REVIEW ARTICLE

Pharmacoeconomics of Surgical Interventions vs. Cyclooxygenase Inhibitors for the Treatment of Patent Ductus Arteriosus

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Management of neonatal patent ductus arteriosus (PDA) often is resource-intensive and costly. Therefore, it is in hospitals' best interests to ensure the most cost-efficient use of associated resources. Clinical status, comorbidities, and response to prior therapy are considered in selecting the most appropriate intervention for PDA management. Currently, supportive measures (e.g., fluid restriction), surgical ligation, and pharmacologically based medical therapy are the primary treatment modalities for correcting PDA. Medical therapy, which comprises a small percentage (2.0%-5.0%)[1] of overall PDA treatment expenses in the United States, consists of either of the 2 intravenous (IV) cyclooxygenase (COX) inhibitors: IV indomethacin and the newly available IV ibuprofen lysine. Although IV COX inhibitors represent a small portion of medical expenses, their benefits appear to be considerable. Pharmacoeconomic studies have evaluated indomethacin's beneficial impact on cost-effectiveness per quality-adjusted life year in PDA prophylaxis; however, no analysis to date prospectively assesses the effect of COX inhibitors on resource use or expenses in treating PDA. Such analysis is desirable and should consider efficacy and safety outcomes, impact on health care resource use and length of stay (LOS), and any differential effects of the agents' safety profiles; notably, IV indomethacin adversely affects renal and mesenteric blood flow and increases serum creatinine and oliguria significantly more than IV ibuprofen. These observations lay the foundation to conduct studies assessing the influence of these differences on resource use, LOS and expenses associated with PDA management.

KEYWORDS cylooxygenase inhibitors; economics, pharmaceutical; ibuprofen; patent ductus arteriosus; quality-adjusted life year

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INTRODUCTION

Patent ductus arteriosus (PDA) is a disorder that primarily affects very low birth weight (VLBW) premature infants. It is characterized by the failure of the ductus arteriosus to spontaneously close within 96 hours of birth.[2] An estimated 42,714 neonates annually[3] are diagnosed with PDA. Decreased smooth muscle responsiveness to oxygen and persistently elevated circulating prostaglandin E_2 levels have been identified as the principle etiologic factors leading to PDA.[4] The precise incidence of PDA as a function of birth weight remains unknown; the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network[5] estimates that

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37% to 50% of infants weighing 1,000 g or less develop PDA, while other sources estimate that it occurs in up to 80% of newborns in the same weight group.[2,6]

ABBREVIATIONS: CI, confidence interval; COX, cyclooxygenase; DRG, diagnosis-related group; HCUP-KID, Healthcare Cost and Utilization Project, Kids' Inpatient Database; ICD-9, International Classification of Diseases, 9th Edition; IVH, intraventricular hemorrhage; LOS, length of stay; NEC, necrotizing enterocolitis; NICHD, National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; OR_a, adjusted odds ratio; PDA, patent ductus arteriosus; QALY, quality-adjusted life year; RDS, respiratory distress syndrome; RR, relative risk; SCHIP, State Children's Health Insurance Program; SD, standard deviation; UDS, United States Dollars; VLBW, very low birth weight

For neonates in whom the ductus arteriosus fails to close spontaneously, there are a number of therapeutic options for managing a symptomatic PDA, including supportive care, surgical ligation, and pharmacologically-based medical therapy. While supportive care measures are often integral and may entail increasing hematocrit levels, implementing fluid restriction, and providing ventilatory support,[2] they also consume neonatal intensive care unit (NICU) resources, including staff time and neonatal incubators. Additionally, renal, cerebral, and mesenteric blood flow are often reduced in neonates with PDA,[2] which could potentially precipitate adverse outcomes and contribute to increased hospital resource utilization. However, some of the largest expenses may be incurred in the correction of PDA itself.

Currently, surgical ligation and medical therapy are 2 approaches that can directly correct the structural vascular defect that defines neonatal PDA, and they are employed for symptomatic cases that fail to close spontaneously or respond to supportive measures. Of the 2 directly corrective interventions, surgery is the more expensive. The purpose of this review is to examine the medical resource utilization considerations and expense drivers associated with the management of PDA in the neonatal population. Among the expenses considered in this analysis are the supportive care resources consumed in treating neonates with PDA and the expenses associated with surgical and medical care. Comparison of the 2 COX inhibitors and their relative efficacy and safety profiles is also examined to establish a basis for further analyses to determine their relative impact on health care resource utilization. Finally, consideration for additional pharmacoeconomic analyses and research is offered for future evaluation.

