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ABSTRACT

Introduction Patent ductus arteriosus (PDA) is the most common cardiovascular problem that develops in preterm infants and evidence regarding the best treatment approach is lacking. Currently available medical options to treat a PDA include indomethacin, ibuprofen or acetaminophen. Wide variation exists in PDA treatment practices across Canada. In view of this large practice variation across Canadian neonatal intensive care units (NICUs), we plan to conduct a comparative effectiveness study of the different pharmacotherapeutic agents used to treat the PDA in preterm infants.

Methods and analysis A multicentre prospective observational comparative-effectiveness research study of extremely preterm infants born <29 weeks gestational age with an echocardiography confirmed PDA will be conducted. All participating sites will self-select and adhere to one of the following primary pharmacotherapy protocols for all preterm babies who are deemed to require treatment.

1. Standard dose ibuprofen (10 mg/kg followed by two doses of 5 mg/kg at 24 hours intervals) irrespective of postnatal age (oral/intravenous).
2. Adjustable dose ibuprofen (oral/intravenous) (10 mg/kg followed by two doses of 5 mg/kg at 24 hours intervals if treated within the first 7 days after birth. Higher doses of ibuprofen up to 20 mg/kg followed by two doses of 10 mg/kg at 24 hours intervals if treated after the postnatal age cut-off for lower dose as per the local centre policy).
3. Acetaminophen (oral/intravenous) (15 mg/kg every 6 hours) for 3–7 days.
4. Intravenous indomethacin (0.1–0.3 mg/kg intravenous every 12–24 hours for a total of three doses).

Outcomes The primary outcome is failure of primary pharmacotherapy (defined as need for further medical and/or surgical/interventional treatment following an initial course of pharmacotherapy). The secondary outcomes include components of the primary outcome as well as clinical outcomes related to response to treatment or adverse effects of treatment.

Sites and sample size The study will be conducted in 22 NICUs across Canada with an anticipated enrollment of 1350 extremely preterm infants over 3 years.

Analysis To examine the relative effectiveness of the four treatment strategies, the primary outcome will be compared pairwise between the treatment groups using χ^2 test. Secondary outcomes will be compared pairwise between the treatment groups using χ^2 test, Student's t-test or Wilcoxon rank sum test as appropriate. To further

Strengths and limitations of this study

- The study will establish the safety and effectiveness of commonly used patent ductus arteriosus (PDA) treatment options in a large contemporary patient cohort in Canada.
- Use of an innovative research design like comparative effectiveness research will make the conduct of such a large study feasible in a cost-efficient fashion.
- The study will examine clinical outcomes related to PDA treatment practices in the real world, which will inform future practice and reduce practice variability.
- The observational nature of the study increases the risk of bias from unmeasured confounding which will be partially accounted for by the proposed analyses strategies.

examine differences in the primary and secondary outcomes between the four groups, multiple logistic or linear regression models will be applied for each outcome on the treatment groups, adjusted for potential confounders using generalised estimating equations to account for within-unit-clustering. As a sensitivity analysis, the difference in the primary and secondary outcomes between the treatment groups will also be examined using propensity score method with inverse probability weighting approach.

Ethics and dissemination The study has been approved by the IWK Research Ethics Board (#1025627) as well as the respective institutional review boards of the participating centres.

Trial registration number NCT04347720.

BACKGROUND

The most common cardiovascular problem that infants born extremely preterm experience early in life is a patent ductus arteriosus (PDA).[1] Prolonged patency of the ductus arteriosus in extremely preterm infants is associated with longer duration of endotracheal mechanical ventilation, higher rates of death, chronic lung disease (CLD), necrotising enterocolitis (NEC), renal failure, intracranial haemorrhage and cerebral palsy.[1–7]

