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Does Mortality Risk Increase with Active Treatment of Patent Ductus Arteriosus in Preterm Infants? A Critical Appraisal Skills Programme (CASP) Assessment of a Meta-Analysis

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Type of Investigation: A meta-analysis of randomized controlled trials (RCT).

Question: Do clinical outcomes differ when active treatment is compared to expectant management of hemodynamically significant Patent Ductus Arteriosus (hsPDA) in preterm infants enrolled in randomized controlled trials?

METHODS

Design. Systematic review with meta-analysis of RCTs.

Setting. Ten internationally located neonatal intensive care units.

Participants. RCTs that compared active treatment group (ATG) to expectant management group (EMG) for hsPDA in preterm infants.

Inclusion Criteria. RCTs that enrolled preterm infants born before 33 weeks' gestation, diagnosed with hsPDA by clinical or echocardiographic criteria, which compared ATG vs. EMG.

Exclusion Criteria. Studies that administered treatment for prophylaxis against hsPDA.

Randomization. Method of randomization varied by study.

Intervention. Infants in ATG received either indomethacin, ibuprofen, acetaminophen, or a combination of medications.

Controls. Premature infants in EMG did not receive treatment or received placebo.

Consent. Details of ethical review and informed consent were reported in the eligible RCTs.

Primary Outcomes. Composite outcome of death at 36 weeks postmenstrual age (PMA) or at discharge, or moderate to severe bronchopulmonary dysplasia (BPD); Composite outcome of death at 36 weeks PMA or moderate to severe BPD; Death at 36 weeks PMA; Death at 36 weeks PMA or at discharge; Moderate to severe BPD.

Secondary Outcomes. Death before hospital discharge; death at 28 days; cause of death; intraventricular hemorrhage; periventricular leukomalacia (PVL); retinopathy of prematurity (ROP; stage 3 or treated ROP); pulmonary hemorrhage; cardiovascular support (hypotension, inotropic support, or both); pulmonary hypertension; necrotizing enterocolitis (NEC; Bell stage >2); gastrointestinal perforation; gastrointestinal bleeding; time to full enteral feeding; use of diuretics; sepsis; kidney failure; use of postnatal steroids; ligation of hsPDA; duration of respiratory support (supplemental oxygen, non-invasive ventilation, or invasive ventilation); length of hospital stay; hsPDA status at discharge; weight gain; and discharge home with respiratory support or supplemental oxygen.

Analysis and Sample Size. Analyses included relative risk (RR), risk difference (RD), and random-effects models. Heterogeneity among studies was assessed using the Cochran Q test and I^2 statistic. Publication bias was evaluated using Egger and Begg tests (results not reported). Subgroup analyses included studies of infants born before 29 weeks' gestation. Statistical significance was set at $p < 0.05$ (two-tailed). All analyses were conducted using Stata version 18 (StataCorp LLC). The meta-analysis included 10 randomized controlled trials with a total of 2,035 infants (ATG: 1,018; EMG: 1,017).

RESULTS

The mean gestational age, birth weight, and proportion of male infants were similar between groups. Treatment of hsPDA was initiated within the first 72 hours of life in seven trials and after 72 hours but within the first two weeks of life in three trials. Six trials used ibuprofen, one used indomethacin, and three used a combination of ibuprofen, indomethacin, or acetaminophen. Open-label medication use was higher in the EMG than in the ATG (29.2% vs 16.1%).

Primary Outcomes:

1. The composite outcome of death at 36 weeks PMA or at discharge, or moderate to severe bronchopulmonary dysplasia (BPD), was significantly higher in the ATG compared with the EMG (56.2% vs 50.8%; RR 1.10, 95% CI 1.01-1.19; p = 0.02).
2. The composite outcome of death at 36 weeks PMA or moderate to severe BPD did not differ significantly between groups (55.6% vs 50.1%; RR 1.10, 95% CI 1.00-1.21; p = 0.06).
3. Death at 36 weeks PMA was significantly higher in the ATG (14.3% vs 11.2%; RR 1.27, 95% CI 1.01-1.61; p = 0.04).
4. Death at 36 weeks PMA or at discharge (whichever occurred later) also was significantly higher in the ATG (15.5% vs 12.4%; RR 1.25, 95% CI 1.01-1.56; p = 0.04). 0.02).
5. The risk of moderate to severe BPD did not differ significantly between groups (RR 1.08, 95% CI 0.95-1.23; p = 0.25).

Secondary Outcomes. The risk difference for PVL was significantly higher in the ATG (RD 1.8%, 95% CI 0.4-3.2%; p = 0.01); however, the relative risk was not statistically significant (RR 1.5, 95% CI 0.98-2.30; p = 0.06). No other secondary outcomes differed significantly between the two groups.