PDA: EXPENSES INVOLVED WITH CARE

The management of neonates with PDA is often costly,[1] and there is no guarantee that a hospital will recoup the expenses associated with treatment. The reimbursement amount a hospital receives for caring for these cases is dependent on the type of payer. On average, State Children's Health Insurance Program (SCHIP) and State Medicaid programs reimburse 86% of hospital expenses for PDA, while private insurers reimburse hospitals 135% of their expenses on an estimated national average basis.[1] In other words, hospitals' expenses outweigh their payments when caring for patients covered by public payers, whereas the opposite tends to be true when caring for those covered by private insurers.

A hospital may have little control over modifying its patient demographic or payer mix; however, to some degree health system administrators and health care providers have the ability to control or curtail health care expenditures without sacrificing the quality of care provided.

Neonatal PDA is often associated with resource-intensive comorbidities such as respiratory distress syndrome (RDS),[2] which occurs in as many as 40% of VLBW infants with RDS.[7,8] One of the primary treatments for neonatal RDS is surfactant therapy, which may be associated with a higher risk of clinically symptomatic PDA.[2] In an era of heightened focus on containing rising health care expenses and resource utilization, the outcome of the most interest to hospitals, neonates, and their families alike should be the rapid, effective, and safe correction of the anatomical abnormality that defines PDA.

SURGICAL MANAGEMENT

Surgical correction of PDA involves the ligation, or clipping, of the ductus, providing the short-term functional closure needed by the

Table. National estimates of costs (USD) to health care institutions of surgical ligation versus no surgical ligation for patent ductus arteriosus correction

	Total hospital expenditures by DRG*	
	Extreme immaturity or RDS‡	**Prematurity with major problems§**
Surgical ligation†		
Yes	176,739	84,662
No	99,733	49,457
Ligation vs no ligation		
Difference in expenditure	77,006	35,205
Expense ratio	1.772	1.712

DRG, diagnosis-related group; ICD-9, International Classification of Diseases, 9th edition; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; USD, United States Dollars
** Each patient also had an ICD-9 code of 747.0 = anomaly, congenital patent ductus arteriosus.*
† ICD-9 procedure code 38.85
‡ DRG 386
§ DRG 387
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body to promote the slower process of fibrosis that affords permanent anatomical closure.[2] Although surgical ligation remains an effective treatment of PDA and carries a low rate of mortality (<1%),[2,9] it is invasive and expensive, and it typically requires additional recovery time. In fact, according to 1 observational study, surgical PDA ligation appears to be associated with an increased risk of developing neurosensory impairment (adjusted odds ratio [OR_a] = 1.98; 95% confidence interval [CI] = 1.18-3.30; P = .0093), bronchopulmonary dysplasia (OR_a = 1.81; 95% CI = 1.09-3.03; P = .023), and severe retinopathy of prematurity (OR_a = 2.20; 95% CI = 1.19-4.07; P = .012).[10] However, it should be noted that, given the study's lack of experimental control, the observed differences may have been due to differences in disease severity, active treatment, or other variables.

A recent analysis of the Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID) by Navigant Consulting demonstrates that PDA treatment expenses may be as low as $49,457 for neonates who do not receive surgery and as high as $176,739 for infants who do (Table).[1] The analysis of the database, which contains data from over 2.9 million pediatric discharges from 3,438 community hospitals, specialty hospitals, and academic medical centers in 36 states,[3] demonstrates that the institutional expenses associated with ligation can engender over $77,000 in additional expenses as compared to the nonsurgical resolution of PDA (Table).[1]

Although policymakers and researchers frequently use KID, the only all-payer inpatient care database for children in the United States, there are a number of limitations to using this data to estimate the impact of surgical ligation on length of stay (LOS) and charges. First, the use of diagnosis-related groups (DRGs) and International Classification of Diseases (ICD-9-CM) diagnosis and procedure codes to identify neonatal cases with PDA may not capture all relevant cases, resulting in an underestimation of the actual prevalence of the condition; this can affect other important outcome measures such as LOS, discharge status, and mean hospitalization charges. Second, because not all states provide a unique patient identifier with HCUP-KID data, all analyses are conducted at the discharge, rather than the patient, level; therefore, detailed and precise information is not available to validate the recording of diagnoses and comorbidities of interest. Lastly, data in KID are based on the charges for the hospitalization only, not physician fees, and reported charges do not necessarily reflect costs or reimbursements actually received by hospitals.

