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Inotrope Use and the Risk of Intraventricular Hemorrhage in Preterm Neonates: A Systematic Review and Meta Analysis

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Abstract

More than 40% of neonatal hypotension cases are managed with inotropes; however, recent evidence indicates that inotrope administration, rather than hypotension itself, is independently associated with an increased risk of intraventricular hemorrhage (IVH) after adjustment for confounding factors. This systematic review and meta-analysis aimed to evaluate the association between inotrope use and the occurrence of IVH among preterm neonates. The study followed PRISMA guidelines. A systematic literature search was conducted through PubMed, Scopus, ScienceDirect, and Google Scholar. The methodological quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) for case-control and cohort designs. Relevant data were extracted for qualitative and quantitative synthesis. Meta-analysis was performed using a random-effects model based on adjusted odds ratios (aORs) reported in each study, and the results were presented as pooled aORs with 95% confidence intervals. Eight studies met the inclusion criteria. The meta-analysis showed that inotrope use was significantly associated with a higher risk of IVH in preterm neonates, including IVH of any grade (pooled OR 2.03, 95% CI 1.25-3.29) and severe IVH (pooled OR 2.00, 95% CI 1.33-3.02). Overall, inotrope use doubled the risk of IVH (pooled OR 2.00, 95% CI 1.48-2.70). The uniqueness of this study lies in demonstrating that inotrope administration, rather than hypotension alone, serves as an independent predictor of IVH in preterm neonates, highlighting the need for cautious, strictly indicated use and standardized hemodynamic management protocols. These findings provide quantitative guidance for clinicians to optimize neonatal care and minimize IVH risk.

Keywords**: **inotropes, preterm neonates, intraventricular hemorrhage, risk factors

INTRODUCTION

Preterm infants are particularly susceptible to intraventricular hemorrhage (IVH), a common and serious complication of prematurity that contributes substantially to long term neurodevelopmental morbidity. IVH affects approximately one-third of preterm neonates, with the highest incidence observed in infants born before 26 weeks of gestation and a clear inverse relationship between gestational age and IVH risk (Rees et al., 2025). Infants who survive severe IVH continue to face a considerable risk of lifelong neurological impairment. A global meta-analysis by Lai et al. (2022) reported an overall IVH incidence of 34.3% among infants born before 28 weeks, with severe IVH accounting for 15%. Even low-grade IVH has been linked to increased rates of cerebral palsy, cognitive and motor delay, hearing and visual impairment, and poorer developmental scores, whereas severe IVH is associated with more pronounced and persistent deficits (Zhou et al., 2024).

The pathogenesis of IVH is multifactorial. Instability in cerebral blood flow, hemodynamically significant patent ductus arteriosus, abnormal arterial carbon dioxide levels, impaired venous drainage, fragile germinal matrix vasculature, and genetic predisposition all increase susceptibility to hemorrhage (Tsao, 2023). Preventive efforts span antenatal, perinatal, and postnatal periods and include the administration of antenatal corticosteroids and magnesium sulfate, delivery at tertiary centers, and postnatal strategies aimed at maintaining cardiovascular stability.

Hypotension occurs in 15% to 50% of extremely preterm infants, although the absence of a universal definition complicates clinical decision-making. Mean arterial blood pressure below gestational age in weeks is commonly used as a threshold, yet it remains an imperfect indicator of systemic and cerebral perfusion (Tsao, 2023). Inotropes are administered in up to 40% of hypotensive or hemodynamically unstable preterm infants, largely to increase mean arterial pressure (Wong et al., 2015). However, emerging evidence suggests that inotrope administration, rather than hypotension alone, may independently contribute to an elevated risk of severe IVH, even after adjustment for confounders (Aziz et al., 2020).

These uncertainties regarding the benefits and potential harms of inotropes underscore the need for a clearer understanding of their relationship with IVH. Therefore, this systematic review and meta-analysis was undertaken to evaluate the association between inotrope use and the occurrence of intraventricular hemorrhage in preterm neonates.

