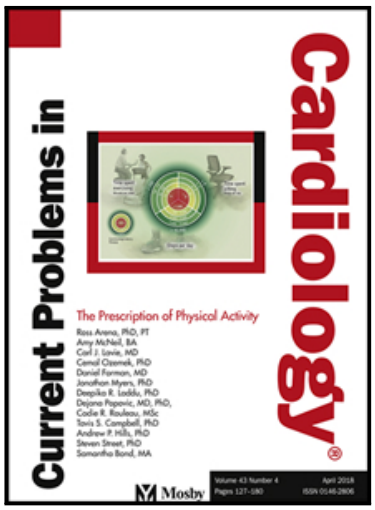

Cost-effectiveness Analysis of Ibuprofen versus Indomethacin or Paracetamol for the Treatment of Patent Ductus Arteriosus in Preterm Neonates

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Highlights

- There is considerable uncertainty regarding the most appropriate treatment approach including the dosage form for patent ductus arteriosus (PDA) closure in preterm infants.
- The study evaluated the cost-effectiveness of oral paracetamol and intravenous (IV) indomethacin as alternatives to oral and IV ibuprofen for PDA in neonates in the intensive care setting in Qatar.
- Oral ibuprofen is dominant/cost-effective over IV indomethacin in 97.9% of simulated cases with an average cost saving of QAR 193,789 (USD 53,239).
- Against IV ibuprofen, IV indomethacin was 55.3% dominant/cost-effective, with an average incremental cost-effectiveness ratio of QAR 12,556 (USD 3,448.5) per additional case success.
- Oral paracetamol was 75.2% dominant/cost-effective over oral ibuprofen with an average cost saving of up to QAR 124,091 (USD 34,091).
- Against IV ibuprofen, oral paracetamol was dominant/cost-effective in 98.5% of the cases with an average cost saving of up to QAR 165,922 (USD 45,583).
- Sensitivity analyses confirmed the robustness of the study conclusion and results.

Title: Cost-effectiveness Analysis of Ibuprofen versus Indomethacin or Paracetamol for the Treatment of Patent Ductus Arteriosus in Preterm Neonates

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Abstract

Objective: This was a first-time evaluation that sought to analyze the cost-effectiveness of oral paracetamol and intravenous (IV) indomethacin as alternatives to ibuprofen for PDA in neonates.

Methods: Decision-analytic, literature-based, economic simulation models were constructed, to follow up the use and consequences of oral/IV ibuprofen versus IV indomethacin, and oral/IV ibuprofen versus oral paracetamol, as first-line therapies for PDA closure. Model outcomes of interest were 'success', defined as PDA closure with/without adverse events, or 'failure' due to no response to the first course of treatment, death or premature discontinuation of therapy due to AEs.

Results: Oral ibuprofen is dominant/cost-effective over IV indomethacin in 97.9% of simulated cases, but oral paracetamol was 75.2% dominant/cost-effective over oral ibuprofen. Against IV ibuprofen, IV indomethacin was 55.3% dominant/cost-effective, whereas oral paracetamol was dominant/cost-effective in 98.5% of the cases. Sensitivity analyses confirmed the robustness of the study results.

Conclusion: For PDA closure, while IV indomethacin was cost-effective against IV ibuprofen, oral paracetamol was cost-effective against both oral and IV ibuprofen.

Keywords: Patent ductus arteriosus, cost effectiveness analysis, Ibuprofen, Indomethacin, Paracetamol

Introduction

A patent ductus arteriosus (PDA) is a congenital condition where the ductus arteriosus (DA) fails to close post-delivery and remains patent or, in other words, "open". The physiological consequences of the PDA, and the significance of its therapy, depend primarily on the scale of the PDA [1]. PDA accounts for 5% - 10% of all congenital heart diseases [2, 3]. However, the incidence surges up to 60% in preterm infants and is inversely related to gestational age (GA) and birth weight [3- 5]. Since targeted PDA management has become the preferential approach, pharmacotherapy selection has become more relevant [6]. The first-line therapy for hemodynamically significant PDA (hsPDA) is the non-steroidal inflammatory drugs (NSAIDs), either indomethacin or ibuprofen. For patients who do not respond to NSAIDs or where pharmacologic treatment is not suitable, surgical ligation is the last resort [7-9]. Traditionally, indomethacin has been the preferred medication in the treatment of hsPDA. Yet, despite its proven effectiveness, its use has been associated with complications related to reduced cortical, renal, and mesenteric perfusion [10, 11]. Ibuprofen has demonstrated a similar effectiveness value of up to 80%; and it was associated with a lower incidence of adverse events (AEs) such as necrotizing enterocolitis (NEC) and acute renal insufficiency relative to indomethacin [10, 11]. Acetaminophen, a prostaglandin synthase inhibitor, has lately emerged as a new therapeutic choice as an alternative to ibuprofen, although it is still considered an off-label medication for PDA treatment. It was first reported in 2011, when Hammerman et al. documented a case series of paracetamol use as hsPDA treatment in five neonates that had either failed or had contraindication of ibuprofen therapy [12]. The rate of ductus closure was 100%, with no AEs recorded. Other case series and research studies testing this novel therapeutic choice were reported in the subsequent years [13-22].