Currently available options to treat a PDA include cyclo-oxygenase inhibitor (COX-I) drugs such as indomethacin, ibuprofen or acetaminophen. Indomethacin and ibuprofen act by inhibition of the COX enzyme thereby leading to downregulation of PGE2, a potent relaxant of the PDA.[8] Recently, acetaminophen has also emerged as a potential treatment option for PDA closure. Acetaminophen is postulated to exert its action through inhibition of the peroxidase enzyme thereby leading to downregulation of PGE2 production.[9] If one course of medical therapy is ineffective in treating a PDA then clinicians may try a second (and sometimes a third) course of the same or a different medication. If the PDA still remains symptomatic, then surgical or interventional closure of the PDA is considered. Over 70 randomised clinical trials have been conducted to date to explore the efficacy of the available treatment options to treat a symptomatic PDA, the results of which have been summarised and updated on six Cochrane Neonatal reviews.[10–15] It has been shown that COX-I drugs are effective in closing a PDA compared with placebo.[16] Based on the earlier placebo-controlled trials, intravenous indomethacin was considered to be the gold standard for PDA treatment.[1 8 17] Subsequent randomised controlled trials (RCTs) suggest that ibuprofen appears to be as effective as indomethacin in closing a PDA while reducing the risk of NEC and transient renal insufficiency.[10] The dosage of ibuprofen used in these RCTs were consistent and was therefore referred to as standard dose ibuprofen (10 mg/kg followed by 2 doses of 5 mg/kg at 24 hours intervals).[10] Based on these studies, standard dose ibuprofen has been increasingly used as the first choice for treatment of a symptomatic PDA.

However, the generalisability of the results from the clinical trials and consequently the effectiveness of standard dose ibuprofen in real-world clinical practice remains controversial.[18] Systematic reviews of earlier RCTs using standard dose ibuprofen had shown that only 26%–29% of the treated infants fail primary pharmacotherapy.[10 16] However, a recent Canadian study by Dersch-Mills *et al*[19] showed that failure rate with the first course of ibuprofen was above 40%. Furthermore, the primary pharmacotherapy failure rate for ibuprofen in two recent RCTs comparing PDA treatment between 6–14 days versus expectant management were noted to be 57% (PDA-TOLERATE trial; Clyman *et al*) and 80% (Sung *et al*), respectively.[20 21] This observed difference in effectiveness is likely due to the fact that infants in previous RCTs were treated much earlier (median ~3 days) as compared with real-world practice as well as in the more recently conducted RCTs.[20–23] Such observations seem congruent with pharmacokinetic studies on ibuprofen dosage in premature infants. Hirt *et al*[24] showed that irrespective of gestational age (GA), increasingly higher doses are required with increasing postnatal age to achieve optimal concentrations of ibuprofen for successful PDA closure. One small RCT (n=70) (Dani 2012) compared high-dose intravenous ibuprofen versus standard dose and found a significant improvement in primary PDA closure rates without increased incidence of oliguria or NEC.[25] Similar results have been obtained with high dose oral ibuprofen in three other RCTs (Pourarian 2015 (n=60), Fesharaki 2012 (n=60) and Bagheri 2016 (n=129)).[26–28] In the systematic review and Bayesian network meta-analysis conducted by Mitra *et al*,[16] it was found that higher doses of ibuprofen were associated with a higher likelihood of PDA closure vs standard doses of intravenous ibuprofen or intravenous indomethacin. However, the effect estimates were derived from the four small trials mentioned above which contributed only 157 infants for high dose ibuprofen out of a total sample size of 4256 infants thereby lowering the confidence in these estimates. Furthermore, the mean GA of included infants in 3 out of the above 4 trials were 30 weeks or more.[26–28] Therefore, the effectiveness and safety of high-dose ibuprofen in extremely preterm infants (<29 weeks GA) is largely unknown precluding its universal adoption. The controversy around pharmacotherapeutic practices is evident from the wide practice variation across Canada. A survey conducted specifically to inform this project, through the Canadian Neonatal Network (CNN) in 2019 identified that 56% of the centres (14/25 respondents) use standard dose ibuprofen while 32% (8/25) use higher doses of ibuprofen.