RESEARCH METHODS

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines and was prospectively registered in PROSPERO (ID: CRD420251139905). A comprehensive literature search was performed in May 2025 across PubMed, Scopus, ScienceDirect, and Google Scholar to identify studies examining the association between inotrope administration and intraventricular hemorrhage (IVH) in preterm neonates. The search strategy used combinations of controlled vocabulary and free-text terms, including “inotrope,” “dopamine,” “dobutamine,” “epinephrine,” “norepinephrine,” “vasoactive agents,” “intraventricular hemorrhage,” “severe intraventricular hemorrhage,” “periventricular hemorrhage,” “germinal matrix hemorrhage,” “preterm,” “premature infant,” “very low birth weight,” “extremely low birth weight,” “neonate,” and “newborn.” Duplicate records were removed prior to screening, and two reviewers independently evaluated titles and abstracts for eligibility, with full-text articles retrieved for further assessment. Discrepancies were resolved through discussion and consensus.

Studies were eligible for inclusion if they investigated preterm neonates (<37 weeks of gestation), including very low birth weight (<1500 g) and extremely low birth weight (<1000 g) infants; evaluated the association between inotrope use, such as dopamine, dobutamine, epinephrine, norepinephrine, milrinone, or other vasoactive agents, and intraventricular hemorrhage; defined IVH based on the Papile classification or equivalent cranial ultrasound criteria; reported adjusted effect estimates such as adjusted odds ratios with 95% confidence intervals; used a cohort, case control, randomized controlled trial, or cross-sectional design; and were published in English between January 2015 and May 2025. Studies were excluded if they did not report adjusted effect estimates, did not present data on both inotrope exposure and IVH outcomes, lacked full text availability, or were reviews, systematic reviews, meta-analyses, editorials, commentaries, conference abstracts, case reports, or non-English publications.

Data extraction was performed independently by two reviewers using a pre-piloted Excel form. Extracted variables included the first author, year of publication, study location, study period, study design, sample size, population characteristics, type and timing of inotrope exposure, IVH definitions, and adjusted effect estimates. The methodological quality of all included studies was assessed using the Newcastle, Ottawa Scale (NOS), which evaluates participant selection, comparability of study groups, and outcome assessment. Studies with NOS scores of six or higher were classified as high quality.

The primary analysis pooled adjusted odds ratios with 95% confidence intervals to estimate the association between inotrope administration and IVH risk. A random effects model was applied to account for anticipated heterogeneity across studies. Forest plots were generated to present individual and pooled effect sizes. Statistical heterogeneity was evaluated using the Cochran Q test (with $p < 0.10$ considered significant) and the I^2 statistic, where values of 50% or greater indicated substantial heterogeneity. Sensitivity analyses were conducted by sequentially excluding individual studies to test the robustness of the findings. When ten or more studies were available, publication bias was assessed using funnel plots. All analyses were performed using Review Manager (RevMan) version 5.4.1.

RESULTS AND DISCUSSION

Literature Search

A total of 504 articles were identified through the database search conducted across PubMed, Scopus, ScienceDirect, and Google Scholar. After the removal of 75 duplicates, 429 unique records remained for title and abstract screening. Of these, 25 full text articles were assessed for eligibility, and ultimately 8 studies met the inclusion and exclusion criteria and were included in this systematic review and meta analysis. The overall study selection process is presented in the PRISMA flow diagram (Figure 1).

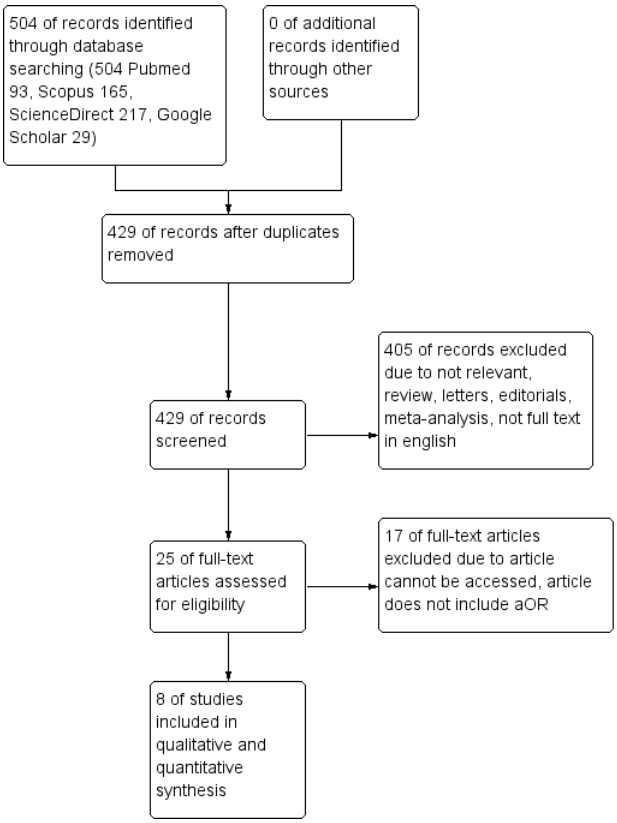

Figure 1. PRISMA Flow Diagram

Characteristics of Included Studies

Eight studies, comprising a pooled sample of 33,966 preterm neonates, were included in this meta analysis. Two studies were conducted in Canada (Wong et al., 2015; Aziz et al., 2020), two in the United States (Verma et al., 2019; Vesoulis et al., 2020), and the remaining studies