Despite the limitations of Navigant Consulting's descriptive analysis, the finding that neonates receiving surgical ligation incur over 77% more in expenses than nonsurgical cases[1] warrants additional evaluation. A difference in cost of this magnitude is likely to be of great concern to health care administrators and practitioners alike. Therefore, a more robust data analysis of KID using multivariate logistic regression modeling to control for comorbidities, severity

of illness, treatment failures, and other key variables is necessary to accurately estimate the impact of surgical vs. medical PDA closure on LOS, charges, and clinical outcomes.

MEDICAL THERAPY

Expenses Associated with Medical Therapy

Strategies that can eliminate the need for surgery or lower the rate of ligation procedures may be attractive from a health care resource vantage point. COX inhibitors represent a preferable alternative to surgical ligation because they are less invasive and less expensive. These agents represent first-line treatment aimed at directly resolving PDA in eligible cases;[2,6] contraindications to COX inhibitors include the presence of known or suspected untreated infection, heart disease in which PDA is necessary for the maintenance of blood flow, serious bleeding or coagulopathy, thrombocytopenia, known or suspected necrotizing enterocolitis (NEC), or significant renal impairment.[11,12]

Two intravenous (IV) COX inhibitors are currently approved for the treatment of PDA in the United States: indomethacin (Indocin; Ovation Pharmaceuticals, Deerfield, IL) and ibuprofen lysine (NeoProfen; Ovation Pharmaceuticals, Deerfield, IL). For the management of PDA in neonates, it is important for pharmacy departments to look beyond the departmental budget and to examine expenses associated with COX inhibitors and other pharmacologic agents in light of surgical-closure-related and total PDA treatment expenditures.

Based on data derived from the Maryland Health Services Cost Review Commission's Hospital Inpatient Public Use Database, which contains information similar to but more detailed than that provided by HCUP KID (e.g., distribution of charges by drugs, supplies, and diagnostic testing), the average total drug charge (of which COX inhibitors are but 1 component) represents between 3.8% and 6.2% of average overall hospital charges (depending on birth weight) for the most common PDA-related DRGs.[1] Assuming that the cost of 1 vial of IV COX inhibitor is $600 (the approximate 2007 average wholesale price for both commercially available products),[13] that the contents of the vial in excess of the dose must be discarded (in accordance with United States Pharmacopeia Chapter <797> requirements[14] and the Joint Commission's Medication Management standard 4.40[15]), and that 1 vial must be used per dose with 3 doses total, then the cost of COX inhibitor therapy is $1,800 per PDA case.[1]

At these costs, COX inhibitor therapy represents 16.3% of total drug charges for VLBW infants (500-749 g).[1] Further, for these VLBW neonates, the expenses associated with COX inhibitor therapy represent 1% of the total average inpatient charges; for neonates as a whole (500-1750 g), the expenses associated with COX inhibitors represent 2.0%-5.0% of the total average inpatient charges, depending on the particular PDA-associated DRG.[1] It is therefore important for hospital administrators, pharmacy directors, and pediatric clinicians who are responsible for institutional costs of care to keep a global perspective in mind and to remember that institutional expenses are the sum of all the resources consumed when a product or service reaches its end user.[16,17]

Pharmacoeconomic Studies of Cyclooxygenase Therapy in PDA Prophylaxis

There are some compelling pharmacoeconomic findings that support the benefits of COX inhibitor therapy; however, published pharmacoeconomic studies investigate the COX inhibitors' impact only on resources for prophylaxis, not for the treatment of PDA.

