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Outcome Of Two Prophylactic Treatment Choices For Patent Ductus Arteriosus In A Neonatal Intensive Care Unit

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Abstract

Prophylactic treatment of patent ductus arteriosus (PDA) in premature infants with indomethacin (INDO) or ibuprofen (IBU) has been shown to be effective in decreasing rescue medical and surgical treatment rates. However, routine use of prophylactic treatment remains controversial due to potential for adverse effects from the pharmacologic treatment. We compared the outcome and adverse effects of three different PDA treatment practices used sequentially in a level 3C neonatal intensive care unit (NICU). We conducted a retrospective case control study on infants born at less than 28 weeks gestational age between January 2005 and September 2009. We compared PDA prophylactic treatment with INDO (n=20) and IBU (n=60) to a control group of no prophylactic treatment (n=59). There was a statistically significant decrease in the frequency of PDA rescue treatment associated with both methods of PDA prophylaxis (p <0.0001, control 63%, INDO 20%, IBU 17 %). The rate of PDA ligation decreased significantly only in the comparison of IBU to control (p=0.04) (control 27%, INDO 30%, IBU 12%). The frequency of any intestinal perforation was significantly higher only in the INDO group (p=0.03) compared to the control group, (control 8%, INDO 30%, IBU 15%).Results illustrate how a choice of a prophylactic pharmacologic agent for PDA can alter outcomes (in this case the incidence of perforation) in an individual NICU.

Key Words: Ibuprofen, Indomethacin, Intestinal perforation, Patent ductus arteriosus, Prophylaxis

INTRODUCTION

The contribution of hemodynamically persistent ductus arteriosus (PDA) in preterm infants to the development of significant clinical consequences associated with prematurity including development of chronic lung disease, intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) is presumed and is debated. The timing and proper type of treatment for PDA is still being investigated and is controversial. Prophylactic treatment with indomethacin (INDO) or ibuprofen (IBU) was reported to be effective in decreasing the need for subsequent rescue pharmacologic treatment and surgical ligation. Prophylactic treatment with INDO was also associated with a decrease in the rate of severe IVH, but failed to show improvement in mortality or 18 month neurosensory impairment. However, surgical PDA ligation was found to be associated with an increased risk for compromised neurodevelopmental outcome compared to medical (supportive) and pharmacologic treatments in a recent retrospective analysis of data from large number of infants.

The neonatologist in our neonatal intensive care unit (NICU) did not use prophylactic PDA treatment since there was no compelling evidence that such intervention would improve neurodevelopmental outcome of very low birth weight infants, less than 1500 grams, and (VLBW) infants. However, during this time period, a quality improvement data evaluation at the study site revealed an increased incidence of surgical ligations for treatment of PDA. Prophylactic PDA treatment protocol using INDO was introduced in the Neonatal Intensive Care Unit (NICU) in September 2006 with an aim to reduce the rate of PDA ligation. Practicing neonatologist initially chose INDO for prophylactic treatment because of its potential additional benefit of reducing the incidence of IVH. Six months after the introduction of the initial protocol (April 2007), prophylactic treatment was changed from INDO to IBU due to the perceived increase in the rate of intestinal perforations with INDO. We compared the short term outcomes associated with shifts in our NICU's choices for pharmacologic prophylactic treatment of PDA. We previously reported on effect of prophylactic PDA treatment with INDO on the utilization of hospital resources by analyzing data from part of the population in this study.

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MATERIALS AND METHODS

This was a retrospective cohort study of infants cared for in the level 3C NICU at the University of Michigan Health System (UMHS). The institutional review board approved the study and waived the need for informed consent. We collected data from medical records of the patients included in the analysis. We included a cohort of infants who received pharmacologic PDA prophylactic treatment and a control cohort prior to the implementation of the PDA prophylaxis protocols that were matched for patient characteristics used to establish eligibility for PDA prophylaxis. Infants with gestational ages less than 28 weeks who were born at or transported to the UMHS on their first day of life, survived more than two days and were born between January 2005 and September 2009 (n=139) were included in the study. We compared PDA prophylactic treatment with INDO (September 2006 to April 2007, n=20) or IBU (June 2007 to September 2009, n=60) to a control group of no prophylactic treatment (January 2005 to August 2006, n=59). The PDA in the treatment groups and 95% of the controls who received rescue pharmacologic treatment was diagnosed with an echocardiogram.