were conducted in Saudi Arabia (Al-Mouqdad et al., 2021; Alotaibi et al., 2020), Egypt (Hedia et al., 2025), and China (Xiao et al., 2024).

Study designs varied across the included research: three retrospective cohort studies (Wong et al., 2015; Alotaibi et al., 2020; Xiao et al., 2024), two retrospective case control studies (Verma et al., 2019; Al-Mouqdad et al., 2021), two prospective cohort studies (Aziz et al., 2020; Vesoulis et al., 2020), and one prospective case control study (Hedia et al., 2025).
Gestational age (GA) criteria differed across studies. Three studies included infants with GA ≤34 weeks (Al-Mouqdad et al., 2021; Alotaibi et al., 2020; Hedia et al., 2025), one included infants with GA ≤30 weeks (Vesoulis et al., 2020), and two focused on infants <29 weeks (Wong et al., 2015; Aziz et al., 2020). Verma et al. (2019) enrolled exclusively extremely low birth weight (ELBW) infants, while Xiao et al. (2024) included infants ≤32 weeks or ≤1500 g. In terms of birth weight thresholds, Alotaibi et al. (2020) and Xiao et al. (2024) explicitly included infants ≤1500 g.

Across the included studies, dopamine was the most commonly reported first-line inotrope, followed by dobutamine, epinephrine, and norepinephrine. IVH assessment was predominantly conducted using cranial ultrasound within the first week of life, with most studies applying the Papile grading system (Grades I–IV). Assessment of methodological quality using the Newcastle, Ottawa Scale (NOS) indicated that all studies demonstrated a low risk of bias, with each achieving a score of six or higher.

Table 1. Baseline Characteristic of Studies

Author	Period	Location	Study Design	Sample Size	Inclusion Criteria	Type & Timing of Inotropes Exposure	IVH assessment	NOS score
Al-Mouqdad et al (2021)[11]	2015-2018	Saudi Arabia	Retrospective case control	216	Preterm neonates ≤32 weeks, birth weight <1500 g, admitted to level 3 NICU; excluded if born outside hospital, congenital anomalies, asphyxia, death <72 h, etc.	NA (within first 7 days of life)	Head ultrasound (days 5–7 of life), classified by Papile (Grades I–IV)	7
Aziz et al. (2019)[8]	2013-2016	Canada	Prospective cohort	497	GA ≤29 weeks, admitted to NICU; excl: major anomalies, antenatal injury, congenital infection	Dopamine, Dobutamine, Epinephrine/Norepinephrine (within 72 h of life)	Cranial US in week 1; using Papile classification for IVH, plus PHVD and cPVL evaluation	8
Verma et al. (2019)[9]	2003-2009	USA	Retrospective case controle	267	ELBW, non-anomalous, admitted to NICU; excl: death/transfer <24 h, major anomalies	Dopamine, Dobutamine, Epinephrine (within first 7 days of life)	Cranial US; IVH recorded within first 14 days; Papile grading	7
Hedia et al. (2025)[13]	NA	Egypt	Prospective case-control	50	GA <34 weeks; excl: HIE, major anomalies, bleeding tendency, congenital infection	Dopamine, Dobutamine, Adrenaline, Noradrenaline (within first 7 days of life)	Cranial US on day 1, day 7, and after starting inotropes; Papile grade I–IV	8
Wong et al. (2015)[6]	2003-2010	Canada	Retrospective cohort	7913	Infants <29 weeks gestational age admitted to NICUs; excluded <23 weeks GA, moribund on admission, or major congenital anomalies	Dopamine, Dobutamine, Epinephrine, Norepinephrine; (Day 1 & 3)	Head ultrasound, worst findings during admission, classified by Papile criteria (Grade I–IV).	8
Vesoulis et al. (2020)[10]	2012-2017	USA	Prospective cohort	157	GA ≤30 weeks; cranial US in week 1; ≥7 days hemodynamic data	Dopamine, Epinephrine (within first 7 days of life)	Cranial US in week 1; classified as none, grade I/II, severe (III/IV	7
Xiao et al. (2024)[14]	2015-2019	China	Retrospective cohort	24.226	GA 24+0 – 31+6 weeks, admitted to NICU within 24h of	Dopamin, Dobutamin, Epinefrin, Norepinefrin	Cranial ultrasound within 3–7 days after birth and	8