Moya and Goldberg[18] conducted a cost-effectiveness analysis of indomethacin for the prophylaxis of PDA from a societal perspective. The authors built a decision-tree model, basing incidence of PDA on the results of a published meta-analysis, expenses of surgical ligation on the North Carolina Department of Medical Assistance DRG weight table, and drug expenditure data on a published wholesale pharmaceutical catalog. Another factor in the model was the presence of intraventricular hemorrhage (IVH), for which incidence and associated costs were derived from historical data. Despite relatively minimal expense avoidance between groups (indomethacin groups incurred expenses of $95,157 vs. $99,955 for the groups that did not receive indomethacin), the authors found an improvement in quality-adjusted life years (QALYs: indomethacin 11 years vs. control 10 years) and cost effectiveness per QALY

Ref	N IBU	N INDO	Difference	N Total	P Value
8	94	81	.359	175	.018
7	20	20	.626	40	.050
33	74	74	.479	148	.004
29	9	8	.712	17	.144
30	32	31	.366	63	.147
	229	214	.437	443	.000

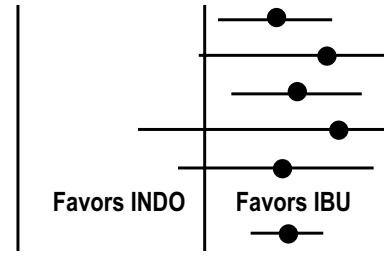

Figure 1. Relative risk of difference in serum creatinine levels associated with cyclooxygenase inhibitors in 5 trials. IBU, ibuprofen lysine; INDO; indomethacin; N, sample size. Thomas RL, Parker GC, Van Overmeire B, et al. A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. Eur J Pediatr 2005;164:135-140. With kind permission of Springer Science and Business Media.

(indomethacin $8,443 vs. control $9,168).

Zupancic et al. conducted a retrospective cost-effectiveness evaluation from a third-party payer perspective of 428 neonates who were enrolled in the Trial of Indomethacin Prophylaxis in Preterms (TIPP) and received indomethacin for PDA prophylaxis.[10,19] The authors conducted a retrospective chart review using 89 items to account for resource utilization. These items included expenses associated with respiratory support, vascular access, nutritional support, environmental support, radiological tests, transfusions, minor procedures, formal surgical procedures, laboratory and diagnostic tests, and medications. Surgical expenses were obtained from a Canadian provincial medical reimbursement plan, medication expenses were reflective of pharmacy acquisition costs, and other expenses associated with resource use were derived from the Ontario Case Cost Project of the Ministry of Health Joint Policy and Planning Committee and a time-and-motion study conducted by the same authors.

Although the mean expense of care was similar between groups (USD $46,651.43 in the indomethacin group vs. USD $45,746.93 in the placebo group), the authors found an incremental cost-effectiveness point estimate of USD $45,225 for the composite primary endpoint of death or organ impairment averted and an incremental cost-effectiveness point estimate of USD $42,263.60 for the secondary endpoint of death averted. These calculations suggest that considerable savings result when adverse outcomes are avoided and that cost-efficacy may be achieved even when expenses themselves between groups are generally similar.

It is worth reiterating that both the Moya and Zupancic studies considered indomethacin when used prophylactically for PDA, which is not considered a current standard of care. The recently completed TIPP indicates that, although indomethacin prophylaxis can prevent some surgical ligations and associated long-term neurosensory impairment, the prophylactic benefit is small and may be offset by long-term adverse effects.[10] Additionally, the authors of a large, retrospective, case-control study comparing indomethacin prophylaxis for PDA to "expectant" therapy concluded that prophylaxis offered no advantages and predisposed infants to potentially serious adverse effects.[20] These side effects may be the reason for the relative expense-neutrality of prophylactic COX-inhibitor therapy. However, the quality of life and indirect expenditure impact benefits highlighted in the aforementioned pharmacoeconomic analyses may be even more substantial when COX inhibitors are employed in the *treatment* of PDA, where the clinical benefits are unequivocal.

Comparisons of IV Ibuprofen Lysine vs. IV Indomethacin

Ibuprofen lysine is a newly available IV COX inhibitor that has an efficacy profile similar to indomethacin.[7,8,21-33] The 2 agents lead to clinically and statistically similar rates of PDA resolution, ligation prevention, and PDA reopening.[7,8,21-33] Other similarities include a lack of strong literature support for the agents' use for PDA prophylaxis.[34,35]

Several key differences in safety outcomes between the 2 IV COX inhibitors merit men-