Controversy also exists on whether treatment of a PDA actually improves clinical outcomes. Previous observational studies on PDA treatment trends in Canada show that with conservative management strategies, clinical outcomes are significantly better.[29] However, residual confounding cannot be completely ruled out in these studies. For example, in a recent study comparing

PDA management outcomes in Canada and Japan by Isayama *et al*,[30] review of 6981 very low birth weight infants (birth weight <1500 g) across CNN centres showed that infants treated conservatively were more mature (mean GA 27.4 (±2.1) vs 25.6 (±1.7) weeks), had higher birth weight (mean birth weight 1019 (±257) vs 832 (±208) g) and were clinically more stable at birth (% of infants with Apgar score <7 at 5 min 33% vs 41%) compared with infants who received pharmacotherapy and then went on to receive surgical PDA ligation. Therefore, whether non-treatment of PDA across all extremely preterm gestations irrespective of PDA size is the right approach remains questionable, which in turn leads to large practice variation.

Based on the variation in practice with respect to PDA treatment across Canadian neonatal intensive care units (NICUs), our primary objective in this study is to compare the different pharmacotherapeutic practices aimed at closure of PDA and evaluate their impact on clinical outcomes in extremely preterm infants (<29 weeks GA). Our secondary objective is to understand the relevance of PDA treatment with respect to patient-important clinical outcomes.

Specific aims

1. To compare the relative effectiveness of commonly used pharmacotherapeutic agents in extremely preterm infants (<29 weeks GA) requiring treatment for PDA in achieving successful PDA closure.
2. To evaluate the relative safety of commonly used pharmacotherapeutic agents in extremely preterm infants (<29 weeks GA) requiring treatment for PDA on patient-important clinical outcomes.
3. To understand the clinical relevance of PDA treatment by comparing clinical characteristics and outcomes of extremely preterm infants (<29 weeks GA) treated for a PDA versus (1) a control group of extremely preterm infants (<29 weeks GA) who were diagnosed with but never treated for a PDA; (2) a reference group of extremely preterm infants (<29 weeks GA) not diagnosed with a PDA.

Study hypotheses

(1) In preterm neonates <29 weeks GA with a PDA, use of adjustable dose ibuprofen (as compared with standard dose ibuprofen or acetaminophen or indomethacin) is associated with higher PDA closure rate and lower need for repeat medical treatment or surgical PDA closure without increasing adverse effects; (2) Preterm infants <29 weeks GA, treated for PDA, have improved clinical outcomes compared with infants with similar clinical and PDA characteristics who did not receive treatment; (3) Preterm infants <29 weeks GA, receiving PDA treatment have similar clinical outcomes compared with infants with similar clinical characteristics not diagnosed with PDA.

METHODS

Study design

Multicentre prospective observational comparative-effectiveness research (CER) study planned to be conducted over 3 years (January 2020 to December 2022).

Proposed study participants

All infants born at less than 29 weeks of gestation admitted to participating sites will be included in the study. For aims (1) and (2), the population of interest will be those preterm infants<29 weeks gestational age (including outborns) with echocardiography confirmed PDA who will be treated according to attending team. For aim (3, i) infants <29 weeks GA with echocardiography-confirmed PDA but never received treatment will be included as the control population. For aim (3, ii), infants <29 weeks GA who were never diagnosed with PDA will be included as the reference population. Infants who received prophylactic COX-I drugs in the first 24 hours after birth for prevention of intraventricular haemorrhage will be included. Any infant who received pharmacotherapy for a clinically symptomatic PDA without prior echocardiographic confirmation of the presence of PDA will be excluded from all analyses.

Interventions

Each site will choose one of the following four interventions as their initial pharmacotherapy for infants requiring PDA treatment:

1. Standard dose ibuprofen (10 mg/kg followed by 2 doses of 5 mg/kg at 24 hours intervals) irrespective of postnatal age (oral/intravenous).
2. Adjustable dose ibuprofen [Oral/intravenous) (10 mg/kg followed by two doses of 5 mg/kg at 24 hours intervals if treated within the first 7 days after birth. Higher doses of ibuprofen up to 20 mg/kg followed by two doses of 10 mg/kg at 24 hours intervals if treated after the postnatal age cut-off for lower dose as per the local centre policy).
3. Acetaminophen (oral/intravenous) (15 mg/kg every 6 hours) for 3–7 days.
4. Intravenous indomethacin (0.1–0.3 mg/kg intravenous every 12–24 hours for a total of 3 doses).