				life, complete data; Excluded: major congenital anomalies, no head US	(within first 3 days of life)	repeated as indicated; IVH graded by Papile classification (Grades I–IV)	
Alotaibi et al. (2020)[12]	2016-2018	Saudi Arabia	Retrospective cohort	640	Infants 24–32 wks GA and/or ≤1500 g; excluded: born outside hospital, died <7 days, major congenital anomalies	NA (Within first 72 h)	Cranial US within first 7 days; Papile grade I–IV	8

Inotrope Use and IVH (Based on Adjusted Data)

The meta-analysis included eight studies evaluating the association between inotrope administration and intraventricular hemorrhage (IVH) in preterm neonates. The pooled analysis of adjusted odds ratios showed that inotrope use was significantly associated with a higher risk of IVH of any grade, with an adjusted odds ratio of 2.03 and a 95 percent confidence interval of 1.25 to 3.29 ($p = 0.004$; $I^2 = 53$ percent). A similar association was observed for severe IVH, with an adjusted odds ratio of 2.00 and a 95 percent confidence interval of 1.33 to 3.02 ($p = 0.0009$; $I^2 = 87$ percent). When all IVH outcomes were combined, inotrope administration was associated with a two fold increase in the adjusted odds of IVH (adjusted odds ratio 2.00, 95 percent confidence interval 1.48 to 2.70, $p < 0.00001$), and heterogeneity was substantial ($I^2 = 77$ percent). Subgroup comparisons showed no significant difference between the effect estimates for any grade and severe IVH (p for subgroup difference = 0.97).

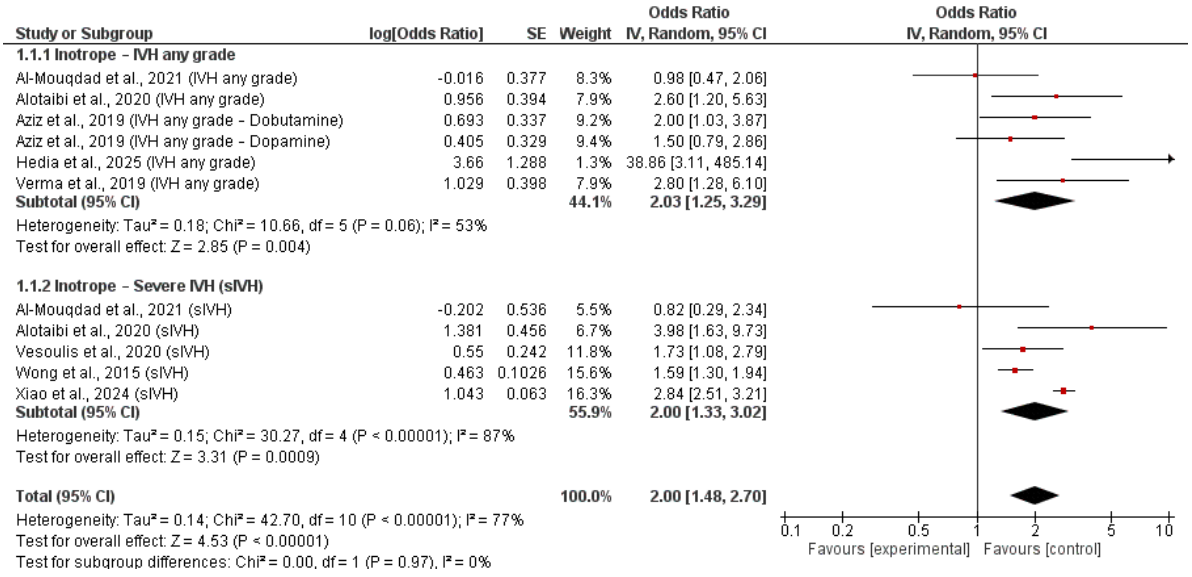

Figure 2. Forest plot of inotrope use and risk of intraventricular hemorrhage

Sensitivity Analysis

Sensitivity analysis comparing fixed effect and random effects models showed consistent results across all analyses. The stability of the effect estimates indicated that small study effects were unlikely to influence the findings. Overall, the results of this meta analysis were considered robust.

