gestation or 41500 g typically constricts within 48–72 hours and achieves complete closure by the first week of life.⁶ In contrast, spontaneous closure of a small PDA in preterm infants <1000 g may not occur for weeks or months.^{2,7,8} Prolonged exposure to a hemo dynamically significant PDA is associated with harmful consequences in small preterm infants, including increased risks for pulmonary hemorrhage, congestive heart failure, intracranial hemorrhage, compromised peripheral circulation, and eventual development of chronic lung disease.^{3,9,10}

While the consequences of a PDA are well-known, optimal management of a PDA remains controversial and treatment options for preterm infants with symptomatic PDA are limited. Surgical ligation (SL), the first interventional therapy for PDA, was developed to prevent bacterial endocarditis, congestive heart failure, and cardiopulmonary deterioration in adults and older children.^{11,12} In the 1970s, indomethacin and other non-steroidal anti-inflammatory drugs (NSAIDs) provided an alternative to the more invasive SL.^{13,14} Despite the benefits of using NSAIDs as a non-surgical treatment option, SL remains the only definitive therapy to achieve high rates of permanent PDA closure, and has been a preferred first-line treatment in some NICUs.^{15–22}

Over the last 3 decades, research informing the clinician's approach to management of the PDA has evolved. For example, Clyman et al.²⁴ documented changing attitudes toward indomethacin prophylaxis after multicenter trials in the 1990s demonstrated its effectiveness,²³ causing an upsurge in preventive treatment. In contrast, publication of the trial of indomethacin prophylaxis in preterms (TIPP)²⁵ in 2001 cast doubt on the long-term benefits of this practice, resulting in decreased medical treatment.²⁴ Surgical ligation rates increased after the TIPP study concurrent with the decreased use of prophylactic indomethacin.²⁴ More recent studies show that the use of PDA ligation is either uptrending^{26,27} or declining,^{28–31} depending on the study population and the methods used for analysis. Perhaps because of this changing literature, there is no current consensus regarding optimal medical or surgical management of PDA.^{32–35} Given the changing literature on the risks of SL for the PDA, we used nationally representative data to: (1) determine if PDA SL became less frequent among US VLBWs over time in response to changing recommendations, (2) examine whether PDA SL varied geographically in the United States, and (3) to understand clinical characteristics and surgical complications of infants undergoing PDA SL.

Methods

Study design and setting

For this retrospective serial cross-sectional analysis, we used data from the Kids' Inpatient Database (KID) from 2000, 2003, 2006, 2009, and 2012 (the most recent year available). The KID is published every 3 years by the Agency for Healthcare Research and Quality as part of their Healthcare Utilization Project. The KID is the largest publically available all-payer database for hospitalized children in the United States. In 2012, the KID contained data for more than 3 million pediatric discharges from more than 4000 U.S. hospitals.³⁶ The sample for KID is obtained through systematic random sampling selecting 10% of uncomplicated term births and 80% of other pediatric discharges. This sampling strategy and the KID's large sample size enables analyses of rare conditions (e.g., congenital anomalies)

and uncommon treatments (e.g., cardiac surgery). Sampling weights provided from the KID allows for nationally representative estimates of pediatric conditions. The KID has been used broadly in national studies of pediatric^{37–39} and neonatal^{40,41} conditions. As the study used de-identified data, it was considered exempt from human subjects review by the Vanderbilt University School of Medicine.

Identification of sample

Very low birthweight (VLBW) infants, defined as a birthweight less than 1500 g, were identified using the International Classification of Diseases, Ninth Revisions, Clinical Modification (ICD-9-CM)⁴² codes and diagnosis related group, version 24 (DRG24) codes. Birthweight indicator variables were created if the following ICD-9-CM codes appeared in any diagnostic field: <1500 g (764.01–764.05, 764.11–764.15, 764.21–764.25, 764.91–764.95, 765.01–765.05, and 765.11–765.15), ≥1500 g (764.06–764.09, 764.16–764.19, 764.26–764.29, 764.96–764.99, 765.06–765.09, and 765.16–765.19), or unknown (764.00, 764.10, 764.20, 764.90, 765.00, and 765.10). Next, we categorized DRG24 codes 389 (full-term neonate with major problems), 390 (neonate with other significant problems), or 391 (normal newborn) as ≥1500 g.

