



A Clinical Risk Model for Spontaneous Intestinal Perforation during Patent Ductus Arteriosus Medical Treatment for Very Low Birthweight Infants

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Abstract

Introduction: Spontaneous Intestinal Perforation (SIP) is one of the most concerning complication of PDA treatment in VLBW infants with a relative lack of studies quantifying the risk factors.

Objective: To create a predictive risk model for SIP, which will assist in weighing the pros and cons of PDA treatment in VLBW infants.

Methods: A retrospective cohort study of VLBW infants comparing SIP infants with non-SIP controls was conducted to obtain significant risk factors. The impacts of SIP in terms of mortality, BPD, IVH and ROP were assessed.

Results: The 389 VLBW infants were included, with a 2.3% incidence of SIP. Risk factors for SIP were lower gestations, higher need for resuscitation at birth, hypotension, PDA medication and culture proven late onset sepsis.

A clinical risk model was created to assess PDA treatment risk. If VLBW babies were not medically treated with intravenous ibuprofen, the risk of SIP was completely precluded. However, if PDA medications were started, the use of Hosmer and Lemeshow testing created a risk model incorporating the 4 risk factors of gestation, hypotension, culture proven sepsis and extensive resuscitation. An AUROC of 90.4% was achieved.

If a PDA is medically treated with intravenous ibuprofen, the presence of 2 or more of the 4 risk factors will render the risk high at more 10%. A clinical risk prediction score model derived can also be developed, with risk scores of 100 or less as low risk, 101 to 125 assigned as moderate risk and above 125 as high risk.

Amongst infants with SIP, mortality was 44.4% and SIP was associated with BPD requiring postnatal steroids, IVH, severe IVH and cholestasis. No association was found with ROP.

Conclusion: SIP is a complication of PDA medical treatment associated with high risk of mortality and morbidities. Risk modeling based on VLBW infants who were given PDA medications, and using the 4 major risk factors of gestation, hypotension, extensive resuscitation and culture proven sepsis, can help inform the clinical decision on whether to proceed with treatment.

Keywords: Neonatal department; Birthweight; Infants

Abbreviations

SIP: Spontaneous Intestinal Perforation; PDA: Patent Ductus Arteriosus; VLBW: Very Low Birth Weight; SGH: Singapore General Hospital

Introduction

The treatment of patent ductus arteriosus in premature infants remained an area of controversy, not least because there remained significant concerns about the side effects of medical treatment [1,2]. One of the most concerning complication associated with medical treatment of PDA was Spontaneous Intestinal Perforation (SIP).

The entity was initially found in premature babies exposed to postnatal steroids and indomethacin,

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but in recent years, with the reduction in use of postnatal steroids, the risk factors had changed. Due to its relative uncommon incidence and also the lack of studies looking into risk factors for SIP, particularly in recent times, it was difficult for clinicians to weigh the exact risks of medical treatment for PDA.

We aimed to create a clinical predictive rule model for SIP among Very Low Birthweight (VLBW) infants by assessing the risk factors of SIP. In addition, we assessed the clinical impact by reviewing the adverse outcomes associated with SIP. It is hoped that with a clearer view towards the risk associated with medical treatment of PDA, the clinician could be assisted to better weigh the pros and cons of medical treatment in VLBW infants.

Methods

Retrospective cohort study of all very low birth weight infants was conducted in a single tertiary NICU. Inclusion criteria were all Very Low Birthweight (VLBW) infants admitted to the NICU, defined as birthweight less than 1,500 grams. The study was conducted on infants admitted between August 2012 and February 2019.

The primary goal was to formulate a clinical risk model combining all known significant risk factors for SIP in VLBW infants, particularly in the context of PDA treatment. Comparison was made between SIP and non-SIP patients to obtain significant risk factors before the perforation. The factors reviewed included Apgar scores, resuscitation interventions, hypotension, sepsis and Patent Ductus Arteriosus (PDA) medical treatment. All patients treated medically for PDA were given intravenous ibuprofen. Extensive resuscitation was defined as requiring intubation, chest compression and/or medications. Hypotension was defined as blood pressure mean arterial pressure less than gestation and requiring treatment either by fluid boluses or inotropes. Culture proven sepsis was defined as blood culture positive and requiring appropriate antibiotics treatment. SIP was diagnosed by histological report from tissue samples sent during laparotomy. Outcomes associated with SIP were assessed, including mortality, Intraventricular Hemorrhage (IVH), Retinopathy of Prematurity (ROP), Necrotizing Enterocolitis (NEC) and Bronchopulmonary Dysplasia (BPD).