Publication Bias

Although fewer than ten studies were included, a funnel plot was generated to explore potential publication bias (Figure 3). The distribution of studies was somewhat asymmetrical, with several points located to the right of the mean effect. This pattern suggested the possibility of

publication bias or small study effects. However, due to the limited number of studies, these observations should be interpreted with caution.

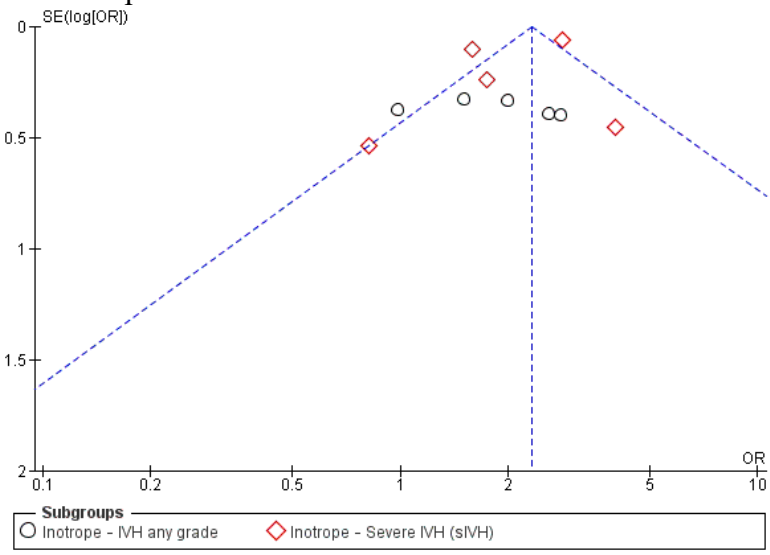

Figure 3. Funnel plot of inotrope use and risk of intraventricular hemorrhage

Discussion

In this systematic review and meta-analysis, 504 records were initially identified, and 429 remained after duplicate removal. Following title and abstract screening, 405 records were excluded. Of the 25 full text articles assessed for eligibility, 17 were excluded because adjusted odds ratios were not available or the full text could not be retrieved. Finally, eight studies met the inclusion criteria. The pooled analysis demonstrated that inotrope administration in preterm infants was associated with a significantly increased risk of intraventricular hemorrhage. Specifically, inotrope use was linked to a two-fold increase in the risk of any grade IVH and an equally elevated risk of severe IVH. These findings indicate that inotropes, while often used to support circulatory stability, may contribute to adverse neurological outcomes among preterm neonates.

Preterm infants are especially vulnerable to cardiovascular instability during the transition to extrauterine life due to immature myocardial, vascular, and cerebral autoregulatory mechanisms. Increased systemic vascular resistance after birth, patent ductus arteriosus related volume overload, impaired venous return, and fluctuating cerebral blood flow contribute to the risk of IVH (Tsao, 2023). The germinal matrix is highly sensitive to hemodynamic instability, and even small fluctuations in perfusion pressure can precipitate hemorrhage. Therapeutic interventions intended to stabilize hemodynamics, such as intravenous fluids, inotropes, and postnatal corticosteroids, may inadvertently cause rapid changes in blood pressure that further increase IVH risk (Al-Mouqdad et al., 2021).

Blood pressure instability, both hypotension and hypertension, is strongly associated with IVH. Hypotension occurs in 15 to 50 percent of extremely preterm neonates (Tsao, 2023). Yet, defining normal blood pressure in this population is challenging. Clinical thresholds vary widely, ranging from a mean arterial pressure (MAP) below gestational age in weeks, to MAP below the fifth or tenth percentile for gestational age and weight, or an absolute MAP below 30 mmHg (Abdul Aziz et al., 2020). The absence of consensus contributes to inconsistent clinical practice. Evidence suggests that aggressive treatment may worsen outcomes, including increased mortality and IVH, compared to permissive hypotension in infants who remain clinically stable. Similarly, the use of vasopressors remains controversial because some studies have linked them to impaired cerebral autoregulation and an elevated risk of brain injury (Abdul Aziz et al., 2020).