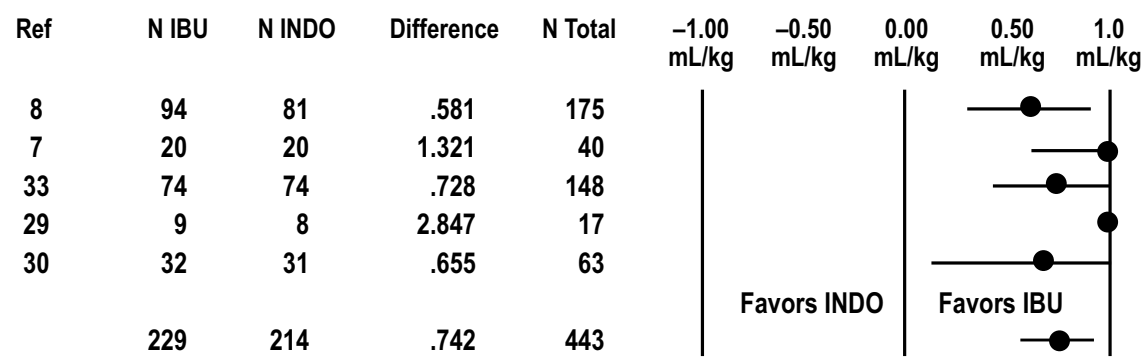

Figure 2. Relative risk of difference in urine output associated with cyclooxygenase inhibitors in 5 trials. Thomas RL, Parker GC, Van Overmeire B, et al. A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. Eur J Pediatr 2005;164:135-140. With kind permission of Springer Science and Business Media.

tion because a single preventable adverse event is estimated to incur $5,857 in expenses in the adult population, corresponding to $2.8 million in annual expenditures for a 700-bed hospital.[36,37] (Such figures pertaining to the pediatric and neonatal populations are currently unavailable.) Ibuprofen has consistently demonstrated statistically superior outcomes or measures compared to indomethacin with respect to renal effects.[8,22,24,25,27,29-33,38-41] A meta-analysis[41] of 5 trials[7,8,29,30,33] demonstrated that serum creatinine levels are 0.437 mg/dL higher in neonates who receive indomethacin as compared to ibuprofen ($P < .001$; Figure 1). Similarly, newborns who received indomethacin demonstrated significantly lower urine output of 0.742 mL/kg ($P \leq .02$; Figure 2). A separate meta-analysis by Ohlsson[27] that pooled urine output data from 2 trials[8,23] demonstrated similarly significant outcomes. Another trial demonstrated lower use of the diuretic furosemide in infants receiving ibuprofen relative to indomethacin for PDA closure ($P = .009$).[38] These findings may be due, in part, to a significant increase in the relative vascular resistance and reduction in the blood velocity of the renal artery associated with indomethacin.[29]

Less consistent indications of differences between the COX inhibitors include their relative mesenteric blood flow[24,29,38,39,42,43] and regional hemodynamic[44] effects, as well as their measured impacts on hospital resources.[8,30] Indomethacin significantly decreases mesenteric blood velocity, while ibuprofen does not.[29]

In a randomized controlled trial[38] of 30 preterm neonates with PDA that assessed the relative safety and efficacy of oral indomethacin or ibuprofen, the authors observed a nonsignificantly higher rate of NEC (indomethacin 66.67% vs. ibuprofen 40%). A pooled analysis[27] of 5 studies[7,8,30,33,38] ($N = 456$) also did not find a statistically significant difference in NEC incidence between treatment groups (Figure 3). As evidenced by Figure 3, however, the data trend toward a significant difference. These findings are further supported by animal studies[40,42,43] and are of concern because mortality rates are higher in infants who experience NEC with COX inhibitor therapy than in those who do not.[45]

RESOURCE USE AND EXPENDITURES: FUTURE DIRECTIONS

Of continued interest is COX therapy's impact on the utilization of health care resources. In a study of 63 VLBW preterm neonates with PDA and respiratory distress syndrome, Su et al. observed a mean NICU LOS of 25.1 days ± 12.3 with indomethacin vs. 23.9 days ± 12.1 with ibuprofen.[30] The mean overall hospital stay was 38.9 days ± 16.8 with indomethacin vs. 37.9 days ± 15.3 with ibuprofen (probability values reported as not significant). Likewise, Lago et al. reported a mean of 14 days of ventilation ± 16 and a total hospital stay of 73 days ± 37 with indomethacin vs. 12 days of ventilation ± 12 and a total hospital LOS of 65 days ± 34 with ibuprofen.[8] However, these differences were not statistically significant.