Outcomes

The primary outcome is failure of primary pharmacotherapy (defined as need for further medical and/or surgical/interventional treatment following an initial course of pharmacotherapy). The secondary outcomes include components of the primary outcome as well as clinical outcomes that are related to response to treatment or adverse effects of treatment. The secondary outcomes are: (1) Receipt of second course of pharmacotherapy; (2) Surgical/interventional PDA closure; (3) CLD (defined as oxygen or respiratory support requirement at 36 weeks' postmenstrual age or at discharge)[31]; (4) NEC (stage 2 or greater)[32]; (5) Severe intraventricular haemorrhage (defined as Grade III-IV according to Papile Criteria)[33]; (6) Definite sepsis (clinical symptoms

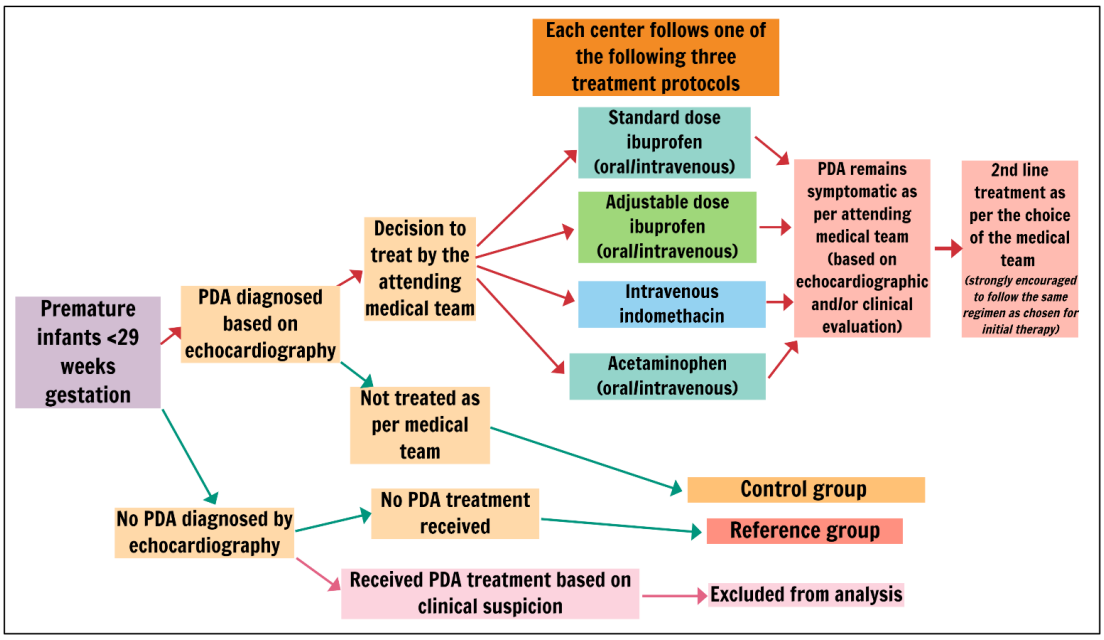

Figure 1 Study flow. PDA, patent ductus arteriosus.

and signs of sepsis and a positive bacterial culture in a specimen obtained from normally sterile fluids or tissue obtained at postmortem)[34]; (7) Stage 1 or greater AKI (according to the Neonatal AKI KDIGO classification)[35]; (8) Post-treatment serum bilirubin (maximum serum bilirubin (*u*Mol/L) within 1 week of initiation of each course of pharmacotherapy); (9) Maximum serum AST and ALT (u/L) during treatment or within 1 week of treatment completion; (10) All-cause mortality during hospital stay.