Definitions

Bronchopulmonary Dysplasia (BPD) was diagnosed as oxygen dependence at 28 days and classified by the NICHD criteria into mild, moderate and severe at post menstrual age of 36 weeks [3]. Intraventricular hemorrhage was classified by Volpe classification, with grade 3 or intra-parenchymal echo densities classified as severe IVH [4]. Retinopathy of prematurity was classified based on the International Classification of Retinopathy of Prematurity (ICROP) [5].

Statistics

Chi-square test was used to assess significance in categorical variables and Mann Whitney U test was used for continuous variables. To generate a clinical prediction rule, we included variables if they were significant. To formulate the score if PDA medications were used, we summed 4 predictor variables; each multiplied by 10 times its logistic regression coefficient (to avoid decimals) and added 400 to the total (to avoid negative scores). We assessed goodness of fit by using the Hosmer-Lemeshow test and discrimination by using Area under the Receiver Operating Characteristic (AUROC) curve [6]. We performed analyses by using SPSS version 25.

Results

A total of 389 VLBW infants were included in the study. The incidence of SIP was 2.3% (n=9).

Table 1 summarized the risk factors for SIP in the study cohort. The significant risk factors found included gestation, birthweight, hypotension, medication for PDA, need for extensive resuscitation and culture proven sepsis. By running logistic regression, the odds ratio adjusted for gestation (aOR) for extensive resuscitation was 10.67 (95% CI 1.32-86.15), hypotension 16.35 (95% CI 3.32-80.46), PDA medications 1.07 (95% CI 1.03-1.13) and culture proven sepsis 4.78 (95% CI 1.15-19.92). In addition, further associations were found with hypotension requiring inotropes obtaining aOR 28.94 (95% CI 5.82-143.99, p<0.01). The incidence of SIP was as high as 77.8% in VLBW infants on PDA medications requiring inotropes, compared to only 10.8% if not on inotropes. Reviewing the entire cohort, if no PDA medication is given for a VLBW infant, there was no incidence of SIP at all.

As the medical treatment of PDA was a pre-requisite of all SIP cases, Table 2 was formed to show the impact of various risk factors on the risk of SIP. From the table, the presence of any 2 additional risk factors would increase the risk by a large margin to more than 10%.

Tables 3 and 4 demonstrated the complications associated with SIP. Namely, there were associations with mortality, IVH, severe IVH, BPD requiring post natal steroids and cholestatic liver disease.

As mentioned earlier, if PDA medications were not used, SIP was completely precluded. Hence, clinical risk modeling was performed only on babies who were given PDA medications. Multiplying the

Table 1: Risk factors for SIP.

| Risk factors | Non SIP | SIP | p value |
|---|----------------|-------------|---------|
| Male (%) | 197/380 (51.8) | 5/9 (55.6) | 0.83 |
| Gestation age, median | 29 | 24 | <0.01 |
| 5 min APGAR <6 (%) | 28/377 (7.4) | 2/9 (22.2) | 0.1 |
| Birth weight, median in g | 1093 | 715 | <0.01 |
| Small for gestational age (%) | 268/375 (20.6) | 0/9 (0) | 0.06 |
| Culture or histological proven chorioamnionitis (%) | 44/351(12.5) | 3/9 (33.3) | 0.07 |
| Extensive birth resuscitation needed (%) | 159/371 (42.9) | 8/9 (88.9) | <0.01 |
| Hypotension (%) | 67/380 (17.6) | 7/9 (77.8) | <0.01 |
| PDA treated medically (%) | 122/380 (32.1) | 9/9 (100.0) | <0.01 |
| Culture proven sepsis (%) | 36/380 (9.5) | 3/9 (33.3) | <0.05 |
| Antenatal abnormal Doppler's (%) | 45/351 (12.8) | 1/9 (11.1) | 0.88 |
| Fetal distress (%) | 57/351 (16.2) | 0/9 (0.0) | 0.19 |
| Meconium stained liquor (%) | 10/380 (2.6) | 0/9 (0.0) | 0.62 |

Defined as requiring intubation, ECM or medications

Table 2: Risk factors for SIP assuming treatment of PDA medically in this VLBW cohort.

| Resus | Hypotension | Late onset culture proven sepsis | SIP incidence (%) |
|-------|-------------|----------------------------------|-------------------|
| + | + | - | 15 |
| + | + | + | 15.4 |
| - | + | + | 14.3 |
| + | - | - | 3 |
| - | + | - | 9.9 |
| + | - | + | 12.5 |

Table 3: Outcomes associated with SIP.