Currently, PDA's optimal management is highly controversial and remains unclear as there are no universal guidelines or consensus regarding the most appropriate pharmacological

treatment and route of administration. This uncertainty in selection is further emphasized when considering that relative variability in the effectiveness and safety performance of therapies is consequentially associated with a relative economic impact. In Hamad medical corporation (HMC) in Qatar, the preferred first-line treatment is intravenous (IV) ibuprofen, which is not based on any local comparative evidence, even though the IV indomethacin is also available in the HMC drug formulary for PDA closure. Traditionally, treatments have been given via the IV route, but the oral route is now increasingly considered [14, 17, 22-23]. Oral ibuprofen and oral paracetamol have become popular options in many neonatal intensive care units (NICUs). In Qatar, there is an increasing trend of using oral ibuprofen as well as oral paracetamol. This, however, is based on personal preferences, not based on any local evidence. One element in favor of the decision is the lower cost of oral administration compared to the IV [24]. Indeed, the lower acquisition cost of oral ibuprofen has not only been a driver for use in low-income countries but is reported to be so in 29% of NICUs in high-income European countries as well, despite the lack of proper evaluations of the overall costs with medications [25]. With this context, the impact of resource consumption is most important for better understanding the effect of different pharmacological agents on hospital budgets for decision-makers and practitioners to consider beyond the acquisition costs, including when revising HMC's protocols and practices. Internationally, however, there are no robust cost-effectiveness evaluations on how different formulations compare for the treatment of PDA.

This study aims to construct a comprehensive simulation-based economic decision-analytic model to evaluate the cost-effectiveness among different formulations of ibuprofen against each of indomethacin and paracetamol as first-line treatment options for PDA closure in preterm infants in the intensive care setting of HMC in the State of Qatar.

Methods

Model structure

A cost-effective evaluation that entails two basic decision-analytic simulation models was constructed to reflect the use of different treatment alternatives and their possible consequences of interest as first-line therapies for PDA closure in premature infants, whereby the relative costs and outcomes of treatment pathways in the model were rigorously compared. One decision-analytic model was constructed to compare (i) oral ibuprofen versus IV indomethacin and (ii) IV ibuprofen versus IV indomethacin, Figure 1. The second decision-analytic model compared (i) oral ibuprofen versus oral paracetamol and (ii) IV ibuprofen versus oral paracetamol, Figure 2. Directly comparing oral to IV ibuprofen, or indomethacin to paracetamol, for PDA is not of interest in the current research.

In any of the two decision models, there were six possible terminal pathway outcomes of interest. For each treatment course, neonates were primarily differentiated into a "success" or a "failure" health state. Success was defined as the closure of PDA with or without an AE that causes premature discontinuation. Closure of PDA was the closure within one week of administering the first dose of medication. In contrast, failure was defined as no closure due to no response to the first course of treatment, death, or premature discontinuation of therapy due to AEs. The duration of the model follow-up was based on the duration of hospitalization until discharge.

No response to the first course was defined as neonates with persistent hsPDA that requires a repeat course or is contraindicated to medications and will require surgery. Death was defined as all-cause death during the initial hospital stay. Premature discontinuation was described as an incomplete course of pharmacological treatment due to AEs, which included pulmonary hemorrhage, intraventricular hemorrhage (IVH), NEC >1, gastrointestinal bleeding (GIB), intestinal perforation, and oliguria. AE was defined as an undesirable or harmful outcome

that develops during or after using a drug [26]. In premature infants, an AE can occur in both a success and a failure case. This was distributed in the decision model based on their period of occurrence according to the GA of premature neonates with PDA. The AEs reported were based on the clinical data available in the literature for the evaluation of each pair. The AEs that were reported with success included retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), and bronchopulmonary dysplasia (BPD). In premature infants with a GA of 27 weeks, the mean GA of developing ROP is reported after 30 weeks. Therefore, this was considered a long-term event and was not to occur in the first week of treatment [27]. For PVL evaluation, as part of the routine screening for infants with GA < 30 weeks, ultrasound screening is performed at 10-14 days and repeated at 36 weeks as there are two phases for the evolution of PVL. The first phase is the early acute phase that could occur after the first week to 10 days, and the late chronic phase that evolves over 4-6 weeks [28]. BPD was evaluated in infants who use mechanical ventilators over a long time, where it is diagnosed at 36 weeks of post-menstrual age (PMA) [29]. Hence, as the ROP, PVL, and BPD events do not occur over a short-term exposure to PDA (in the first week of treatment), these events were assumed to not contribute to premature discontinuation of medication in the model. On the contrary, the AEs that are to contribute to the premature discontinuation of treatment were events that could occur over a short time during or after the treatment period, an AE due to medication intake and PDA. These events included pulmonary hemorrhage, IVH [30], NEC >1 [31], GIB, intestinal perforation, and oliguria [20, 32].

An HMC-based expert panel of well-qualified professional healthcare providers validated the model structure. The panel included one neonatology consultant, one specialist and one senior clinical pharmacist, who all have clinical experiences with PDA treatment. Contrasting opinions were discussed among the panel members until consensus.

Study perspective

The decision-analytic model was performed from the HMC perspective. Hence, only the cost of direct medical resources was considered, including medications, hospitalization, diagnosis, treatment, and adverse events management. Other types of costs, including indirect, intangible, and non-medical costs, were neglected.

Clinical model input

Clinical input data for the oral/IV ibuprofen versus IV indomethacin comparative model were primarily extracted from a meta-analysis by Ohlsson et al. [32]. For the oral/IV ibuprofen versus paracetamol model, the clinical inputs were obtained from a second meta-analysis by Ohlsson et al. [20]. These meta-analyses are relevant and are of the highest quality in the literature [33]. They are Cochrane reviews of randomized clinical trials (RCTs) of premature neonates hospitalized for PDA. The ibuprofen versus indomethacin meta-analysis is the most recent and inclusive review in the literature that provide head-to-head evaluations including 39 RCTs of 2843 infants with PDA [32]. While the ibuprofen versus paracetamol MA is a recent review in the literature that provide head-to-head evaluations including 8 RCTs that enrolled 916 preterm infants with PDA [20]. Clinical data that were not reported in the Ohlsson et al. Cochrane reviews were extracted from a recent network meta-analysis (NMA) by Mitra et al., which analyzed 68 RCTs and observational studies of 4802 infants, including all treatment modalities [34].