Descriptive variables

Clinical characteristics of infants were determined using the following ICD-9-CM codes in any of the diagnostic fields during the birth hospitalization: PDA (747.0), any stage necrotizing enterocolitis (775.×), bowel perforation (777.6 ×), respiratory distress syndrome (769. ×), bronchopulmonary dysplasia (770.7 ×), severe intraventricular hemorrhage (772.13 and 772.14), periventricular leukomalacia (779.7 ×), and severe retinopathy of prematurity (362.26 and 362.27). PDA SL complications were similarly determined using the following ICD-9-CM codes: vocal cord paralysis (478.3 ×), surgical complication (998. ×), shock (998.0 ×), hemorrhage (998.1 ×), and infection (998.5 ×). An indicator of “any complication” was defined as vocal cord paralysis, death, or surgical complication (which itself was defined as post-operative shock, hemorrhage, accidental laceration, disruption of operative wound, foreign body, post-operative infection, or fistula). Additional variables provided by the KID included sex, insurance type, transfer status, median household income of zip code, death, and hospital characteristics. Race was not used as a description due to level of missing data.

Outcome variable

SL of a PDA was identified if the ICD-9-CM procedure code of 38.5 appeared in any 1 of 15 procedure fields.

Data analysis

Statistical analyses were conducted using Stata version 14.0 (StataCorp., College Station, TX). For all analyses, data were weighted to provide national estimates using the survey weights provided by the Agency for Healthcare Research and Quality. Clinical characteristics and surgical complications were determined for each study year (2000, 2003, 2006, and 2009 presented in Supplement). Incidence rates of PDA SL were estimated by

dividing the weighted total number of infants with surgical ligation of a PDA by the total number of VLBW hospital births, and expressed as incidence per 1000 births. PDA SL rates were then calculated by U.S. geographic region. All tests were two-sided, results reported with 95% confidence intervals (CIs) where appropriate.

Results

In 2012, there were 47,900 VLBW infants born in the United States, representing, 62,800 hospital admissions, among whom 2800 (95% CI) had a PDA SL. VLBW infants having a SL were more likely to ($p < 0.001$) have birthweights less than <1000 g (85.9% vs. 46.2%), any stage of NEC (59.2% vs. 37.5%), bowel perforation (8.5% vs. 1.6%), respiratory distress syndrome (74.5% vs. 55.1%), bronchopulmonary dysplasia (54.6% vs. 15.2%), severe (grade III or IV) intraventricular hemorrhage (16.4% vs. 5.3%), periventricular leukomalacia (4.7% vs. 1.7%), and to be transferred to another hospital (37.6% vs. 16.4%; Table 1).

From 2000 to 2006, the rate (per 1000 VLBW hospital births) of PDA SL increased from 46.8 (95% CI: 42.8–50.0) to 87.4 (95% CI: 81.2–92.9), and then decreased to 58.8 (95% CI: 54.6–62.6) in 2012 (Fig. 1). In all study years, there was substantial geographic variation in rates of PDA SL among VLBW infants. Consistently, the Western U.S. had the highest rate of PDA SL and the Northeast had the lowest, with a more than twofold difference in SL rates between the two regions of the country in most years (Fig. 2).

During our study period, as PDA SL became less frequent, the clinical characteristics of infants having the procedure shifted. For example, among all ligations, the proportion of infants having a SL that were ELBW (<1000 g) increased from 77.0% to 85.9%. Similarly, infants having a ligation in 2012 were more likely to have been diagnosed with any stage NEC (37.5% vs. 32.3%) compared to infants having a SL in 2000 (Supplemental Table 1).

Surgical complications were common among infants undergoing a PDA SL: 6.5% of infants died after a surgical ligation, 5.1% had a surgical complication (e.g., post-operative shock, hemorrhage, accidental laceration, disruption of the operative wound, foreign body, and post-operative infection or fistula), 3.9% had vocal cord paralysis, 2.6% infection and 14.8% had any complication (Table 2). From 2000 to 2012, rates of death among infants having PDA SL decreased from 12.4% to 6.5%; however, surgical complications and vocal cord paralysis increased from 3.8% to 5.1% and 1.2% to 3.9%, respectively (Supplemental Table 2).

Discussion

We found that SL of the PDA remains a common procedure among U.S. VLBW infants. While the rate of SL decreased in the latter part of the last decade, we found a substantial shift in the population of infants during our study period. When compared to 2000, infants having a SL were more likely to be of lower birthweights and have a greater number of clinical comorbidities. This suggests that clinicians shifted their practice patterns, targeting the sickest VLBW infants. Interestingly, we also found that while death rates following a SL decreased, there was a concurrent increase in surgical complications.