Now that there are clinical data that demonstrate a difference in safety profiles between the COX inhibitor agents for PDA[8,22,24-27,28-33,38-

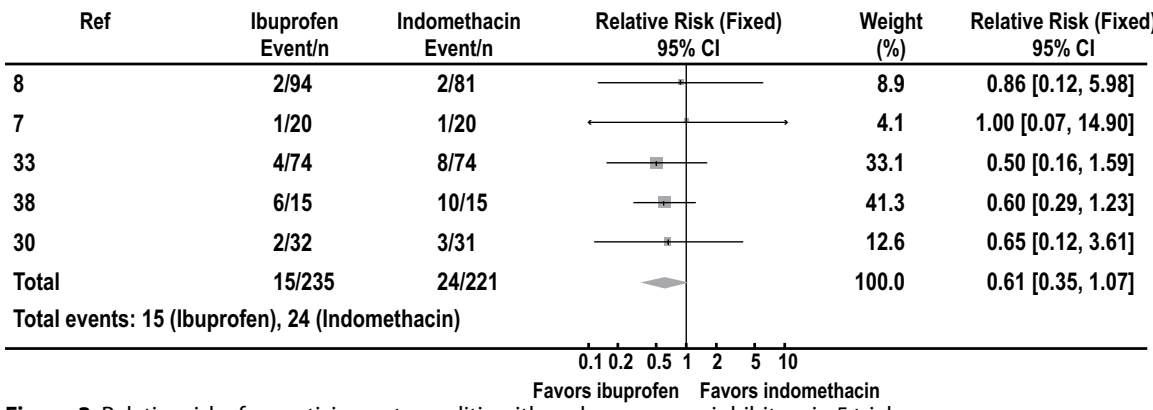

Figure 3. Relative risk of necrotizing enterocolitis with cyclooxygenase inhibitors in 5 trials.
CI, confidence interval; N, sample size.
Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. The Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003481.pub2. DOI:10.1002/14651858. CD003481.pub2. Copyright Cochrane Collaboration, reproduced with permission.

[44,46-48] and the possibility that better powered studies[8,30] might better illustrate whether there are differences in resource utilitzation, there are opportunities for further pharmacoeconomic analysis. Considerations include whether the COX inhibitors allow a shorter duration of stay than surgical correction of PDA and an associated difference in expenses; whether ibuprofen's potential benefits with respect to days on ventilator support and NICU and hospital LOS endure further scrutiny afforded by better powered analyses; and whether ibuprofen incurs less monitoring for side effects than indomethacin and the ramifications on resource consumption with respect to their different renal, cerebral, and mesenteric effect profiles. Additionally, there is a need for time-and-motion studies comparing the agents' preparation and administration. For example, IV indomethacin has limited stability,[11] necessitating reconstitution at the bedside immediately prior to administration in some institutions, while IV ibuprofen is manufactured as a preservative-free solution.[12]

To date, the opportunity remains for a prospective study or analysis that examines resource use or LOS associated with the 2 IV COX inhibitors for PDA treatment as a primary outcome, as retrospective pharmacoeconomic analyses have already addressed the COX inhibitors' utility in PDA prophylaxis.[18,19,34,35] In order to assess each COX-inhibitor agent's impact on LOS and resource use, a sophisticated multivariate regression analysis would be needed, with data from comparator-controlled trials such as those of Lago et al. or Su et al.[8,30]

Extrapolations to expenditures may be made by employing historical data. For example, using health care expense data from the Navigant report[1] and LOS data from the study by Su et al., the expenses associated with a single day of hospital stay for PDA range from $1,271.39 to $2,563.83 (depending on DRG).[30] The Su et al. study suggests that there is a 1-day LOS difference between COX inhibitors (indomethacin 38.9 days vs. ibuprofen 37.9 days); however, when LOS data from Lago et al. are applied, there is an 8-day difference in LOS (indomethacin 73 days vs. ibuprofen 65 days) (Figure 4), which would result in an expenditure difference of $10,339.52 (ibuprofen $10,171.12 vs. indomethacin $20,510.64).[8,30]

These calculations are based on historical data that contains LOS differences that are not statistically significant. However, they highlight the need to resolve such questions, because doing so would help provide a more complete picture of hospital expenses and resource utilization associated with the therapy options for PDA.