With all therapies. i.e., indomethacin, ibuprofen, or paracetamol, neonates received the medication for one course of treatment. Importantly, the study drug regimens in the Cochrane reviews and NMA were identical to the routine clinical practice in HMC Qatar. For comparing ibuprofen to indomethacin, this constituted (i) oral ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (ii) IV ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (iii) IV indomethacin of 0.2 mg/kg given at 12

hourly intervals for three doses. For comparing ibuprofen to paracetamol, this constituted (i) oral ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (ii) IV ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (iii) oral paracetamol of 15 mg/kg given at 6 hourly intervals for three doses.

The definition of hsPDA and the criteria for pharmacological treatment is also similar to the Qatari practice. The simulated decision model was based on a simulated cohort of premature neonates of <35 weeks GA (average of 28 weeks) and < 1.5 kg body weight (average of 1.1 kg) [20, 32]. The prematurely born neonates diagnosed, using echocardiography, to have a hsPDA (> 1.5 mm) were qualified for pharmacological treatment of PDA unless contraindicated. Contraindication criteria for the management of hsPDA using pharmacological treatment included major congenital malformations, life-threatening infection (sepsis), urine output <0.5 ml/kg/hr for 8 hours before treatment, serum creatinine > 1.8 mg/dl, platelets < 50, 000/ uL, active NEC stage 2 or 3 (Bells staging criteria) [31], active bleeding or intestinal perforation, IVH grade 3 or 4 [30] liver dysfunction and severe hyperbilirubinemia.

Outcome probabilities for all model events, as extrapolated from the literature meta-analyses [20, 32] and NMA [34], can be seen in Appendix 1.

To account for underlying uncertainties in the model input data obtained from the literature, the base-case of the simulation model was based on multivariate uncertainty analysis, using Monte Carlo simulation through @Risk-7.6 (Palisade Corporation, NY, US). Monte Carlo is a computerized mathematical technique that permits a simulated cohort of patients based on numerous test runs of the model analysis. For each re-run of the model, the base-case value of the uncertain input variable is randomly replaced by a new input value chosen from within a predefined uncertainty range assigned to a model input. At the base-case of our model, all the

outcome probabilities were simultaneously varied within their 95% CI ranges. The model simulation was run with 5,000 iterations, and a triangular type of distribution for the selection of random inputs within uncertainty ranges was utilized.

The pathway probabilities for each of the study comparators, and their multivariate uncertainties, are presented in Table 1 and Table 2 for the ibuprofen versus indomethacin model, and ibuprofen versus paracetamol model, respectively.

Cost calculation

Cost calculations were based on the financial year 2021/22 and were represented in Qatari riyal (QAR). This research did not include discounting of costs, given the short timeframe of the analysis. It was assumed that patients completed the entire course of therapy unless the medication was discontinued due to AEs. The wholesale prices of medications were acquired through the drug supply department of HMC. Clinical event costs were based on the finance department of HMC, which were available as per resource category, calculated based on a micro-costing approach of involved direct medical resources. The medical resource cost categories constituted the costs of hospitalization, monitoring including laboratory tests, diagnostic tests, supportive care, treatment of events (including AEs, surgery, diagnostic, monitoring and hospitalization costs), and medications acquisition, as relevant to the events.

The average GA of infants treated for PDA as reported in the meta-analyses by Ohlsson et al. [20, 32] is 28 weeks. According to HMC, infants can be discharged from the NICU after 34 weeks of gestation after fulfilling the following criteria (i) the infant can breathe in room air >7 days, (ii) no apneas, (iii) full feeding by sucking, (iv) body temperature is normal in the cot, (v) gaining normal weight of 10-30 g/day, and (vi) mother is ready. Therefore, the neonatal hospital management costs were calculated based on a 7-week duration for success with no event; and where there is an event, the duration of handling the event is added on. A

course of study drug was given for three days. If this is prematurely discontinued, the duration of the drug is assumed to be reduced by half, two days.

The cost of a neonate with PDA closure without AEs is the sum cost of medication acquisition over three days, plus the cost of management of PDA when successful as per HMC. The cost of a neonate with PDA closure with an AE is the cost of a neonate with PDA closure (without AEs), plus the AE management cost, as per HMC guidelines. The cost of a neonate without PDA closure and a second course is the sum cost of a neonate with PDA closure (without AEs) plus the cost of managing a successful course of the therapy without AEs for an additional two weeks. The cost of a neonate without PDA closure and surgical ligation is the sum cost of a neonate with PDA closure (without AEs) plus the cost of undergoing surgical ligations for PDA. The cost of death is equal to the cost of successful management of PDA treatment without AEs. The cost of premature discontinuation of medication due to AEs is the sum of medication acquisition over two days, plus the cost of AEs management.

Based on the decision analysis principles of modeling, the overall cost of treatment, incorporating all health states with uncertainties, is the sum of "proportional costs" of all the different health state pathways. The proportional cost of a health state is the 'cost of the health state pathway' multiplied by the 'probability of the health state pathway'.

Outcome measure

The trade-off between the comparative cost and effectiveness outcomes of the study drugs in this model was presented via the incremental cost-effectiveness ratio (ICER) per case of overall success, which is the "probability of PDA closure". When an intervention is dominant over another (higher efficacy and lower cost), where an ICER is not reported, the probability of dominance was reported. In this study in Qatar, the willingness-to-pay (WTP) threshold

(i.e., the cost-effectiveness threshold) against which the ICER is interpreted is estimated to be USD 150,000 (QAR 546,150) per case of success.

Sensitivity analysis

The one-way sensitivity analyses included evaluating the acquisition cost of medications using a uniform type of distribution, within an uncertainty range from -90% to +10% of the cost values. Here, a broad –ve uncertainty limit was used as the medication used in HMC for PDA treatment were brand medications, which increases the generalizability of results to practices where cheaper generics are used. As a follow up on the multivariate uncertainty in outcome probabilities performed at base case, the multivariate sensitivity analysis was conducted to incorporate uncertainty in the cost of management of AEs (±10 uncertainty), using a triangular type of distribution. As with the base-case, the one-way and multivariate sensitivity analyses were carried out using 5000 iterations using Monte Carlo simulation via @Risk-7.6® (Palisade Corporation, NY, US).