Study Conclusions. ATG, compared with EMG, was associated with a higher incidence of the composite outcome of death or moderate to severe BPD and an increased risk of mortality in preterm infants with hsPDA diagnosed within the first two weeks of life.

Scientific Commentary. The ductus arteriosus (DA) is a fetal vessel that shunts blood from the pulmonary artery to the aorta, bypassing the lungs.[2] In term infants, it closes shortly after birth; however, in preterm infants, ductal immaturity may prevent closure. Persistent patency beyond the transitional period results in a left-to-right shunt, termed patent ductus arteriosus (PDA), which can reduce gastrointestinal, renal, and cerebral perfusion.[3] In preterm infants, hsPDA is associated with increased risks of pulmonary hemorrhage, intraventricular hemorrhage, BPD, and mortality.[4-7]

Historically, 60-70% of infants born at <28 weeks' gestation with persistent PDA received pharmacologic treatment.[8] Recent evidence supports a shift toward expectant management,[9] coinciding with a marked increase in transcatheter PDA closure.[10] Annual transcatheter procedures increased from 17% to 84% in Lai et al. (see Table 1)[11] and from 0.1% to 2.9% in Shah et al. (see Table II).[12]

Medical Treatment for PDA. Indomethacin, ibuprofen, and acetaminophen commonly are used for PDA closure. Indomethacin reduces treatment failure compared with placebo without affecting mortality.[13] An umbrella review showed all three agents effectively close PDA compared with placebo.[14] However, another meta-analysis of 19 RCTs found no mortality benefit with early or very early treatment compared with expectant management, though early ibuprofen use was associated with increased mortality on sensitivity analysis.[15]

In Buvaneswarran et al.,[1] ATG was associated with increased mortality at 36 weeks postmenstrual age (PMA) but not at hospital discharge. Among infants who died, sepsis and gastrointestinal disease frequent were more in the active treatment group (eTable 8, Supplement[1]), although culture-positive sepsis did not differ significantly between groups (eFigure 2, Supplement[1]). These findings suggest that extreme prematurity, rather than pharmacologic treatment alone, may contribute to excess mortality in the ATG group.

Statistics Commentary. In a methodological assessment of meta-analyses, Ioannidis[16] reported that only 3% are clinically useful. The remainder were classified as redundant or unnecessary (27%), flawed beyond repair (20%), unpublished (20%), decent but not useful (17%), or misleading (13%). Given this context, a critical statistical appraisal of the meta-analysis by Buvaneswarran et al.[1] is warranted. We evaluated the statistical evidence using the Critical Appraisal Skills Programme (CASP) checklist for systematic reviews and meta-analyses of randomized controlled trials.[17] This 10-item tool assesses validity, methodology, trustworthiness, relevance, and applicability.

Table 1 summarizes the CASP results, identifying two strengths (Section A) and multiple weaknesses across Sections B-E (Items 3-10). The full CASP assessment is provided in Supplemental (available online at journals.ku.edu/kjm). Key limitations included a potentially incomplete literature search (CASP Item 3), absence of a certainty-of-evidence assessment (CASP Item 4), unadjusted statistical analyses, and underpowered subgroup analyses (CASP Items 5-6).

To assess the completeness of the literature search, we compared Buvaneswarran et al.[1] with two contemporary systematic reviews (see Table 2). Mitra et al.[15] included 14 studies, seven of which were not captured by Buvaneswarran et al.[1] Matsushita et al.[18] included 14 studies (nine distinct from Mitra et al.[15]), 11 of which also were absent from Buvaneswarran et al.[1] Of the 25 unique studies identified across these reviews, only 10 were included in the Buvaneswarran et al.[1] meta-analysis. Thus, the evidence appears to be insufficient, and may have introduced a bias in the results and conclusion made by Buvaneswarran et al.[1]

Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines recommend assessing certainty of evidence using frameworks such as GRADE, which evaluate study design, risk of bias, inconsistency, imprecision, and publication bias.[19] These assessments are essential for determining the reliability of effect estimates (CASP Items 4, 7-10).

Buvaneswarran et al.[1] did not report certainty-of-evidence assessments or statistical adjustments for zero-event outcomes (e.g., Sidik-Jonkman or Knapp-Hartung methods[20]), nor did they account for small sample sizes in subgroup analyses, some of which included as few as two studies. These limitations raise concerns about the robustness of the reported findings.

Additional statistical concerns include potential confounding and treatment heterogeneity. Treatment initiation timing varied, as did medication type (ibuprofen, indomethacin, or multiple agents), without reported evaluation of regimen differences. Moreover, open-label medication use was higher in the EMG than in the ATG (29.2% vs 16.1%).[1] Given treatment contamination and lack of stratification, it remains unclear which interventions, if any, primarily drove the observed outcomes, limiting interpretability and causal inference (CASP Items 8-10).