Another unresolved question pertains to the clinical and economic impact of COX inhibitors on cerebral outcomes and neurosensory development. Indomethacin has been associated with a reduction in the incidence of IVH,[49,50] possibly due to its reductions in cerebral blood flow, oxygen delivery, blood volume, and reactivity to changes in arterial carbon

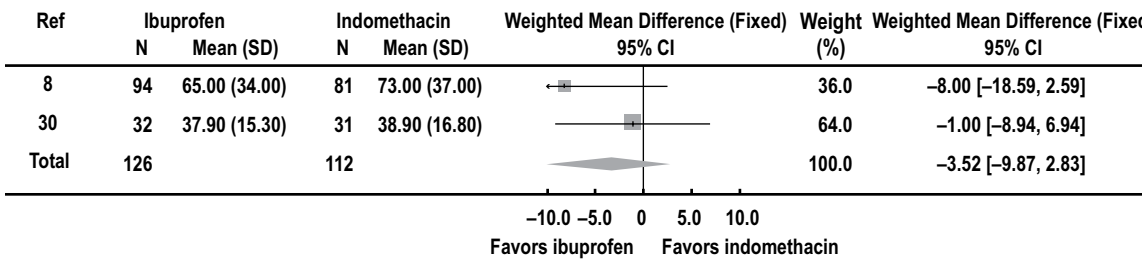

Figure 4. Difference in duration of hospitalization associated with cyclooxygenase inhibitors in 2 trials.
CI, confidence interval; N, sample size; SD, standard deviation.
Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. The Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003481.pub2. DOI:10.1002/14651858.CD003481.pub2. Copyright Cochrane Collaboration, reproduced with permission.

dioxide tension (all $P < .01$).[46] Some evidence from TIPP suggests that children treated with indomethacin overall had higher IQ scores and less difficulty with vocabulary than those treated with placebo.[51] However, this analysis is limited in that there are significant differences in the baseline characteristics between the groups that may have contributed to these differences. Additionally, it is estimated that a trial that could effectively detect a difference in other outcomes, such as cerebral palsy, would require over 6,000 infants.[52] Therefore, while the subject of cerebral outcomes associated with COX inhibitors continues to be an area of clinical interest, the strength of the long-term outcomes data is unclear, as is the question of whether it ultimately may play a role in future pharmacoeconomic or resource expenditure analyses.

CONCLUSIONS AND RECOMMENDATIONS

Depending on treatment modality, the expenses associated with managing neonates with PDA vary significantly. In today's health care environment of per-case reimbursement by Medicare, Medicaid, SCHIP, and private payers, it is in a hospital's best interest to use resources in the most efficient manner to improve health care outcomes, save lives and reduce health care expenses. Both surgical and medical options are available for correcting the underlying structural defect that defines PDA; however, surgery may be associated with additional patient discomfort, extra recovery time, and higher overall costs. The expenses incurred by PDA treatment may be as low as $49,457 for neonates who do not receive surgery and as high as $176,739 for infants who do.[1]

Medical therapy, consisting of the COX inhibitor drug class, is generally considered the preferred or first-line option for a majority of neonates and may be a more cost-effective option when compared with surgical ligation. COX inhibitors themselves represent a small percentage of total expenses (overall 2.0%-5.0%) associated with PDA.[1] Medical therapy consists of indomethacin and ibuprofen, COX inhibitor agents that have similar efficacy measures in the treatment of PDA.[7,8,21-33] However, clinical data suggest a difference in safety profiles between the COX inhibitor agents for PDA as they pertain to renal,[8,22,24,25,27,29-33,38-41] mesenteric,[24,29,38-40,42,43] and other[44] effects. There may also be a difference between the agents in terms of hospital resources used or associated measures, such as hospital or NICU LOS or days on ventilator therapy.[8,30] If prospective pharmacoeconomic analyses determine that differences in outcomes exist and are attributable to differences in the COX inhibitor agents' safety profiles, then there may be important safety, resource and expenditure considerations when determining the appropriate medical treatment of PDA. Thus, the opportunity remains to assess the impact of ibuprofen lysine's improved safety profile on LOS and resource use—areas that warrant continued research.

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