Ethical approval

The study model is based on literature and available HMC data. Hence, an institutional review board (IRB) approval was not required by HMC.

Results

Based on the economic decision-analytic model, the clinical outcomes, their costs, and the overall costs of treatment strategies are summarized in Appendix 2. The ICER among all PDA treatment options is summarized in Table 3.

Oral ibuprofen versus IV indomethacin

The mean difference in the therapy success between oral ibuprofen and IV indomethacin was 0.1488 (95% CI, 0.0865-0.2353) in favor of oral ibuprofen, which was also associated with a cost saving of up to QAR 193,789 (53,239 USD), Appendix 3_Figure 1. With a higher rate of

success and a lower cost, oral ibuprofen is dominant over IV indomethacin which was maintained in 63.24% of the simulated cases. Based on the WTP threshold, oral ibuprofen was considered cost-effective in 34.66% of the cases. Overall, oral ibuprofen is dominant/cost-effective over IV indomethacin in 97.9% of simulated cases.

The resource category that contributed most to the overall patient cost was the hospitalization, followed by the monitoring of clinical events. The cost of hospitalization was higher with IV indomethacin, QAR 393,116 (107,999 USD), compared to oral ibuprofen, QAR 378,671 (104,030 USD)), Appendix 2_Figure 1.

A tornado analysis of the ranking of different clinical inputs based on the strength of the relationship with the model outcome is presented in Appendix 3_Figure 2. The outcome with the strongest impact on outcome was the probability of 'success with BPD >36 weeks' with either oral ibuprofen or IV indomethacin. This was followed by probability of 'success with no AEs' with oral ibuprofen, and then the 'success with ROP >II' probability with IV indomethacin.

IV ibuprofen versus IV indomethacin

The mean difference in therapy success between IV ibuprofen and IV indomethacin was 0.0289 (95% CI, 0.0062-0.0852) in favor of IV indomethacin, but at an average added cost of QAR 364 (100 USD). IV indomethacin was between dominant (53.9 %) and cost-effective (1.4%) over IV ibuprofen in 55.3% of simulated cases, Appendix 4_Figure 1, with an average ICER of QAR 12,556 (3,448.5 USD) with indomethacin over ibuprofen per additional case success.

The resource category that contributed most to the overall patient was the cost of hospitalization where IV ibuprofen (QAR 396,727) [108,991 USD] was higher than that with IV indomethacin (QAR 393,115) [107,999 USD], Appendix 2_Figure 1.

Based on the tornado analysis, Appendix 4_Figure 2, the probability of 'success with BPD >36 weeks', with either IV ibuprofen or IV indomethacin, was the model outcome that has the highest strength of association with the ICER outcome, followed by the probabilities of 'success with ROP >II' and 'success with no AEs' with the IV indomethacin.

Oral ibuprofen versus oral paracetamol

The mean difference in the therapy success between oral ibuprofen and oral paracetamol was 0.0069 (95% CI, 0.0002-0.0545) in favor of oral paracetamol, with a cost saving of up to QAR 124,091 (34,091 USD) with paracetamol, Appendix 5_Figure 1. This dominance with oral paracetamol was maintained in 72.6% of the cases and cost-effective in 2.6% of the cases. Thus, oral paracetamol was dominant/cost-effective in 75.2% of the simulated cases over oral ibuprofen.

Similar to the ibuprofen versus indomethacin model, the resource category that contributed the most to the patient cost in the ibuprofen versus paracetamol model was the hospitalization, followed by the monitoring of clinical events. Oral ibuprofen, QAR 371,211 (101,981 USD), was associated with a higher hospitalization cost compared to oral paracetamol, QAR 364,304 (100,084 USD), Appendix 2_Figure 2.

The tornado analysis of the regression coefficient shows that the outcome that has the strongest association with the cost saving is the probability of 'success with no AEs' with oral paracetamol, followed by the probability of 'no response to first course, with a second course' with oral paracetamol, Appendix 5_Figure 2.

IV ibuprofen versus oral paracetamol

The mean difference in therapy success between IV ibuprofen and oral paracetamol was 0.1620 (95% CI, 0.0943-0.2468) in favor of oral paracetamol, and with an average cost saving of up to QAR 165,922 (45,583 USD), Appendix 6_Figure 1. Oral paracetamol was in

overall dominant over IV ibuprofen in 61.6% of the simulated cases. When not dominant, oral paracetamol was cost-effective in 36.9% of the cases. Thus, oral paracetamol was dominant/cost-effective in 98.5% of the simulated cases over IV ibuprofen.

The resource category that contributed most to the overall patient was the cost of hospitalization where IV ibuprofen QAR 381,575 (104,828 USD), was associated with a higher cost compared to oral paracetamol, QAR 364,305 (100,084 USD), Appendix 2_Figure 2.

The tornado diagram of the regression coefficient rank demonstrates that the probability of 'success with no AEs' with oral paracetamol had the strongest correlation with the cost saving, followed by the probability of 'no response to the first course, with receiving a second course' with both study drugs, Appendix 6_Figure 2.

Sensitivity analyses

One-way sensitivity analyses

Overall, the model was insensitive to changes in acquisition costs, not affecting the superiority of an agent over another. Changing the acquisition costs of ibuprofen (oral or IV) or the IV indomethacin only increased the superiority of IV indomethacin against IV ibuprofen from being cost-effective to becoming dominant. Similarly, for the ibuprofen (oral or IV) versus oral paracetamol model, none of the model outcomes was affected by the changes in the acquisition costs of any of the study drugs. The variability in acquisition costs, uncertainty distributions, and the outcomes of the one-way sensitivity analysis can be found in Appendix 7_Tables 1 and 2.