Study design and implementation

In this CER study, participating sites will self-select and adhere to any one of the above pharmacotherapy protocols for all preterm babies who are deemed to require treatment for a PDA (figure 1). Presence of a PDA on echocardiography prior to starting pharmacotherapy will be documented for an infant to be eligible. However, to mimic the real-world scenario, clinical and echocardiographic criteria for initiating treatment will be left up to the attending medical team. If the PDA is deemed to remain symptomatic after the first course of pharmacotherapy then a second course of treatment may be initiated at the discretion of the treating team. The choice of the second course of pharmacotherapy is at the discretion of the treating medical team. It is strongly encouraged that the second course of pharmacotherapy be with the same regimen as chosen for the initial pharmacotherapy. If after the second course of pharmacotherapy, the PDA is still deemed to be symptomatic, then the attending team will choose their further management plan that may include: a third course of pharmacotherapy with the same or a different medication, or surgical PDA ligation, or a third course of pharmacotherapy, followed by surgical ligation (if required) or no further treatment.

The participating centres will be allowed to continue the use of concomitant neonatal interventions such as use of prophylactic NSAIDs (non-steroidal anti-inflammatory drugs), prophylactic and rescue corticosteroids, blood product transfusion practices, enteral feeding practices including use of donor breast milk and probiotics as per their usual NICU policy. This information is collected as routine in the CNN database and will be compared between groups and any imbalances will be adjusted at the analyses stage.

Patient and public involvement in study design

No patient involved.

Sample size

Sample size estimation is based on the primary hypothesis and the primary outcome: proportion of infants with failure of primary pharmacotherapy. The best estimates of pharmacotherapy failure with ibuprofen reported in RCTs is between 26% and 29%.[10 16] However, data from Canadian observational studies suggest that in the real-world primary pharmacotherapy failure rate with ibuprofen is about 40%.[18 19] To reduce the pharmacotherapy failure rate from the current 40% to the best achievable reported rate of 26%, an absolute reduction of 14% (relative reduction of 35%) would be required. To detect a 14% absolute (35% relative) decrease in the rate pharmacotherapy failure for adjustable dose ibuprofen group compared with the other treatment groups with 80% power, we will require at least 263 infants in the adjustable ibuprofen group and 198 infants each in the remaining treatment groups (~850 infants total who receive PDA treatment). The two-sided significant level of 0.05 was used for the sample size estimation, adjusted for the multiple comparisons. In addition, we will collect baseline clinical and outcome data on 500 infants who will not receive PDA treatment (that includes the control

and reference groups) to make up a total sample of 1350 infants.

Statistical analysis

Since the proposed study is a comparative effectiveness study using prospective observational data, we will examine and account for potential confounders at the analyses stage. The analyses will be conducted in two stages: unit-level protocol effectiveness analysis and a secondary drug-dosage effectiveness analysis.

Unit-level protocol effectiveness analysis

In this analysis, the infants will be classified into four treatment groups (standard dose ibuprofen, adjustable dose ibuprofen, indomethacin and acetaminophen) as per their treatment protocol assignment irrespective of the actual dosage received.

Univariate analyses*:* We will first compare the baseline characteristics of neonates among the treatment groups using the χ^2 test for categorical variables and F test (one-way analysis of variance) or Kruskal-Wallis test as appropriate for continuous variables. The characteristic variables will include maternal variables (age, parity, hypertension, diabetes, receipt of antenatal steroids, magnesium sulphate), birth characteristics (mode of birth, birth outside a tertiary centre, presence of chorioamnionitis), resuscitation characteristics (need for extensive cardiopulmonary resuscitation) and infant characteristics (sex, small-for-gestational age, Apgar score at 5 min, SNAP (score for acute neonatal physiology) II score, receipt of surfactant, respiratory status at the time of treatment (mean airway pressure, fraction of inspired oxygen). To examine the relative effectiveness of the four treatment strategies, the primary outcome will be compared pairwise between the treatment groups using χ^2 test. The secondary outcomes will be compared pairwise between the treatment groups using χ^2 test, Student's t-test or Wilcoxon rank sum test as appropriate.

Multivariable logistic or linear regression: To further determine differences in the primary and secondary outcomes between the four groups, we will apply multiple logistic regression models for each outcome on the treatment groups, adjusted for potential confounders identified from the univariate analyses. To account for the clustering within units, the generalised estimating equations (GEE) method will be used for the regressions. We will also examine the variation of the relative effectiveness of the treatments between sex (or race) by including the interaction term between treatment and sex (or treatment and race group) in the multiple logistic regression model for the primary outcome. If the interaction term is significant, which indicates the relative effectiveness of the treatment varies between male and female (or race), subgroup analyses stratified by sex (or race) will be further conducted to assess the relative effectiveness of treatment for different sex (or race) if applicable.