Infants less than 28 weeks of gestation were candidates for prophylactic PDA treatment regimen within 6 hours of life if they were inborns and within 12 hours if they were out born. However, some out born infants prophylactic treatment started within the first 24 hours of life (these were also included in the analysis). Infants with suspected bleeding diathesis, platelet count less than 50,000/mL at the time of treatment, ductal dependent congenital heart disease, or a known major renal anomaly or dysfunction did not receive prophylactic PDA treatment. Infants from the prophylactic and control groups where the treating neonatologists considered the PDA to be hemodynamically

Table I: Patient demographics

* Comparing the indomethacin and control groups, ‡ Comparing Ibuprofen and control groups, SGA=small for gestational age

	No prophylaxis (Control) N=59	Indomethacin Prophylaxis (INDO) N=20	Ibuprofen Prophylaxis (IBU) N=60	P* INDO-CONT	P‡ IBU-CONT
Gestational age, weeks, mean (SD)	25.7 (1.2)	25.9 (1.2)	25.6 (1.2)	0.605	0.674
Birth weight, grams, mean (SD)	838 (198)	964 (247)	864 (227)	0.024	0.518
SGA, n (%)	8 (14%)	1 (5)	8 (13)	0.435	1.000
Male, n (%)	28 (47)	10 (50)	33 (55)	1.000	0.465
Inborn, n (%)	49 (83)	15 (75)	53 (88)	0.512	0.444
White, n (%)	37 (63)	12 (60)	48 (80)	1.000	0.044
Prenatal steroid, n (%)	43 (73)	15 (75)	51(85)	1.000	0.120
C-Section delivery, n (%)	45 (76)	10 (50)	47 (78)	0.047	0.829

Table II: Intervention and outcome variables

LOS= hospital length of stay

* Comparing the indomethacin and control groups, ‡ Comparing Ibuprofen and control groups

PDA=Patent ductus arteriosus, NEC=Necrotizing enterocolitis, CLD=Chronic lung disease, ROP=retinopathy of prematurity

	No prophylaxis (Control) N=59	Indomethacin Prophylaxis (INDO) N=20	Ibuprofen Prophylaxis (IBU) N=60	P* INDO-CONT	P+ IBU-CONT
PDA rescue treatment, n (%)	37 (63)	4 (20)	10 (17)	0.001	<0.000
PDA Ligation, n (%)	16 (27)	6 (30)	7 (12)	0.781	0.038
Age of PDA ligation, days, Mean (SD)	23 (18)	20 (9)	19 (19)	0.941	0.253
Hospital mortality, n (%)	14 (24)	3 (15)	12 (20)	0.537	1.000
Ventilator days, mean (SD)	33 (31)	32 (28)	30 (26)	0.955	0.686
Postnatal treatment with steroids, n (%)	36 (61)	10 (50)	39 (65)	0.438	0.706
Intestinal perforation, n (%)	5 (8)	6 (30)	9 (15)	0.026	0.394
Abdomen surgery, n (%)	5 (8)	6 (30)	10 (17)	0.026	0.269
NEC, n (%)	8 (14)	4 (20)	10 (17)	0.487	0.799
Late onset sepsis, n (%)	27 (46)	7 (35)	32 (53)	0.444	0.465
Severe IVH, n (%)	10 (17)	5 (25)	12 (20)	0.512	0.814
CLD 36wks, n (%)	21 (36)	7 (35)	21 (35)	1.000	1.000
ROP surgery, n (%)	8 (14)	3 (15)	16 (27)	1.000	0.109

significant after the first day (first 24 hours) of life were treated with rescue intravenous course of INDO or IBU. All infants in the control group received rescue pharmacologic PDA treatment with intravenous INDO. If rescue treatment was needed for infants who received IBU or INDO prophylaxis, IBU rescue treatment was used. Infants with hemodynamically significant PDA who did not respond to the rescue treatment or those who had contraindications to rescue treatment underwent PDA surgical ligation. Physical findings such as murmur, increased pulse pressure and pulmonary hemorrhage in association with worsening respiratory failure and hypotension were considered as clinical findings suggestive of hemodynamically significant PDA.

Prophylactic intravenous INDO treatment course included 0.2 mg/kg first dose and 0.1mg/kg second and third doses, administered no less than 12 hours apart if the infant did not have contraindications to the subsequent doses. Prophylactic intravenous IBU treatment courses included 10 mg/kg first dose and 5 mg/kg second and third doses, administered no less than 24 hours apart if the infant did not have contraindications to the subsequent doses. The control group received intravenous INDO for PDA rescue treatment (0.2 mg/kg for the first dose and 0.2-0.25 mg/kg for second and third doses, depending on postnatal age at time of treatment, administered no less than 12 hours apart). The INDO and the IBU groups received intravenous IBU for PDA rescue treatment using the same prophylactic IBU dosing regimen described above. These dosing regimens are used as standard of care on our unit and are in common use. 6, 7, 10 Contraindications for subsequent IBU or INDO dosing included overt bleeding, platelet count less than 50,000/ml, NEC, intestinal perforation, urine output less than 0.5 mL/kg/hr, and serum creatinine greater than 1.8 mg/dL. Ibuprofen intravenous infusions were given over 15 minutes and Indomethacin intravenous infusions were given over 20 minutes in the NICU. Umbilical arterial lines were not used to infuse these medications. These PDA prophylaxis regimens did not include options for cross over between groups.