Multivariate sensitivity analyses

All the model outcomes were insensitive to any uncertainty that was associated with the cost of AEs, in addition to the base-case probability input uncertainty, except for the ICER

evaluation of IV ibuprofen and IV indomethacin. Here, however, the superiority of the IV indomethacin did not change but only increased from being cost-effective to becoming dominant. Furthermore, the distribution of dominance, cost-effective, and not cost-effective states remained robust against the base-case scenario. The costs of AEs, their uncertainty ranges, and the outcomes of the multivariate sensitivity analysis are in Appendix 8.

Discussion

Indomethacin and ibuprofen are the two cyclooxygenase (COX) inhibitors approved by the US Food and Drug Administration (FDA) for the closure of ductus in premature babies. Apart from efficacy and safety, the choice of one drug over the other is also influenced by the availability of both drugs and the IV or enteral preparation in the local area. When it comes to paracetamol use for PDA, whether oral or IV, several advantages for a first-line use can be proposed. First, the cost of oral or IV paracetamol acquisition is very low compared to IV indomethacin and IV ibuprofen. Second, paracetamol is associated with reduced GIB and renal insufficiency, which could further add to the economic advantage of paracetamol. Although the use of paracetamol to close a hsPDA has increased in recent years, it is still considered off-label. There is no commercially available indomethacin oral formulation for use in infants. In studies where indomethacin was administered orally, the authors prepared a saline–dextrose solution or water suspension of the drug powder from capsules [35]. As for paracetamol, all formulations were oral in the RCTs reported in the Cochrane systematic review conducted in 2020, except for one RCT that reported IV paracetamol [20].

To date, there is no comprehensive cost-effectiveness evidence that guides the comparative use of different drugs for PDA, including in Qatar. The only other comparative cost-effectiveness study of drugs for PDA was a local Qatar study, by Abushanab et al. [24], but this only compared the oral versus IV formulations of ibuprofen, which was a cohort-based cost-effectiveness study on 124 neonates from the primary NICUs in HMC. The oral

ibuprofen was between dominant and cost-effective against IV ibuprofen for PDA treatment. This is how the current study is particularly important as it follows up on how ibuprofen compares economically to other available interventions, indomethacin and paracetamol, for the management of PDA.

A Recent study by Godin et al. provided another economic analysis of PDA medications [36]. This, however, was not a cost-effectiveness analysis, but only looked at the difference in the acquisition cost between IV ibuprofen and IV paracetamol, and was only based on the IV formulation of drugs. In addition, the cornerstone probabilistic or deterministic sensitivity analysis was not conducted. Cost of successful closure of PDA with paracetamol was between USD 892-1,487, which was lower than that with ibuprofen (USD 2,585) and indomethacin (USD 2,661) [36].

Therefore, the objective of the second phase of this thesis was to conduct a first-time cost-effectiveness evaluation to compare between ibuprofen and each of indomethacin and paracetamol as first-line for the closure of PDA in premature neonates. The interest here, within the context of HMC, is to examine indomethacin and paracetamol as potential alternatives to the currently commonly used in HMC, ibuprofen.

Compared to IV indomethacin, the base-case results of the respective model illustrated an increased probability of success, by 0.1488 (0.1704, 0.1198), in favor of oral ibuprofen. For the cost difference, this was over QAR 21,000 (5,769 USD) in favor of the oral ibuprofen (Appendix 2_Table 1). While the proportional cost associated with the success outcomes was higher with oral ibuprofen (QAR 46,686) [12,826 USD], this was overtaken by over QAR 68,000 (18,681 USD) proportional costs in favor of the oral ibuprofen associated with the failure (Appendix 2_Table 1). Taking cost into consideration, the oral ibuprofen was overall dominant.

Compared to IV ibuprofen, however, the difference in the probability of success at base-case was 0.029 in favor of IV indomethacin. For the cost difference, this was minimal, over QAR 300 (82 USD), in favor of the IV ibuprofen. While the proportional cost associated with the success outcomes was higher with IV indomethacin (QAR 14,213) [3,905 USD], this was almost balanced by over QAR13,000 (3,571 USD) proportional costs in favor of the IV indomethacin associated with the failure (Appendix 2_Table 1). The IV indomethacin was mostly between dominant and cost-effective.

The superiority of IV indomethacin over IV ibuprofen, but not oral ibuprofen, is further confirmed via improved effectiveness and reduced cost with oral ibuprofen over IV oral ibuprofen as reported by Abushanab et al. in their local cohort-based study [24]. Oral ibuprofen had a higher success rate for PDA closure by 27% with a lower cost, dominating IV ibuprofen in 72% of the patient cases with a mean saving of QAR 48,751 (95% CI 47,500-50,000) (13,393 USD) [95% CI 13,049-13,736] [24].

Regarding the comparison between oral paracetamol and ibuprofen, the mean difference in the success of PDA closure was a minimal 0.0069 in favor of oral paracetamol compared to oral ibuprofen. For the cost difference, this was over QAR 7,000 (1,923 USD) in favor of oral paracetamol (Appendix 2_Table 2). The proportional cost associated with the success and failure outcomes was higher with oral ibuprofen by QAR 4,317 (1,186 USD) and QAR 2,855 (784 USD), respectively (Appendix 2_Table 2). Taking cost into consideration, oral paracetamol was overly between dominant and cost-effective.

Also, compared to IV ibuprofen, the mean difference in the success of PDA closure was in favor of oral paracetamol, by 0.1621. For the cost difference, this was over QAR 17,000 (4,670 USD) in favor of the oral paracetamol (Appendix 2_Table 2). While the proportional cost associated with the success outcome was higher with oral paracetamol (QAR 49,471)

[13,591 USD], this was overtaken by an over QAR 67,000 (18,407 USD) proportional costs in favor of the oral paracetamol associated with the failure (Appendix 2_Table 1). Oral paracetamol was dominant over IV ibuprofen.