Inverse probability weighted (IPW) analyses: As a sensitivity analysis for the study, we will also examine the difference in the primary and secondary outcomes between the treatment groups using propensity score method with IPW approach.[36] The generalised propensity score (GPS), that is, the conditional probability of receiving a particular level of treatment (standard dose ibuprofen, adjustable dose ibuprofen, acetaminophen or indomethacin), will be first estimated using a multiple multinomial logistic regression model for treatments (four level dependent variable) on covariates (independent variables) including all available baseline characteristics as mentioned above. As a second step, the multiple weighted logistic regression models for each outcome, where the weight is defined as the inverse of the GPS, will be used to examine the difference in the relative effectiveness between treatment groups or the association between the clinical outcomes and the treatments. The GEE approach will be applied for the regressions to account for the possible clustering within each NICU.

Secondary drug-dosage effectiveness analysis

If a substantial proportion of infants in the adjustable ibuprofen group are treated within the first 7 days then they would receive the same dosage as standard dose ibuprofen. Infants exposed to similar ibuprofen dosages are likely to have similar outcomes. Hence, any true difference in effectiveness between standard and higher doses of ibuprofen may be missed in the former analysis. As a secondary analysis, the infants will be grouped based on the actual dosage received during the first course of treatment, that is, standard ibuprofen dose, adjustable (higher) ibuprofen dose, acetaminophen and indomethacin. In other words, infants receiving treatment within the first 7 days in the adjustable ibuprofen group will be reclassified as standard ibuprofen patients if they receive standard doses of ibuprofen. The same analytical approach as described above, including the sub-group analyses, will be used to examine the relative effect of treatments on the primary outcome (secondary outcomes may be related to the entire treatment protocol rather than dosage of the first treatment course, hence will not be included in the secondary analysis). A two-sided $p<0.05$ will be considered statistically significant. We will use SAS V.9.4 (SAS Institute) and R V.3.4.446 for all analyses.

DISCUSSION

In spite of a large number of RCTs, the most effective and safe management of PDA in extremely preterm infants remains controversial. As various treatment strategies have become well established practices in respective centres, it would be challenging to conduct large RCTs to generate effectiveness and safety data without significant protocol violations. With our proposed CER study, we intend to analyse real-world data (defined as data generated during routine clinical practice) in a registry-based CER study.[37] This study also provides a unique opportunity to compare the clinical characteristics and outcomes of a reference group of extremely premature infants who

were not diagnosed with PDA versus the ones who were diagnosed and received treatment for PDA.

The study will be conducted using the principles of Hypotheses Evaluating Treatment Effectiveness research, which are designed to evaluate the presence or absence of a prespecified effect and/or its magnitude.[37] We will follow good practices for the design, analysis, and reporting of observational real-world data studies as outlined by the International Society for Pharmacoeconomics and Outcomes Research.[37] Data for the study will be collected using the CNN database. The CNN is a well-established patient registry that includes members from 31 hospitals and 17 universities across Canada.[31] The Network maintains a standardised NICU database and provides a unique opportunity for researchers to participate in collaborative projects. We have gathered stakeholder engagement by conducting a CNN-wide survey regarding PDA pharmacotherapeutic practices and exploring the need for such a project. With at least 22 out of the 31 CNN centres participating in this CER, we believe that evidence generated from this project would be promptly implemented.

Anticipated challenges and solutions

We have thought of and planned for challenges likely to be faced in our study design and execution.