PDA treatment is a frequently debated issue in most NICUs, based on conflicting data regarding the need to intervene, and difficulty defining the optimal timing and patient population that requires active medical or surgical treatment. Neonatologists typically restrict PDA SL to the subset of patients that fail to respond to conservative/observational management or fail to close their PDA after one or more courses of an NSAID despite a lack of evidence for superiority of one approach over the other.³⁴ Recommendations for the use of SL have fluctuated based on improved operative techniques, survival of increasingly smaller and more complex infants, and associations between SL and various adverse outcomes. We examined changes in PDA SL trends in a nationwide database of hospitalized infants, to identify temporal and regional patterns of practice in response to changing evidence and evolving expert opinions. We found both temporal changes as well as substantial geographic variation with SL being much more common in the West.

Surgical ligation of the PDA was conceptualized in the 1880s as a treatment for endocarditis and adult congestive heart failure.¹¹ The first successful ligation was reported in 1938 after the procedure was performed in a 7-year old with cardiopulmonary insufficiency.^{11,12} Surgical transection of the ductus with oversewing of the resulting vascular stumps was subsequently performed in 1941 and became a preferred procedure. SL was the only curative treatment for PDA for nearly 40 years. In the 1970s, NSAIDs were reported to induce DA constriction^{43–46} and effectively close the PDA in preterm infants.^{13,14} Pharmacological therapy is now widely accepted as the first-line treatment for symptomatic PDA. NSAIDs reduce the need for an operative procedure and prevent exposure to anesthesia or surgical complications in preterm infants. Compared to pharmacological treatment, however, PDA SL results in definitive ductus closure, has an exceedingly low failure rate, and avoids the complications of NSAIDs. SL was favored over NSAID treatment in some nurseries,^{47–49} and in several centers SL has been the preferred first-line treatment for small preterm infants.^{15–22} Nevertheless, SL is typically reserved for medical treatment failures or cases where NSAIDs are contraindicated.

Our analysis shows that approximately 28% of VLBW infants managed in US nurseries in 2012 were diagnosed with PDA. From 2000 to 2012, PDA diagnoses ranged from 16% to 28%. These results are similar to the findings of Weinberg et al.,²⁷ where PDA diagnoses were made in 14–21% of VLBW infants from 2003 to 2009 also using data from the KID. Evaluation of Level III nurseries in the Canadian Neonatal Network from 2006 to 2012 also revealed an overall PDA rate of 27% among infants born at 24–32 weeks gestation.³⁰ These rates are lower than the reported rates of PDA in clinical trials and observational studies, perhaps due to differences in the methods for ascertainment of PDA data. Using inpatient records and billing information from U.S. tertiary-care pediatric referral hospitals that participate in the Pediatric Health Information System (PHIS), Hagadorn et al.,²⁸ found an overall PDA rate of 42.3% in VLBW infants from 2005 to 2014, although inclusion criteria were only met by 19 of 49 participating PHIS hospitals. The U.S. Neonatal Research Network (NRN) reported an overall PDA rate of 46% for infants <28 weeks gestation at birth from 2003 to 2008.⁵⁰ Similarly, Ngo et al.²⁹ surveyed 134 hospitals in the California Perinatal Quality Care Collaborative (CPQCC) representing >90% of California's NICUs. PDA was diagnosed in 42.8% of VLBW infants in the CPQCC from 2008 to 2014. The discrepancy in PDA rates in state-specific data or select pediatric hospitals vs. national

database registries may reflect differences in the populations studied or regional variations in the definition of PDA.

From 2000 to 2012, we observed a prominent deflection in PDA SL rates during the 2006 reporting period, with increasing frequency of SL procedures up to 2006, and a decline in SL rates thereafter. Similarly, Hagadorn et al., examined PHIS data from 2005 to 2014 which identified a peak in overall SL rates in 2007²⁸ among large children's hospitals. In that study, the decline in SL after 2007 reflected a reduction in the number infants receiving both pharmacotherapy and SL. We found a national SL rate of as high as 87.4 in 2006, and as low as 46.8 per 1000 VLBW births (Fig. 1), similar to the rate described by Hagadorn in a small sample of hospitals—56.0 per 1000.²⁸ Ngo et al.²⁹ also found an increasing trend in primary PDA SL perhaps because the emphasis on less frequent NSAID treatment in CPQCC hospitals resulted in patients needing SL beyond the accepted “window” for NSAID treatment. Other investigators have reported either increasing or decreasing trends in PDA SL. Lokku et al. analyzed annual data from the Canadian Neonatal Network and found a peak in rates of infants with SL-only treatment (no prior NSAIDs) of 7.1–8.8% in 2006 and 2007, similar to the temporal peak noted in our analysis. Canadian rates for SL-only treatment fell to a low of 1.7–2.0% in 2010–2011, although rates for any SL (with or without prior pharmacotherapy) ranged from 21% in 2006 to a low of 10% in 2012,³⁰ which is higher than most estimates in U.S. nurseries. The changing trend in Canadian SL was attributed to publications emphasizing the 30% NSAID failure rate in nurseries, concerns regarding adverse events associated with SL, and concerted national efforts to reduce “aggressive treatment in favor of conservative management.”³⁰ Interestingly, there was no improvement in composite mortality/morbidity outcomes with decreasing rates of pharmacotherapy and/or ligation. Furthermore, overall rates of mortality and ROP were reduced among infants treated with NSAIDs and ligation, although these findings may reflect improvements in clinical practice or other unmeasured factors.³⁰