Conclusions

Our critical appraisal of Buvaneswarran et al.[1] identified strengths in CASP items 1-2 but also multiple weaknesses across items 3-10, including potential confounding, treatment contamination, and unreported treatment differences. Given these substantial limitations, we conclude that there is insufficient evidence to determine that active management within the first two weeks of life is associated with increased mortality.

If complete evidence was collected from the published trials (as listed in Table 2), and treatment contamination along with statistical issues listed in CASP were addressed, Buvaneswarran et al.[1] conclusion to "question the conventional wisdom in the management of PDA in preterm infants" may have been different.

Table 1. CASP General SR Checklist: Collation of critical appraisal responses.

Checklist question	Yes	No	Can't tell
A. Is the basic study design valid for a systematic review?			
1. Did the systematic review address a clearly formulated research question?	X		
2. Did the researchers search for appropriate study designs to answer the research question?	X		
B. Is the systematic review methodologically sound?			
3. Were all relevant primary research studies likely to have been included in the systematic review?		X	
4. Did the researchers assess the validity or methodological rigour of the primary research studies included in the systematic review?		X	
5. Did the researchers extract, and present information on the individual primary research studies appropriately and transparently?		X	
C. Are the results of the systematic review trustworthy?			
6. Did the researchers analyse the pooled results of the individual primary research studies appropriately?		X	
7. Did the researchers report any limitations of the systematic review and, if so, do the limitations discussed cover all the issues in your critical appraisal?		X	
8. Would the benefits of intervention outweigh any potential disadvantages, harms and/or additional demand for resources associated with acting on the results?		X	
D. Are the results of the systematic review relevant locally?			
9. Can the results of the systematic review be applied to your local population/in your local setting or context?			X
10. If actioned, would the findings from the systematic review represent greater or additional value for the individuals or populations for whom you are responsible?		X	

Table 2. Comparison of articles included in three meta-analyses of the same topic and period.

Trial	Intervention	Comparison	Included in the systematic review
Clyman 2019	more than one	expectant	Buvaneswarran[1]
Sung 2020	ibuprofen	expectant	Buvaneswarran1
de Waal 2021	more than one	expectant	Buvaneswarran1 / Mitra[15]
Gupta 2024	ibuprofen	expectant	Buvaneswarran1 / Mitra[15]
Kluckow 2014	indomethacin	expectant	Buvaneswarran1 / Mitra[15]
Potsiurko 2024	more than one	expectant	Buvaneswarran1 / Mitra[15]
Hundscheid 2023	ibuprofen	expectant	Buvaneswarran1 / Matsushita18 / Mitra[15]
Rozé 2021	ibuprofen	expectant	Buvaneswarran1 / Matsushita18 / Mitra[15]
Sosenko 2012	ibuprofen	expectant	Buvaneswarran1 / Matsushita18 / Mitra[15]
Babaei 2018	acetaminophen	expectant	Matsushita[18]
Bagheri 2018	paracetamol	placebo	Matsushita[18]
Ding YJ 2014	ibuprofen	placebo	Matsushita[18]
Harkin P 2016	paracetamol	placebo	Matsushita[18]
Kanmaz G 2013	ibuprofen	expectant	Matsushita[18]
Kluckow M 2013	indomethacin	placebo	Matsushita[18]
Kluckow M 2019	paracetamol	placebo	Matsushita[18]
Noori NM 2023	expectant	acetaminophen	Matsushita[18]
Sung SI 2020	ibuprofen	expectant	Matsushita[18]
El-Khuffash 2021	ibuprofen	placebo	Matsushita18 / Mitra[15]
Schindler T 2021	paracetamol	placebo	Matsushita18 / Mitra[15]
Bagnoli 2013	ibuprofen	placebo	Mitra[15]
CTRI 2009	indomethacin	no treatment	Mitra[15]
Ghanem 2010	ibuprofen	placebo	Mitra[15]
Knight 2011	indomethacin	placebo	Mitra[15]
Lin 2012	ibuprofen	placebo	Mitra[15]

Note: Expectant, placebo, and no treatment all indicate expectant management of patent ductus arteriosus.

Given the concern of potential harm from active treatment, it would be prudent to selectively treat premature infants with Patent Ductus Arteriosus that is >1.5 mm in diameter with unrestricted left to right flow, left atrium to aortic root ratio of >1.5 and moderate to large shunt volumes. Active treatment is best avoided when the PDA diameter is <1.5 mm, and in those with heart dysfunction, pulmonary hypertension, and low shunt volume.[21-23]

ARTICLE INFORMATION

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