From the perspective of HMC, results are in contrast to HMC practices in relation to two aspects. First, while IV ibuprofen is currently the first-line of therapy for the treatment of PDA, IV indomethacin and oral ibuprofen are potentially superior alternatives, noting the availability of both oral ibuprofen and IV indomethacin in the formulary of HMC. Second, oral paracetamol has only been used so far in HMC on an arbitrary basis, based on personal experiences and opinions. However, this is a practice that may need to change; whereby, adopting oral paracetamol as a solid alternative to ibuprofen might be ideal for the NICU in HMC.

Further establishing the importance of looking at secondary costs of therapies, in addition to their acquisition costs, is our breakdown analysis of the cost components of the study regimens, which, as anticipated, indicated that over 85% of the cost per patient with any of the study drugs in either model is hospitalization costs, followed by monitoring costs, Appendix 2_Figures 1 and 2.

Based on the base-case tornado regression findings for both evaluations between ibuprofen versus IV indomethacin, the most influential model input on the study outcome was the likelihood of success with BPD >36 weeks with either ibuprofen or indomethacin, Appendix 3_Figure 2 and Appendix 4_Figure 2. This is not unanticipated given that the health state of success with BPD >36 weeks did not only have the higher cost per event to it but was associated with the highest event probability in the model, just second to the outcome of success with no AEs.

For the ibuprofen versus oral paracetamol comparative model, the base-case tornado regression analysis demonstrated that the most influential model event on the study outcome was the likelihood of success with no AEs with oral paracetamol against either oral or IV ibuprofen, Appendix 5_Figure 2 and Appendix 6_Figure 2. While the health state of success with no AEs is not associated with the highest cost per patient, it had the highest outcome probability in the model, adding to a proportional cost that contributes to the patient cost the most.

Apart from being the first pharmacoeconomic study, nationally and internationally, to evaluate the cost-effectiveness among all main pharmacotherapeutic options available for the closure of PDA in premature neonates, the study is unique in how comprehensive the decision-analytic model is. The model represents all the possible consequences of using a study drug for PDA, including discontinuation due to AEs, failure of treatment, surgical pathway, death, and the AEs that do not constitute failure and, hence, an overall cost of resource utilization is more accurately represented. Also, another strength, is that the current comparative model was able to simulate a follow up of patients until discharge from the NICU at 34 weeks, as per HMC practices.

The model was populated with data to a different extent from different sources available in the literature, which was to account for missing data in each of the individual sources. The sources of clinical inputs used in our model are considered another strength in the study as they constituted recent highest quality Cochrane MAs, including large sample sizes of RCT patients [20, 32]. Here, it is important that the inclusion criteria of the patients in the meta-analyses are consistent with the PDA population receiving the study drugs in the local HMC setting. In addition, the success of the PDA closure study outcome is also consistent with what decision-makers look to follow-up in PDA infants in HMC. Moreover, the regiment of

study medications given to neonates for PDA treatment is identical to that routinely provided in the NICU of HMC.

There is no approved WTP cost-effectiveness threshold in Qatar. While the WHO suggests using 1-3 times the GDP per capita as the value of the threshold in a country, it is acknowledged that this is arbitrary and not based on any methodological justification [37]. In addition, the average 2022 GDP per capita (PPP) in Qatar exceeds USD 100,000 [38], one of the world's highest. Thus, adopting the WHO recommendation for calculating the WTP will result in a range of values that is too wide to be directly useful. In this study, we adopt a threshold value of USD 150,000, which is increasingly accepted as a higher threshold value in the literature, which is also within the range suggested by WHO for Qatar [37].

While relying on a pooled analysis of well-established RCTs comes with strong internal validity due to randomization, blindness, and control of confounding variables in the RCTs [39], the use of meta-analyses as a source of data comes with considerable limitation to the economic assessment in this research. The meta-analyses jeopardized the generalizability of results to the local setting due to the enrichment in included RCTs and the differences in patient demographic characteristics [40]; whereby, none of the meta-analyses included Qatari-based research as an example. Consequently, there can be inherent uncertainties associated with the clinical input, and it is for this reason that the decision-analytic model was based on multivariate uncertainty analysis of probability inputs at its base-case. This is an innovative approach that has been in use [41, 42]. This is thought to be a more meaningful and reliable representation of the outcomes, whereby the base-case was based on a hypothetical cohort of 5,000 neonates instead of a single case, with uncertainties in a variety of input values randomly interacting, as in real-life situations. To further account for the uncertainty about generalizability, additional uncertainty was added to analyzing the model via the one-way and multivariate sensitivity analyses, which confirmed robustness.

To emphasize, however, despite robustness against uncertainty, the results of this analysis are specific to the Qatari setting and should not be easily extrapolated to patients in different settings, especially due to variations in resource utilization.

During study analysis, two recent studies were released in 2022 comparing the efficacy and safety of paracetamol versus ibuprofen and indomethacin for PDA treatment. Although these studies were more recent than the systematic review used for this study (2020) [20], study outcomes did not change and both studies concluded that there was no significant difference between paracetamol and ibuprofen for failure of ductal closure after first course of drug [43, 44]. Moreover, the safety outcome regarding GIB reported in Ohlsson et al [20] was consistent with the most recent systematic review and meta-analysis [44]. Other safety parameters were not reported between paracetamol and ibuprofen in the study [43, 44].

Although the findings of the current study are comprehensive and robust, they can only be completely validated by a follow-up future local study that assess the comparative clinical and economic impacts of ibuprofen versus indomethacin or paracetamol in premature neonates with PDA in the Qatari HMC setting. However, this is currently difficult, mostly due to the relatively low/lacking number of patients who have received indomethacin and paracetamol as first-lines for PDA. Therefore, locally specific simulation studies, such as the current one, are considered fundamental for decision-making in local practices.