(1) Unreliable data quality*:* We plan to improve reliability through training and reinforcement of abstractors, range checks at entry level, and random self-audits. However, we are confident as the CNN database has shown very high internal consistency and reliability[38]; (2) Inconsistency in participation at unit level: We will focus on stakeholder engagement from the outset, in-principle agreement by units and collection of data for protocol deviations; (3) Slow recruitment*:* With increasing emphasis on conservative management, the number of infants being treated for PDA may decline over time. Based on our current projections even if the recruitment rate declines by 10%–12% we should still be able to achieve our sample size by 3 years. Since all the outcome measures are obtained through routinely collected clinical data that are entered by data abstractors after discharge of the patient, COVID-19 related research restrictions are unlikely to affect data collection and entry (4) Variation in treatment initiation criteria*:* We refrained from prescribing criteria for the initiation of PDA treatment for participating sites so as to mimic a pragmatic real-world scenario. Variation in criteria for initiating treatment may affect response to treatment and clinical outcomes. As long as there is minimal within centre variation in treatment initiation criteria, we hope that accounting for site in our analytical model will account for part of this site related variation; (5) Overlap of treatment protocols*:* Infants treated early (within 7 days after birth) in the adjustable dose group may receive the same dose of ibuprofen as infants in the standard dose group. If these infants are only analysed as per their treatment assignment then in spite of being entered in the model as adjustable dose patients, in essence they would be the same as standard dose patients if they never receive further treatment. This might lead to a type II error as a true difference in effectiveness between the standard and higher doses of ibuprofen would be missed if a substantial proportion of adjustable dose infants are treated early. To mitigate this effect we have planned a secondary drug-dosage effectiveness analysis for the primary outcome where the infants will be reclassified according to the actual dosage received rather than their original treatment assignment; (*6*) Change in treatment protocol*:* A centre that has committed to one particular choice of initial pharmacotherapy may choose to change to a different medication based on their local safety and efficacy data, lack of availability of existing medication or availability of a new medication. The centre will continue to remain part of the study as long as their treatment choice still falls under one of the four predefined choices and the change occurs at the level of the centre rather than at the level of the individual practitioner. If a centre uses multiple different medications as routine initial therapy based on the choice of the practitioner, that centre will be excluded from the study (this does not include protocol deviation for a valid reason such as use of acetaminophen in infants with contraindications to NSAIDs).

ETHICS AND DISSEMINATION

The study has been approved by the IWK Research Ethics Board (#1025627) as well as the respective institutional review boards of the participating centres. All participating centres are part of the CNN patient registry where routinely collected clinical data, required for this study, is abstracted from patient charts, and recorded in an anonymised fashion after an infant is discharged from a participating hospital. Therefore, need for written informed consent from the parents/guardians was waived for this study.

We will use the following knowledge translation (KT) strategies for dissemination of our study findings:

Integrated KT: (1) Involvement of stakeholders in protocol development by organising regular teleconferences prior to submission of proposal; (2) Engagement of local site investigators for adherence to protocol by organising in-person meetings at CNN's annual meeting and by development and dissemination of infographics of study schema to all participating sites; (3) Troubleshooting challenges during study period by using the CNN forum for collaborative learning from ongoing CER projects.

End of study KT: (1) Dissemination of results to the wider Canadian and international neonatal community by presenting results at the CNN annual meeting, Canadian Paediatric Society's annual meeting and Paediatric Academic Society's Annual Meeting; (2) Dissemination of results to hospital administrators by preparing written summaries, reaching them through our e-newsletters and further raise awareness regarding our findings through academic presentations; Increase knowledge in the

scientific community, print and electronic media and parent groups through use of social media platforms such as Twitter (@IWKHealthCentre, @Neo_FICareIWK, @EBNEO, @CIHR_IRSC, @CNN_neonatal) and Facebook.

Through this project, we aim to address the controversy around choice of PDA pharmacotherapy in preterm infants using an innovative research design. We believe this study will not only provide real-world evidence for PDA management strategies through a large contemporary cohort of more than 1000 extremely preterm neonates across Canada in a cost-efficient fashion but also strengthen neonatal teams and the national network including policy-makers, clinicians and researchers through integrated KT.

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Contributors The project was planned by SM under the mentorship and supervision of AJ and PS. JYT, NBF, CD, AAM, AS, BJ, DL, AL, JD, FK, AH, JB, DW, RA, MA, MS, AM, SB, JK, RC and KK participated in the development of the project at their respective centres. TH and CEG coordinated the project development. Biostatistician XYY provided input to research design and analysis. All authors reviewed and edited the final manuscript.

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