| | OR (95% CI) |
|-----------------------------------|--------------------|
| Death | 10.62 (2.69-41.94) |
| Moderate-severe BPD | 2.74 (0.72-10.41) |
| BPD requiring post natal steroids | 9.01 (2.30-35.27) |
| IVH | 6.67 (1.74-25.55) |
| Severe IVH ^{**} | 5.09 (1.22-21.26) |
| Severe ROP ^{***} | 1.94 (0.23-16.18) |
| ROP requiring laser | 3.43 (0.40-29.51) |
| Cholestasis | 12.69 (3.18-50.63) |

^{**}Grade 3 IVH or IPE

^{***}ROP stage 3-5

Table 4: Mortality and morbidities among infants with SIP.

| Outcome measures | Prevalence |
|-----------------------------------|------------|
| Mortality | 44.40% |
| BPD requiring post natal steroids | 44.40% |
| Severe IVH (grade 3 or worse) | 33.30% |
| IVH (any grade) | 55.60% |
| Cholestatic jaundice | 44.40% |

logistic coefficients by 10 and adding 400 as previously described, incorporating the risk factors of gestational age, hypotension, extensive resuscitation and hypotension, resulted in the following equation for the score, where the presence of the risk factor would be coded as 1 and absence as 0:

Clinical risk score = (7.5 × hypotension) + (13.7 × extensive resuscitation) + (2.4 × culture proven sepsis) – (11.9 × gestation in weeks) + 400.

The discrimination and fit of the predictive model using the generated score was excellent. Hosmer-Lemeshow chi-square test (8 degrees of freedom) was 1.89 (p=0.984) with the ability to discriminate 92.4% of cases. The AUROC for this predictive model was 0.904 (95% CI 0.837-0.972) (Figure 1). An incremental of the risk scores against the probability of SIP was shown (Figure 2).

Discussion

Spontaneous intestinal perforation risk is approximately 2% to 3% in VLBW infants [7,8]. Unfortunately, other than prematurity being the only well-established risk factor, other risk factors were uncertain. SIP risk factors data were mainly based on either case series or a single data set from the Pediatric Medical Group, based on a retrospective study done between years 1998 to 2000 [9,10].

In a meta-analysis of 4 studies using early postnatal steroids for Bronchopulmonary dysplasia, it was found that there was significantly higher risk of SIP in extremely low birthweight infants exposed to early postnatal steroids [11]. The combined use of both indomethacins with early postnatal steroids in VLBW infants may pose a higher risk for spontaneous intestinal perforation. Some had coined this as the “double hit” hypothesis [12]. The roles of other risk factors were less certain. For instance, some publications found an association with maternal chorioamnionitis, while others did not [13].

Since the early 2000s, the use of postnatal steroids had undergone major decline after concerns were raised about the possible adverse impact on future neurodevelopment [14]. In addition, the medical

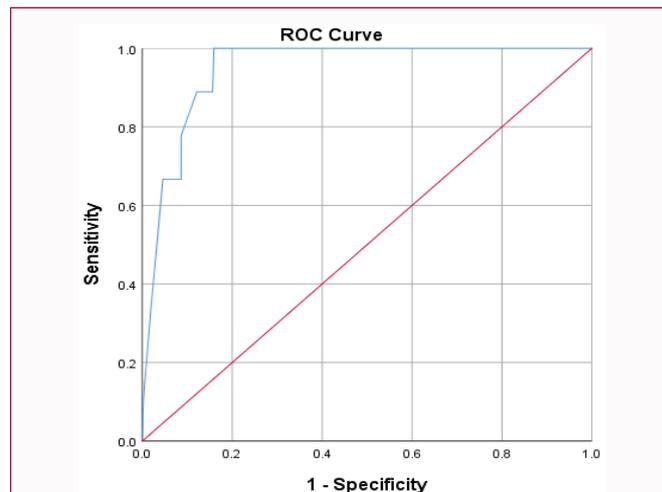


Figure 1: Receiver Operator curve for clinical risk score. Clinical risk score = (7.5 × hypotension) + (13.7 × extensive resuscitation) + (2.4 × culture proven sepsis) – (11.9 × gestation in weeks) + 400