Conclusion

IV ibuprofen is currently the first-line therapy for the management of PDA in Qatar. Our results, however, taking into consideration the assumptions and limitations made in our research, seem to favor oral paracetamol as the superior alternative first-line therapy to ibuprofen for PDA in Qatar. Oral paracetamol was between cost-effective and dominant over both oral and IV ibuprofen formulations. Next to oral paracetamol, oral ibuprofen is

favorable. The latter was also between cost-effective and dominant against indomethacin as a potential first-line alternative to the IV ibuprofen for PDA. The same was not true for the IV ibuprofen, which was dominated by IV indomethacin as a proposed alternative.

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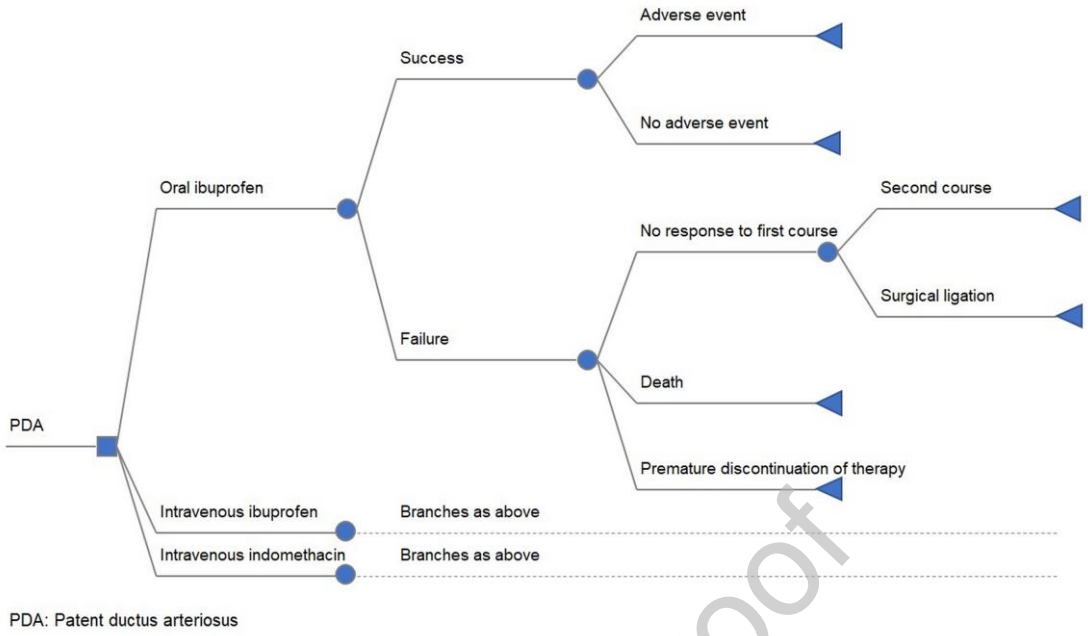

Figure 1: Decision-tree based model for patent ductus arteriosus (PDA) therapy of oral (PO) /intravenous (IV) ibuprofen versus IV indomethacin.

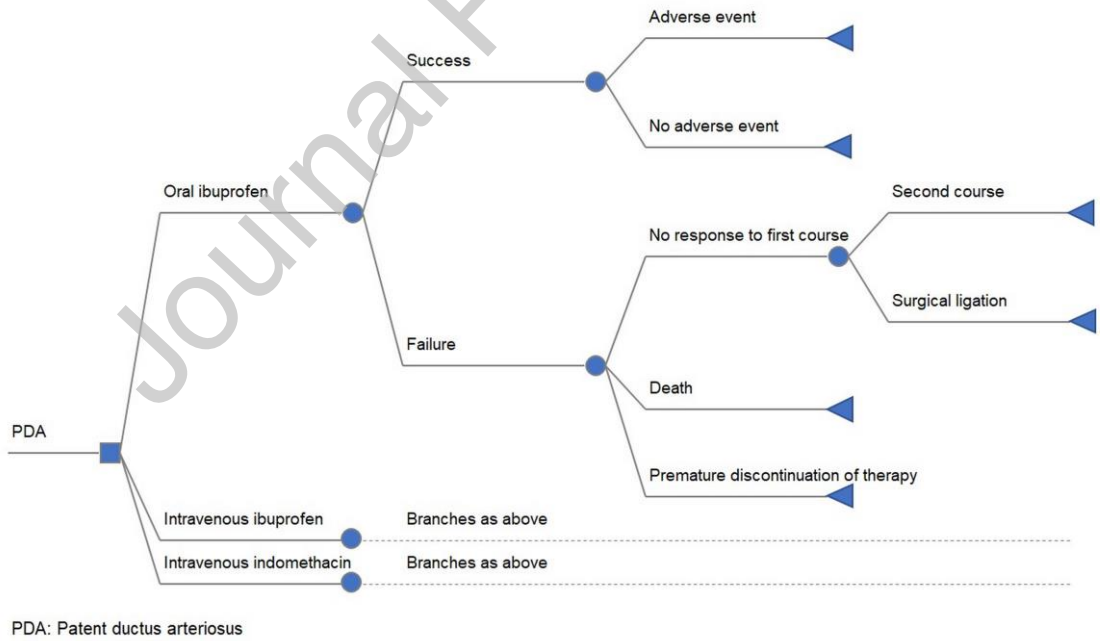

Figure 1: Decision-tree based model for patent ductus arteriosus (PDA) therapy of oral (PO) /intravenous (IV) ibuprofen versus IV paracetamol.