The inconsistency surrounding treatment thresholds is reflected in clinical practice patterns. Batton et al. (2013) observed that among 367 infants born at 23 to 26 weeks of gestation, 55 percent received at least one antihypotensive therapy. Notably, 49 percent of infants classified as hypotensive were not treated, whereas 41 percent without hypotension still received treatment. These findings highlight that treatment decisions are influenced by factors beyond blood pressure measurements alone, and they underline the uncertainty regarding the benefits of inotrope therapy. The adjusted odds ratios in the present meta-analysis reinforce these observations, showing significantly increased risks of IVH in infants who received inotropes.

Variability in inotrope use across NICUs has been reported for decades. For instance, Al-Aweel et al. (2001) documented that inotrope administration ranged from 4 to 39 percent across six centers in the northeastern United States. This variability likely reflects the limited evidence supporting the efficacy of inotropes in neonates, as well as differences in institutional protocols and clinician preferences. The administration of inotropes may also reflect underlying illness severity. However, growing evidence indicates that inotropes themselves can impair cerebral autoregulation (Bouyssi-Kobar et al., 2018). Immature myocardium and impaired vasoregulation limit the ability of preterm infants to adapt to hemodynamic changes, increasing susceptibility to hypotension and associated complications (Wong et al., 2015).

Dopamine was identified as the most frequently used inotrope in the included studies. Although it is commonly selected as a first line agent, prior research suggests that dopamine may reduce organ perfusion and impair cerebral autoregulation without improving cerebral blood flow despite raising systemic blood pressure (Abdul Aziz et al., 2020). Consistent with findings from pediatric and adult populations, dopamine has been associated with higher mortality rates compared to norepinephrine or epinephrine, and may also decrease ventricular output in preterm infants, potentially triggering fluctuations in cerebral perfusion that predispose to IVH (Ventura et al., 2015; De Backer et al., 2012).

Recent discussion has emphasized the importance of considering not only pharmacodynamics and pharmacokinetics, but also the delivery kinetics of vasoactive agents in preterm infants. Garvey et al. (2018) noted that low flow continuous infusions of inotropes, often administered at rates of 0.1 to 1 mL per hour, may experience delays in onset and steady state due to catheter dead space. These delivery limitations may lead to unpredictable drug exposure, particularly for medications with narrow therapeutic indices. Despite widespread use, the effects of inotropes on end organ perfusion and long-term neurodevelopmental outcomes remain poorly understood. Studies have reported mixed findings, with some demonstrating improved cerebral perfusion, while others describe unchanged or even reduced perfusion depending on blood pressure changes, pulmonary vascular resistance, and the infant's underlying autoregulatory capacity.

This meta analysis has several strengths. It is among the few studies to examine the independent effect of inotrope use on IVH risk while controlling for confounding variables. The requirement for adjusted effect estimates strengthened internal validity, and the overall sample size of more than 33,000 infants provided strong statistical power. However, the study also has limitations. The small number of included studies restricted the ability to perform detailed subgroup analyses and limited the assessment of publication bias. Heterogeneity was substantial, likely due to differences in study design, patient populations, timing and type of inotrope administration, and approaches to IVH assessment. Residual confounding from unmeasured variables cannot be excluded. Additionally, limited reporting on the timing, dosage, and duration of inotrope use prevented more detailed analyses of dose-response relationships.

Future research should prioritize multicenter prospective studies or randomized controlled trials to clarify whether inotropes play a causal role in the development of IVH among preterm infants. There is also a need for standardized definitions of neonatal hypotension and consistent

hemodynamic management protocols across NICUs. Alternative strategies for managing hypotension, including optimized fluid management or non pharmacologic interventions, warrant further evaluation. Incorporating advanced hemodynamic monitoring may also enable more individualized and physiologic approaches to circulatory support, potentially reducing reliance on inotropes and minimizing IVH risk.

CONCLUSION

This meta-analysis demonstrates that inotrope use in preterm neonates is independently associated with a significantly increased risk of intraventricular hemorrhage (IVH), including both any-grade and severe forms. Infants receiving inotropes exhibited approximately twice the risk of developing IVH compared to those who did not, highlighting the importance of careful, justified administration. The study classifies the risk according to IVH severity, providing clear performance indicators for clinical decision-making. These findings contribute to neonatal care by emphasizing the need for standardized hemodynamic management protocols to minimize unnecessary exposure to inotropes. Future research should focus on large-scale prospective studies and randomized controlled trials to clarify causality, refine risk stratification, and identify safer and more effective strategies for managing hypotension in preterm infants. Long-term follow-up studies are also warranted to assess neurodevelopmental outcomes associated with inotrope use.

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