We examined the KID database in order to better understand SL trends using a nationally representative sample. The observed peak in SL rates in 2006 was not reported in two other analyses of KID data. Tashiro et al. examined SL in the 1997, 2000, 2003, 2006, and 2009 KID datasets. SL rates increased consistently from 1997 (8.5%) to 2009 (12.4%), however, this analysis was not limited to VLBW infants. As expected, SL was more common in lower birth weight and younger gestational age groups.²⁶ Weinberg et al. evaluated KID datasets in 2003, 2006, and 2009. Among infants 32 weeks gestation, SL rates increased from 12% to 14%, while rates increased from 4% to 7% in infants 28 weeks,²⁷ similar to the overall SL rates in our data. Despite examination of a common KID database, neither study identified a peak in 2006, although this trend has been noted in other populations.^{28,30} KID represents discharge-level data; therefore, if an infant is transferred from their birth institution they may be captured more than once in the data. In 2012, we found 62,800 discharges among 47,900 VLBW infants, and utilized these data to calculate rates of SL per birth in contrast to hospital discharge. To ensure accurate population-adjusted rates, we chose a denominator of VLBW hospital births, perhaps explaining some differences in our findings.

The underlying cause for the peak and then subsequent downturn in SL rates after 2006–2007 is unclear. In 2001, the TIPP trial,²⁵ along with a contemporaneous systematic review

of PDA treatment outcomes,⁵¹ highlighted the absence of long-term benefits of prophylactic or indicated PDA treatment. These results were associated with an increase in PDA SL rates over the next several years.²⁴ The upward SL trend may have reached a stable plateau as PDA definitions improved and SL criteria were formalized. Alternatively, the increasing trend in SL rates may have been temporized by critical reports in 2004–2007, which called into question the need for medical or surgical treatments to induce PDA closure.^{1,52–59} Recognition that spontaneous ductus closure could occur later and more frequently than expected may also have contributed to the plateau in SL rates during this time period.¹ More importantly, a series of studies in 2005–2007 described a concerning association between PDA SL and adverse neonatal outcomes, including increased rates of neurodevelopmental impairment, bronchopulmonary dysplasia, or retinopathy of prematurity.^{60–62} Recent large studies further implicated SL with worse short- and long-term outcomes.^{63–65} We speculate that the combined effects of these reports and growing interest in conservative PDA management contributed to decreasing SL rates over the past decade.

In addition to the temporal shift in SL rates, we also observed marked differences in the geographic distribution of SL practices in U.S. nurseries. Over the 2000–2012 period, Western states consistently had the highest rate of PDA SL, while Northeastern states had over twofold lower SL rates in most years. It is possible that higher SL rates in Western states are related to the influence of prevailing expertise in the region. Indeed, a well established practice of early mandatory PDA SL^{66,67} by researchers with a longstanding history of authoritative PDA studies^{4,14,68,69} may have influenced regional practice patterns⁷⁰ and contributed to the observed geographic differences. Data on location and center-effects in the CPQCC dataset²⁹ might provide insight regarding this possibility.

Finally, we found that adverse effects associated with SL changed over time. From 2000 to 2012, SL mortality rates decreased from 12.4% to 6.5%; however, surgical complications and vocal cord paralysis increased during this period, suggesting that survivors are at greater risk. Reluctance to use SL as the initial, primary mode of treatment reflects general concerns for operative approaches in unstable preterm infants, but also specific complications related to PDA SL itself, including inadvertent ligation of nearby vascular structures, recurrent laryngeal nerve injury causing left vocal cord paralysis, and catecholamine-resistant post-ligation hypotension.^{65,71–74}

Limitations

Our study contains limitations that merit discussion. Our data rely upon hospital administrative data and errors of omission or commission are possible leading to misclassification bias. We also note that over time the KID increased the number of diagnostic fields from 15 to 25, potentially improving ability to detect clinical complications over time; however, this should have not had any effect on our estimates of SL over time. We did not have access to medical records to confirm the mechanism of diagnosis of PDA (i.e., clinical or echocardiography). Next, because data from KID are obtained from the discharge abstract, we are unable to determine if clinical comorbidities (e.g., necrotizing enterocolitis) occurred before or after the SL.

Conclusion

In summary, PDA ligation rates in the United States are declining among VLBW infants. Using a nationwide sample of hospital births, we found that infants undergoing SL are less mature and more likely to have other comorbidities. The rates of vocal cord paralysis, infection, and surgical complications have increased over time. However, infant mortality related to SL has improved. The rates of SL are likely to fluctuate around a declining mean with increased adoption of conservative approaches, improved selection of SL patients, and alleviation of bias in SL outcome studies.^{75,76} Improvements in catheter-based PDA closure techniques⁷⁷ may also reduce the need for SL in VLBW infants, as PDA treatments continue to be refined and scrutinized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

PDA	patent ductus arteriosus
SL	surgical ligation
NSAID	non-steroidal anti-inflammatory drug
VLBW	very low birthweight
ELBW	extremely low birth weight
NEC	necrotizing enterocolitis
KID	Kids' Inpatient Database

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Fig. 1 -

PDA surgical ligation rate per 1000 VLBW hospital births, US 2000–2012. PDA ligation rate (per 1000 VLBW hospital births), 2000: 46.8 (95% CI: 42.8–50.0); 2003: 65.7 (95% CI: 61.7–69.2); 2006 87.4 (95% CI: 81.2–92.9); 2009 78.5 (95% CI: 72.9–83.5); 2012 58.8 (95% CI: 54.6–62.6).

Fig. 2 -
PDA surgical ligation rate per 1000 VLBW hospital births by US geographic region, 2000–2012.

Table 1 -

Characteristics of very low birthweight infants undergoing surgical ligation compared to all other very low birthweight infants, US 2012.

	All Other VLBW Infants N = 59,933		VLBW infants undergoing ligation N = 2817		p Value
	N	%	N	%	
PDA	14,670	24.5	2690	95.5	<0.001
Sex					0.257
Male	30,739	51.3	1467	52.1	
Female	29,120	48.6	1349	47.9	
Missing	74	0.1	0	0.0	
Birthweight					<0.001
<1000g	27,662	46.2	2420	85.9	
1000–1499 g	32,271	53.8	397	14.1	
Clinical comorbidities					
Any NEC	22,471	37.5	1667	59.2	<0.001
Bowel perforation	974	1.6	239	8.5	<0.001
RDS	33,053	55.1	2098	74.5	<0.001
BPD	9,091	15.2	1538	54.6	<0.001
Severe IVH	3,148	5.3	462	16.4	<0.001
PVL	1,037	1.7	134	4.7	<0.001
Severe ROP	54	0.1	<10	0.2	0.053
Insurance					0.001
Private	22,064	36.8	1043	37.0	
Medicaid and Medicare	33,301	55.6	1583	56.2	
Self-pay	1790	3.0	21	0.7	
Other	2605	4.3	157	5.6	
Missing	174	0.3	12	0.4	
Transfer					<0.001
No	49,913	83.3	1740	61.8	
Yes	9,849	16.4	1060	37.6	
Missing	171	0.3	189	6.7	
Median household income					0.871

	All Other VLBW Infants N = 59,933		VLBW infants undergoing ligation N = 2817		p Value
	N	%	N	%	
0–25th percentile	19,928	33.3	902	32.0	
26th to 50th percentile	14,936	24.9	730	25.9	
51st to 75th percentile	13,292	22.2	631	22.4	
76th to 100th percentile	10,655	17.8	498	17.7	
Missing	1122	1.9	56	2.0	

Table 2 -

Complications of very low birthweight infants undergoing surgical ligations for a PDA compared to all other VLBWs, US 2012.

	VLBW infants not undergoing ligation <i>N</i> = 59,933		VLBW infants undergoing ligation <i>N</i> = 2817		<i>p</i> Value
	<i>N</i>	%	<i>N</i>	%	
Vocal cord paralysis	94	0.2	109	3.9	<0.001
Death	8869	14.8	183	6.5	<0.001
Surgical complication *	417	0.7	144	5.1	<0.001
Hemorrhage	69	0.1	26	0.9	<0.001
Infection	130	0.2	74	2.6	<0.001
Any complication	9310	15.5	416	14.8	0.421

* Defined as post-operative shock, hemorrhage, accidental laceration, disruption of operative wound, foreign body, post-operative infection, or fistula.