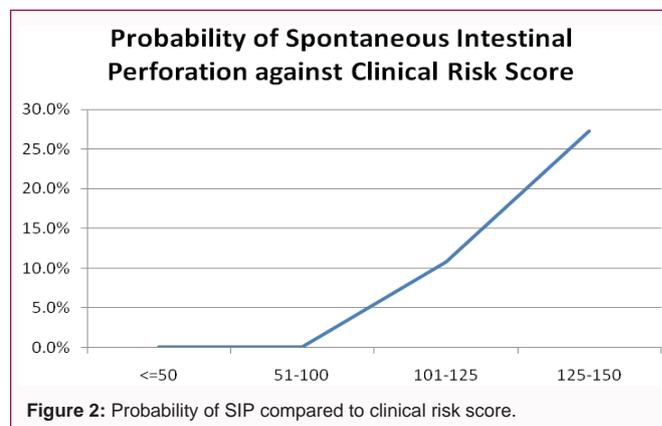


Figure 2: Probability of SIP compared to clinical risk score.

management of Patent Ductus Arteriosus (PDA) had also undergone significant shifts due to the recognition that there may be “treatment paradox”, in that closure of PDA did not seem to improve major neonatal morbidities and even mortality [15]. These shifts in management philosophy may have significantly changed the risk factors for SIP, or at least the magnitude of their importance, in the current era, making it necessary to relook at these risk factors.

In our study cohort, we reviewed the risk factors for SIP in the current management era. The incidence of SIP was consistent with the literature, at 2.3%. We were able to review a comprehensive number of risk factors associated with SIP. Although 6 major significant risk factors were found, namely gestation, birthweight, extensive resuscitation, hypotension, culture proven sepsis and PDA medical treatment, there was also an interesting trend towards significance of the factors of histological or culture proven chorioamnionitis (p=0.07). Furthermore, there was also a trend towards significance for small for gestational age infants, although, paradoxically, this was found to be protective (p value 0.06). We could not find any literature associating small for gestational age with SIP, although there were literature on its association with Necrotizing Enterocolitis (NEC) and NEC induced perforation. The risk factors for SIP found were supportive evidence that the underlying pathophysiology of SIP and NEC was different [16].

One of the interesting finding was that all SIP cases had PDA

medications prior to the event, or conversely non-exposure to PDA medications completely precluded development of SIP. Hence, we built our clinical risk score based on subjects who had PDA medications before. Reviewing VLBW infants requiring PDA medications, 4 risk factors were identified, namely gestation, hypotension, extensive resuscitation and culture proven sepsis. Hypotension had an adjusted for gestation Odd Ratio of (aOR) 16.35, and this further increased if use of inotropes was required to aOR of 28.94, an odds ratio which was the highest among risk factors for SIP. The magnitude of the odds ratio was followed by extensive resuscitation (aOR 10.67) and finally culture proven sepsis (aOR 4.78).

Although the indication of medical closure of PDA remained controversial, and may vary between centers or even among clinicians, the risk of adverse impact of medical treatment is real, and we felt our study could contribute towards addressing this side of the equation. SIP is one of the most feared complications known to be associated with PDA medication use, and in our study, among those who developed SIP, the risk of mortality was more than 40%, and a third had severe IVH.

Looking through the clinical risk score itself, those with a clinical risk score of 100 or less had minimal risk of SIP. Those with scores between 101 to 125 had a risk of 10.7% for SIP, which was approximately a 4 fold rise above baseline incidence, a figure we considered to be of moderate risk. For scores of above 125, the risk was 27.3%, a figure we considered to be high risk. The AUROC for this prediction model was excellent at 0.904.

In a large NICHD study, the mortality till discharge for surgically treated NEC was 54% compared to SIP at 39% [17]. In our cohort, the mortality was 44% among SIP infants, comparable to these international studies. However, it was notable that among the SIP subgroup, the risks of significant morbidities, namely BPD requiring steroids, severe IVH or severe ROP were very high (Table 3). In the literature, SIP and surgical NEC appeared to have similar risks for death or neurodevelopmental impairment. In the same NICHD cohort, the risks of death or neurodevelopmental impairment were 82% for surgical NEC, and 79% for SIP. Most literature had identified both surgical NEC and SIP to be similarly high risk groups for neurodevelopmental impairment [17,18].

Limitations

This model needs to be validated prospectively. In addition, the study was single centre, and due to relatively uncommon incidence of SIP it was conducted over a relatively longer time period and the sample size was small. For instance, if a larger sample size was obtained, we may have found significant association with chorioamnionitis. In addition, all PDA medical treatment was only with intravenous ibuprofen. We welcome external validation of our study results in other centers.

Conclusion

SIP is a complication of PDA medical treatment associated with high risk of mortality and morbidities. Risk modeling based on VLBW infants who were given PDA medications, and using the 4 major risk factors of gestation, hypotension, extensive resuscitation and culture proven sepsis, can help inform the clinical decision on whether to proceed with treatment.

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