Infants with birth weights below the 10th percentile based on updated Babson and Benda's chart were considered small for gestational age (SGA). Infants were considered as having necrotizing enterocolitis (NEC) if they had radiographic evidence of NEC as described in Bell stage 2 and or if they had intraoperative or specimen histology findings suggestive of NEC. Infants with radiographic evidence of extra-luminal peritoneal air but who did not meet the definition of NEC were considered as having spontaneous intestinal perforation. Infants with blood culture proven infections were considered as having sepsis. Infants reported to have grade 3 or 4 IVHs on the Papile's scale were defined as having severe IVH.

When stress hydrocortisone dose was used to treat pressors resistant hypotension associated with presumed adrenal insufficiency, a dose of 0.45 mg /m2/day divided every 6 hours for 8 doses was used. This was followed by a maintenance dose of 15mg/m2/day divided every 6 hours for variable time lengths dependent on the degree of hypotension.

Statistical methods

We hypothesized that the shifts in choices of pharmacologic prophylactic PDA treatment was associated with variation in the rate of PDA ligation and the rate of intestinal complication in the studied population. Data analyses involved both continuous and dichotomous variables. Fisher Exact and Mann Whitney tests were used to compare the IBU and INDO groups separately to the control group. A p-value of < 0.05 was used to identify statistically significant differences between groups for each variable of interest.

RESULTS

One hundred and thirty nine patients met the study criteria, 59 received no prophylactic treatment (control group), 20 received INDO prophylactic treatment (INDO group) and 60 received IBU prophylactic treatment (IBU group). Patient characteristics are presented in Table I. Infants in the INDO group had a higher birth weight compared to control group. The IBU group had a higher percentage of white infants than the control group. The groups differed in the rate of operative birth, with lowest rate (50%) in the INDO group. There was a statistically significant decrease in the frequency of PDA rescue treatment associated with both groups using PDA prophylaxis (Table II). The rate of PDA ligation significantly decreased only in IBU group when compared to the control group. The frequency of any intestinal perforation and the need for abdominal surgeries were significantly higher in the INDO group compared to the control group (15 vs. 8% and 18% vs. 8%).

There was no statistically significant difference between any of the treatment groups and the control group in the frequency of death, postnatal treatment with corticosteroids, sepsis, severe IVH, chronic lung disease or duration of support with mechanical ventilation.

DISCUSSION

We undertook this study to evaluate our unit practices and potential complications associated with routine PDA pharmacologic prophylaxis treatment. In this study, prophylactic PDA treatment with either INDO or IBU was associated with decreased frequency of rescue PDA treatment. The INDO practice was associated with a significantly higher frequency of intestinal perforations and need for abdominal surgeries in the present study. Our report of an increased rate of intestinal perforation with INDO prophylaxis is different from those reported in randomized controlled trials (RCT) and it adds to the findings of other investigators who demonstrated a similar association using similar, retrospective study designs in VLBW infants.

Ibuprofen prophylaxis was associated with a significantly lower rate of PDA ligations compared to infants in the control group. We consider this outcome difference between these two practices important because PDA ligation was identified as an independent risk factor for compromised neurodevelopmental outcome in VLBW infants. We cannot fully explain observed decrease in PDA surgical ligation with IBU prophylaxis (but not INDO prophylaxis). The sample size of this study limits further subgroup analysis, but we speculate that the increased incidence of intestinal complications in the INDO group might have disqualified infants with hemodynamically significant PDA from candidacy for further rescue pharmacologic treatment. There were no major changes in feeding practices introduced in the NICU over the period of this data analysis. Other investigators, Su et al, who described fewer side effects associated with intravenous ibuprofen compared to intravenous indomethacin in a controlled PDA treatment study discussed potential differences in mechanisms of actions contributing to these observed differences in outcome .

Discrepancy between findings of observational studies and RCTs or meta-analysis can exist for multiple reasons. Most RCTs are underpowered to detect differences in secondary outcome variables. More importantly, large RCTs and meta-analyses by design seek “generalizable” truth under controlled or uniform environments. A potential risk of this approach is the failure to recognize variability in outcomes that inevitably occurs because of the inherent variability in practice, population being studied (efficacy of cyclooxygenase inhibitors depends on gestational age), and cultural and environmental differences that exists between intensive care units. Although there were methodological limitations in detecting abdominal complications associated with IBU or INDO prophylactic treatment , these trials were large enough suggesting the existence of unique risk factors in the study site influencing the observed difference in outcome variables with diverse etiologies and multifactorial pathophysiology (like abdominal complications) reported in this study. Reviewing unit specific outcome variables is an integral part of quality improvement. Such a review is necessary in an effort to transform scientific “evidence” to unit specific practices. This can lead to better neonatal outcomes, as exemplified in this report.

CONCLUSION

Although this study is limited by its retrospective method in a single center and the inclusion of a small number of patients, its results illustrate how a shift in the choice of a prophylactic pharmacologic agent for PDA can alter outcomes (in this case the incidence of intestinal perforation) in an individual NICU. Other NICUs can use similar methods to monitor their local outcome data for implementation of potentially better clinical practices if they choose to use such a prophylactic treatment that has unproven long term benefits.

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