TABLE 1. Input variables and uncertainty distributions used in the base-case ibuprofen versus indomethacin multivariate analysis

Parameter	Oral Ibuprofen (95% CI)	IV Indomethacin (95% CI)	IV Ibuprofen (95% CI)
Clinical probabilities			
PDA closure without adverse events[1]	0.538 (0.437, 0.640)	0.351 (0.257, 0.452)	0.341 (0.248, 0.442)
PDA closure with PVL	0.069 (0.029, 0.139)	0.044 (0.011, 0.099)	0.056 (0.022, 0.126)
PDA closure with ROP	0.102 (0.049, 0.176)	0.184 (0.110, 0.270)	0.139 (0.079, 0.224)
PDA closure with BPD	0.194 (0.118, 0.281)	0.177 (0.110, 0.270)	0.190 (0.118, 0.281)
[2]**No response to first course with second course**	0.011 (0.00, 0.055)	0.039 (0.011, 0.099)	0.064 (0.022, 0.126)
[2]**No response to first course with surgical ligation**	0.005 (0.002, 0.055)	0.028 (0.006, 0.085)	0.033 (0.006, 0.085)
[2]**Death**	0.016 (0.002, 0.070)	0.035 (0.006, 0.085)	0.042 (0.011, 0.099)
[2]**Premature discontinuation with pulmonary hemorrhage**	0.001 (0.00, 0.036)	0.014 (0.000, 0.055)	0.022 (0.002, 0.070)
[2]**Premature discontinuation with IVH**	0.017 (0.00, 0.055)	0.024 (0.002, 0.070)	0.036 (0.011, 0.099)
[2]**Premature discontinuation with NEC**	0.007 (0.00, 0.055)	0.019 (0.002, 0.070)	0.018 (0.002, 0.070)
[2]**Premature discontinuation with GIB**	0.036 (0.011, 0.099)	0.027 (0.006, 0.085)	0.028 (0.006, 0.085)
[2]**Premature discontinuation with intestinal perforation**	0.003 (0.00, 0.036)	0.026 (0.006, 0.085)	0.020 (0.002, 0.070)
[2]**Premature discontinuation with oliguria**	0.001 (0.00, 0.036)	0.034 (0.006, 0.085)	0.012 (0.000, 0.055)

PDA: patent ductus arteriosus, IV: intravenous, CI: confidence interval, PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.
[1]Probability of success without adverse event is one minus overall probability of success with adverse event.
[2]The overall probability of all failure events is equal to one minus the overall probability of success.

TABLE 2. Input variables and uncertainty distributions used in the base-case ibuprofen versus paracetamol multivariate analysis

Parameter	Oral Ibuprofen (95% CI)	Oral Paracetamol (95% CI)	IV Ibuprofen (95% CI)
Clinical probabilities			
PDA closure without adverse events[1]	0.440 (0.341, 0.543)	0.512 (0.408, 0.611)	0.271 (0.186, 0.368)
PDA closure with PVL	0.033 (0.006, 0.085)	0.033 (0.006, 0.085)	0.025 (0.002, 0.0704)
PDA closure with ROP	0.097 (0.049, 0.176)	0.042 (0.011, 0.099)	0.124 (0.064, 0.200)
PDA closure with BPD	0.056 (0.022, 0.126)	0.046 (0.016, 0.112)	0.051 (0.0164, 0.113)
[2]No response to first course with second course	0.140 (0.079, 0.224)	0.167 (0.102, 0.258)	0.182 (0.110, 0.270)
[2]No response to first course with surgical ligation	0.022 (0.002, 0.070)	0.014 (0.000, 0.055)	0.031 (0.006, 0.085)
[2]Death	0.066 (0.029, 0.139)	0.073 (0.029, 0.139)	0.040 (0.011, 0.099)
[2]Premature discontinuation with pulmonary [2]hemorrhage	0.031 (0.006, 0.085)	0.033 (0.006, 0.085)	0.112 (0.056, 0.188)
[2]Premature discontinuation with IVH	0.016 (0.002, 0.070)	0.018 (0.002, 0.070)	0.007 (0.000, 0.055)
[2]Premature discontinuation with NEC	0.023 (0.002, 0.070)	0.029 (0.006, 0.085)	0.014 (0.000, 0.055)
[2]Premature discontinuation with GIB	0.035 (0.011, 0.099)	0.014 (0.000, 0.055)	0.006 (0.000, 0.055)
[2]Premature discontinuation with intestinal perforation	0.002 (0.000, 0.036)	0.000 (0.000, 0.036)	0.003 (0.000, 0.036)
[2]Premature discontinuation with oliguria	0.038 (0.011, 0.099)	0.020 (0.002, 0.070)	0.135 (0.071, 0.212)

PDA: patent ductus arteriosus, IV: intravenous, CI: confidence interval, PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.
[1]Probability of success without adverse event is one minus overall probability of success with adverse event.
[2]The overall probability of all failure events is equal to one minus the overall probability of success.

TABLE 3. Results of the Incremental cost-effectiveness ratio (ICER) among patent ductus arteriosus (PDA) treatment options

Treatment options	Cost, QAR (USD)	Effectiveness (Success)	ICER
Oral ibuprofen compared to intravenous (IV) indomethacin			
Oral ibuprofen	414,761 (113,945)	0.9034	Negative value* (oral ibuprofen is dominant over IV indomethacin)
IV indomethacin	436,158 (119,824)	0.7546	
IV ibuprofen compared to IV indomethacin			
IV ibuprofen	435,794 (119,724)	0.7256	QAR 12,546 (USD 3,447) per case of success with IV indomethacin
IV indomethacin	436,158 (119,824)	0.7546	
Oral ibuprofen compared to oral paracetamol			
Oral ibuprofen	404,970 (111,255)	0.6258	Negative value* (oral paracetamol is dominant over oral ibuprofen)
Oral paracetamol	397,798 (109,285)	0.6327	
IV ibuprofen compared to oral paracetamol			
IV ibuprofen	415,588 (114,173)	0.4706	Negative Value* (oral paracetamol is dominant over IV ibuprofen)
Oral paracetamol	397,798 (109,285)	0.6327	

ICER: Incremental cost-effectiveness ratio, QAR: Qatari Riyal, USD: united stated dollars
*Negative ICER indicates that one intervention is less costly and more effective than its comparator

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: