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Effect of Intact Cord Resuscitation Versus Conventional Cord Clamping on Clinical Outcomes in Very Preterm Neonates: A Randomized Controlled Trial from Eastern India

Dinesh Munian
Medical College and Hospital
Arindam Ghosh
Medical College and Hospital
Kushal Mandal
kushalastrophys@gmail.com
Medical College and Hospital
Ayan Das
Medical College and Hospital
Arun Kumarendu Singh
Dr. BC Roy Post Graduate Institute of Pediatric Sciences
Dipankar Jana
Epidemic Intelligence Surveillance Officer
Ramprasad Dey
Medical College and Hospital
Shipra Mondal
Medical College and Hospital

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Abstract

Introduction:

Early umbilical cord clamping during delivery-room resuscitation may interrupt placental transfusion during cardiopulmonary transition, increasing neonatal morbidity and mortality. This study aimed to evaluate whether intact cord resuscitation (ICR) improves delivery-room stabilization and clinical outcomes in very preterm neonates.

Methods

In this single-centre, open-label randomized controlled trial at a tertiary-care hospital in Eastern India, neonates born at 26^{+0}–31^{+6} weeks' gestation requiring delivery-room resuscitation were randomized (1:1) to ICR until physiological placental expulsion or conventional cord clamping (CCC) within 30–60 seconds of birth. The primary outcome was a composite of in-hospital mortality, severe intraventricular haemorrhage (IVH), or bronchopulmonary dysplasia. Secondary outcomes included delivery-room stabilization, maternal safety, and other neonatal morbidities. Analyses followed a per-protocol approach.

Results

A total of 127 neonates were analysed (ICR, n = 64; CCC, n = 63). Median (IQR) cord attachment duration was 330 (240–480) seconds in the ICR group and 60 (45–60) seconds in the CCC group. The composite adverse outcome was less frequent with ICR than CCC (35.9% vs 60.3%), corresponding to an absolute risk reduction of 24.4%. Mortality (26.6% vs 41.3%) and severe IVH (9.4% vs 20.6%) were also lower with ICR. ICR was associated with higher Apgar scores, improved oxygenation, reduced positive-pressure ventilation needs, earlier spontaneous respiration, lower sepsis and retinopathy of prematurity rates, higher haemoglobin at 72 hours, earlier full enteral feeds, and shorter oxygen therapy. Maternal safety outcomes were comparable between groups.

Conclusions

ICR may be a promising strategy to improve early cardiopulmonary stabilization and reduce adverse neonatal outcomes in very preterm infants.

Trial Registration:

CTRI/2025/10/096001; Registration date October 13, 2025

What is Known

- Cord clamping before completion of cardiopulmonary transition may adversely affect haemodynamic stability and clinical outcomes in very preterm infants.
- Intact cord resuscitation (ICR) permits stabilisation while maintaining placental circulation, but evidence regarding its efficacy and safety in very preterm neonates remains limited.

What is New

- ICR reduced the composite adverse outcome including mortality and, severe intraventricular haemorrhage.
- ICR improved delivery-room stabilisation, reduced positive-pressure ventilation requirements, and increased haemoglobin concentration at 72 hours.

INTRODUCTION

Perinatal asphyxia continues to represent a major contributor to neonatal mortality and long-term neurodevelopmental morbidity, particularly within low- and middle-income countries [**1**]. Premature neonates are especially vulnerable because of physiological immaturity, fragile cerebrovascular autoregulation, and limited cardiopulmonary reserve. Optimizing delivery-room stabilization during this critical period is therefore essential for improving survival and reducing subsequent morbidity.

In spontaneously breathing neonates, both the International Liaison Committee on Resuscitation and the World Health Organization recommend delayed cord clamping for 30–60 seconds and 60–180 seconds, respectively, to facilitate placental transfusion, enhance pulmonary blood flow, and support cardiopulmonary adaptation [**2,3**]. Experimental and physiological studies have demonstrated that clamping the umbilical cord before lung aeration reduces venous return, increases left ventricular afterload, and compromises cardiac output during neonatal transition [**4**]. However, in conventional practice, non-breathing or depressed neonates requiring resuscitation frequently undergo early cord clamping, resulting in abrupt interruption of placental circulation during ongoing hypoxia and incomplete lung aeration.

Intact cord resuscitation (ICR) is an emerging physiology-based approach in which ventilation and stabilization are initiated while placental circulation is maintained. By preserving preload, supporting pulmonary blood flow, and allowing continued placental gas exchange during early stabilization, ICR may facilitate smoother cardiopulmonary transition and reduce hypoxic–ischemic injury [**5,6**].

Despite a strong physiological rationale, clinical evidence supporting ICR remains limited, particularly among very preterm neonates requiring active resuscitation in resource-limited settings. Furthermore, whether maintaining placental circulation during neonatal stabilisation translates into improvements in clinically important outcomes beyond immediate physiological transition remains uncertain. Therefore,

this study aimed to evaluate the effects of ICR compared with conventional cord clamping (CCC) on a composite adverse neonatal outcome, as well as delivery-room stabilisation parameters, maternal safety outcomes, and other neonatal morbidities, in very preterm neonates.

METHODS

Study Design and Setting: This single-centre, open-label, parallel-group randomised controlled trial (RCT) was conducted from November 2025 toApril 2026 at a tertiary-care referral hospital in eastern India providing level III neonatal care. The study was reported according to the CONSORT guideline.

Study Participants: Preterm neonates born between 26^{+0} and 31^{+6} weeks' gestation who required delivery-room resuscitation were eligible.Eligible neonates were randomized immediately before delivery to either the ICR or CCC group. Neonates who were clinically stable at birth and did not require resuscitation were excluded and provided standard care as per Neonatal Resuscitation Program (NRP) guidelines [**7**].

Exclusion criteria included maternal seropositivity for HIV or hepatitis B or C with poor treatment compliance; monochorionic twin pregnancies; triplets or higher-order multiple gestations; major congenital anomalies; fetal hydrops; twin-to-twin transfusion syndrome; placental abruption; placenta previa; abnormal fetal umbilical artery Doppler findings; and maternal haemodynamic instability.

Sample size calculation: Based on a previous randomized trial reporting a composite adverse outcome rate of 47% among very preterm infants [**8**], and meta-analyses demonstrating reductions in mortality and IVH with delayed cord-clamping strategies [**9,10**], a 50% relative reduction in the composite outcome was considered clinically meaningful. Assuming event rates of 47% in the control group and 23.5% in the intervention group, with a two-sided α of 0.05 and 80% power, the minimum required sample size was 61 infants per group. Allowing for 5% attrition, the target sample size was increased to 64 infants per group.

Randomization and allocation: Eligible neonates were randomized in a 1:1 ratio using computer-generated stratified block randomization with variable block sizes of 4 and 6, stratified according to mode of delivery (vaginal or caesarean). The sequence was generated by an independent investigator not involved in recruitment, intervention delivery, or outcome assessment. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes opened immediately before delivery after reconfirmation of eligibility and consent.A screening logbook was maintained to document all eligible and excluded neonates with reasons for exclusion.

Interventions:

Standard care common to both groups:Neonates who were non-crying or failed to establish effective spontaneous respiration at birth were wrapped in sterile plastic wrap and transferred to a preconfigured resuscitation trolley. Delivery-room stabilization was performed by NRP-trained personnel under the supervision of a senior resident according to NRP guidelines **[7].** Continuous monitoring included pulse

oximetry and dry-electrode electrocardiographic monitoring (NeoBeat). Positive-pressure ventilation (PPV), when indicated, was delivered using a T-piece resuscitator with ventilation pressures and fraction of inspired oxygen adjusted according to NRP recommendations.

ICR group: Neonates allocated to the ICR group were stabilized on that dedicated intact cord resuscitation trolley positioned adjacent to the mother without tension on the umbilical cord. Initial stabilization and resuscitative interventions, including PPV when indicated, were initiated while placental circulation was maintained. The umbilical cord remained intact until physiological placental expulsion unless earlier clamping was clinically required because of maternal or neonatal indications. Reasons for early cord clamping were documented. Uterotonic agents were administered only after cord clamping following institutional protocol.

CCR group: In the CCC group, the umbilical cord was clamped within 30–60 seconds after birth, and subsequent stabilization and resuscitation were performed according to NRP guidelines.

Equipment:A purpose-designed, battery-operated, easily manoeuvrable intact cord resuscitation trolley (Phoenix) with a foot-operated adjustable height mechanism and 360-degree rotatable bassinet, incorporating an inbuilt CPAP system, humidifier, T-piece resuscitator, and self-inflating bag-and-mask device, was used **(Supplementary Fig. 1A and B).** The trolley was positioned adjacent to the maternal introitus during vaginal deliveries and alongside the operating table during caesarean deliveries without interfering with obstetric management or causing cord tension. Heart rate monitoring was performed using a dry-electrode ECG device (NeoBeat; Laerdal Medical) **(Supplementary Fig. 1C),** and preductal oxygen saturation was monitored using a Masimo pulse oximeter.

Operational Definitions: In the CCC group, the umbilical cord was clamped within 30–60 seconds after birth, whereas in the ICR group, resuscitation was performed while maintaining placental circulation until physiological placental expulsion.Hypothermia was defined as axillary temperature <36.5°C. IVH was diagnosed and graded according to the Papile classification [**11**]. Necrotising enterocolitis (NEC) was staged using modified *Bell's criteria* [**12**]. Bronchopulmonary dysplasia (BPD) was classified according to *Jobe and Bancalari criteria* [**13**]. Severe retinopathy of prematurity (ROP) was defined as stage ≥3 disease and/or ROP requiring treatment. PPH was defined as visually estimated blood loss ≥500 mL following vaginal delivery or ≥1000 mL following caesarean section, or any blood loss sufficient to cause haemodynamic instability requiring intervention.

Data collection and Outcome measures: Maternal and antenatal data were obtained from medical records. Prospective data collection was performed using standardized proformas by trained personnel not involved in intervention delivery. Owing to the nature of the intervention, blinding of outcome assessors was not feasible; however, predefined objective outcome measures were used to minimize assessment bias.

The primary outcome was a composite adverse neonatal outcome comprising death before discharge, severe IVH (grade III–IV), or BPD of any grade.

Secondary outcomes included delivery-room stabilization parameters, maternal safety outcomes, and neonatal morbidities during hospitalization. Delivery-room outcomes included Apgar scores, heart rate, and preductal oxygen saturation at predefined intervals, need for PPV, endotracheal intubation, chest compressions, duration of ventilation, time to spontaneous respiration, axillary temperature at admission, and cord blood gas parameters. Maternal outcomes included postpartum haemorrhage (PPH) requiring transfusion and surgical placental removal.

Additional neonatal outcomes included haemoglobin and bilirubin levels at 72 hours, phototherapy requirement, sepsis, NEC, feed intolerance, cranial ultrasonography findings, duration of respiratory support, transfusion requirements, survival status, and ROP screening findings among surviving infants according to standard guidelines.

Statistical analysis: Data were collected using a predesigned proforma, entered into Microsoft Excel, and analysed using Stata version 16.1 (StataCorp, College Station, TX, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), and categorical variables as number (%). Appropriate parametric or nonparametric tests were applied after assessing the data distribution using the Shapiro–Wilk test. Effect estimates are reported as odds ratios (ORs), mean differences, or Hodges–Lehmann estimates of median differences, each with corresponding 95% confidence intervals (CIs).

As a sensitivity analysis, multivariable logistic regression models were fitted for the primary outcomes of interest. Adjusted odds ratios (aORs) with 95% CIs were reported. Covariates included treatment allocation (ICR versus CCC) and prespecified clinically relevant baseline variables: gestational age, birth weight, sex, completeness of antenatal corticosteroid, and mode of delivery.

A two-sided p-value <0.05 was considered statistically significant.

Ethical consideration: The study was approved by the Institutional Ethics Committee and registered with the Clinical Trial Registry of India. Written informed consent was obtained from parents before enrolment. All procedures were conducted according to the 1964 Declaration of Helsinki and its subsequent amendments.

RESULTS

Baseline characteristics: Of the 128 randomized neonates, one infant allocated to the CCC group was discharged against medical advice before ascertainment of the primary outcome. Consequently, 127 neonates were included in the final complete-case analysis (ICR, n=64; CCC, n=63) (**Fig 1**). Maternal demographic characteristics, antenatal risk factors, intrapartum variables, and baseline neonatal characteristics were comparable between groups (**Table 1**).

The median duration of cord attachment was 330 seconds (IQR 240–480; range 3–14 minutes) in the ICR group compared with 60 seconds (range 45–60 seconds) in the CCC group.

Primary outcomes: The composite adverse outcome occurred significantly less frequently in the ICR group than in the CCC group (35.9% vs 60.3%; OR 0.37, 95% CI 0.18–0.75; p=0.004), corresponding to an absolute risk reduction of 24.4%. Among the components of primary outcome, in-hospital mortality and severe IVH were also significantly lower among neonates undergoing ICR (26.6% vs 41.3%; OR 0.52, 95% CI 0.26–0.99; p=0.036 and 9.4% vs 20.6%; OR 0.40, 95% CI 0.14–0.96; p=0.027, respectively) (**Table 2, Fig 2**). Further, the direction and magnitude of treatment effects for the composite outcome, mortality, and severe IVH remained largely unchanged after adjustment for prespecified baseline covariates (***Supplementary Table S1*)**.

Secondary outcomes:

Delivery Room Outcomes:Apgar scores at 5 and 10 minutes were significantly higher in the ICR group, with median differences of +2 (1 to 3) and +1 (0 to 2), respectively. An Apgar score <7 at 5 minutes occurred less frequently among ICR neonates (12.5% vs 28.6%; OR 0.36, 95% CI 0.14–0.88; p=0.029).

The time to onset of spontaneous respiration was significantly shorter in the ICR group (35 vs 45 seconds; p<0.001). Heart rate and preductal SpO_2 trajectories were more favourable in the ICR group. Oxygen saturation <65% at 2 minutes and <85% at 10 minutes occurred less frequently among ICR neonates (25.0% vs 42.9%; OR 0.44, 95% CI 0.21–0.95; p=0.033 and 10.9% vs 36.5%; OR 0.22, 95% CI 0.09–0.54; p<0.001, respectively).

The requirement for bag-mask ventilation was lower in the ICR group (20.3% vs 38.2%; p=0.03), whereas endotracheal intubation rates were comparable (18.8% vs 26.9%; p=0.18). Cord blood lactate levels were significantly lower among neonates undergoing ICR (**Table 2**).

Post-resuscitation Clinical Course and Early Neonatal Morbidities:Culture-positive sepsis occurred less frequently in the ICR group (28.1% vs 49.2%; OR 0.40, 95% CI 0.20–0.79; p=0.001). Median haemoglobin concentration at 72 hours was higher in the ICR group (17.0 vs 15.6 g/dL; median difference +1.4 [0.3–2.5]; p=0.016), while fresh frozen plasma transfusion was required less frequently (31.3% vs 50.8%; OR 0.44, 95% CI 0.22–0.88; p=0.031). Neonates undergoing ICR achieved full enteral feeding earlier (median difference −7 days [−11 to −3]; p=0.012) and required a shorter duration of oxygen therapy (median difference −6 days [−10 to −2]; p=0.004).

No significant differences were observed in hypothermia at NICU admission, requirement for CPAP, mechanical ventilation, inotropic support >24 hours, neonatal jaundice, polycythemia, BPD, NEC, seizures, NICU stay, or total hospital stay. Maternal safety outcomes, including postpartum haemorrhage and lowest maternal haemoglobin concentration, were comparable between groups (**Table 2**).

Delayed morbidities:Among surviving neonates who completed ROPscreening (ICR=44; CCC=35), any-stage ROP occurred significantly less frequently in the ICR group (13.6% vs 34.3%; OR 0.30, 95% CI 0.10–0.91; p=0.03). Severe ROP was also less frequent in the ICR group (6.8% vs 14.3%), although the difference was not statistically significant (p=0.46) **(Table 3).**

DISCUSSION

In this RCT of very preterm neonates requiring delivery-room resuscitation, ICR was associated with more rapid physiological stabilisation and improved selected neonatal outcomes compared with CCC. Infants managed with ICR achieved higher Apgar scores at 5 and 10 minutes, earlier onset of spontaneous respiration, superior early oxygenation, and reduced need for active ventilatory support. These physiological advantages were accompanied by lower incidences of the composite adverse neonatal outcome, severe IVH, sepsis, ROP, and overall mortality.

Baseline maternal, obstetric, and neonatal characteristics were well balanced between groups, supporting the internal validity of the observed differences, and were comparable to reports from similar resource-limited settings [**14–17**]. The median duration of cord attachment in the ICR group was substantially longer than that reported in time-based delayed cord clamping studies and was comparable to durations described in physiological cord clamping (PCC) trials that maintained placental circulation until completion of placental transfusion or placental separation [**16**]. This strategy prioritises completion of cardiopulmonary transition rather than adherence to an arbitrary time threshold and may facilitate more consistent physiological stability during delivery-room stabilisation.

The composite adverse neonatal outcome comprising death, severe IVH, or BPD occurred significantly less frequently among infants undergoing ICR. This finding is consistent with previous PCC trials [**8–10**] and suggests that maintaining placental circulation during early stabilisation may translate into clinically meaningful improvements beyond immediate transitional physiology. The observed absolute risk reduction of 24.4% further underscores the clinical relevance of this effect, indicating that approximately one major adverse outcome may be prevented for every five infants managed with ICR. Importantly, the direction and magnitude of the treatment effect remained consistent after adjustment for prespecified baseline covariates.

Overall mortality was lower in the ICR group. However, prior trials and meta-analyses have not consistently demonstrated a mortality benefit with intact or physiological cord clamping [**18,19,20**]. This discrepancy may result from heterogeneity in study populations, intervention protocols, and the limited power of many studies to detect differences in mortality. The relatively high baseline mortality observed in our cohort likely reflects the combination of extreme prematurity requiring delivery-room resuscitation and a substantial burden of high-risk referrals with limited antenatal optimisation, which may have increased the ability to detect clinically meaningful differences between groups. Nevertheless, residual confounding related to illness severity and postnatal management cannot be excluded, and these findings require confirmation in adequately powered multicentre trials.

Similarly, severe IVH occurred less frequently among infants receiving ICR, consistent with findings reported by *Mercer et al*. and *Hocq et al*. [**21,22**]. Preservation of placental circulation during early resuscitation may mitigate abrupt fluctuations in cerebral blood flow associated with early cord clamping, a mechanism implicated in IVH pathogenesis [**23,24**]. Although some trials have not

demonstrated significant reductions in IVH [**15–17,25**], most studies and observational data suggest potential benefit, particularly among very preterm infants [**18**].

Several delivery-room outcomes support the physiological rationale underlying ICR. Infants undergoing ICR demonstrated more stable heart-rate trajectories, whereas those in the CCC group exhibited a lower initial heart rate followed by a more pronounced rise, potentially reflecting compensatory tachycardia secondary to reduced preload after early cord clamping. Preservation of placental circulation during ICR may facilitate a smoother haemodynamic transition by maintaining venous return and cardiac output, consistent with previous physiological studies [**26–28**]. Preductal oxygen saturation was also higher in the early postnatal period, with fewer infants experiencing severe hypoxaemia. These findings suggest that ICR promotes earlier respiratory stabilisation through continued placental oxygen transfer, improved pulmonary perfusion, and enhanced placental transfusion. Similar observations have been reported in previous randomized trials and meta-analyses, although many employed fixed or shorter cord-clamping durations [**18,27,28**].

Apgar scores at 5 and 10 minutes were significantly higher in the ICR group, with fewer infants having an Apgar score <7 at 5 minutes. These findings are consistent with reports by *Knol et al*. [**16**], *Raina et al.* [**26**], and *Andersson et al*. [**27**], although statistical significance has not been uniformly demonstrated. *KC A et al.* [**19**] similarly reported fewer infants with Apgar scores <3 at 5 minutes in the intervention group. Preservation of placental circulation may optimize circulating blood volume and arterial pressure, thereby improving tissue perfusion relevant to Apgar components. Supporting this mechanism, *Katheria et al*. demonstrated higher cerebral oxygenation at 12 hours by near-infrared spectroscopy and trends towards reduced supplemental oxygen and positive-pressure ventilation despite no early Apgar differences [**15**]. Consistent with these findings, ICR in our cohort was associated with reduced need for positive-pressure ventilation, greater response to tactile stimulation alone, and shorter time to spontaneous respiration. Lower post-resuscitation cord blood lactate levels further support improved metabolic transition. Similar reductions in advanced respiratory support have been reported by *Nevill et al.* [**17**], although not consistently observed by *Knol et al.* [**16**]. Use of a purpose-designed resuscitation trolley and protocolised care by trained personnel likely facilitated high adherence to the intervention, contributing to favourable immediate resuscitative outcomes [**16,26**].

Beyond the delivery room, these early physiological advantages of ICR culminated in clinically meaningful reductions in neonatal morbidities. Sepsis occurred significantly less frequently in the intervention group, consistent with trends reported previously [**5,16,17**]. This association may reflect reduced exposure to invasive procedures, earlier physiological stabilisation, and greater transfer of immunologically active progenitor cells through enhanced placental transfusion [**29**]. However, as sepsis is influenced by multiple postnatal factors and adjusted analyses were not performed for this secondary outcome, the finding should be interpreted cautiously. Median haemoglobin concentrations at 72 hours were higher in the ICR group without an increase in polycythaemia, consistent with previous trials, while the lower requirement for FFP may reflect a reduced burden of sepsis-related coagulopathy [**30**]. Furthermore, infants managed with ICR achieved full enteral feeding earlier and required a shorter

duration of supplemental oxygen therapy, findings consistent with improved physiological stability and reduced respiratory morbidity. However, both outcomes may be influenced by clinician-dependent practices. Few previous trials have reported time to full enteral feeding, limiting direct comparison. No significant differences were observed in inotropic support, NEC, BPD, or duration of NICU stay, consistent with previous reports [**18**] and likely reflecting the multifactorial nature of these morbidities.

Among delayed morbidities in surviving infants, any-stage ROP occurred less frequently in the ICR group. This finding may partly relate to improved early physiological stabilisation and a shorter duration of oxygen therapy, as suggested by previous studies [**17,20**]. However, as ROP is influenced by multiple postnatal factors and no adjusted analyses were performed for potential confounders, a causal relationship cannot be inferred, and these findings require confirmation in larger, adequately powered trials.

To our knowledge, this represents one of the first RCTs of ICR in a very preterm population from eastern India. Strengths include the randomized design, prospective data collection, and use of a standardized delivery-room resuscitation protocol with detailed assessment of physiological and clinically relevant outcomes. The presence of NRP-trained personnel, strict protocol adherence, and use of a purpose-designed intact cord resuscitation trolley with continuous dry-electrode electrocardiographic monitoring (NeoBeat) enabled consistent implementation of the intervention, including during caesarean delivery. Important limitations include the open-label design, unavoidable lack of blinding, and single-centre setting, which may limit generalisability. Although adjusted analyses for the primary outcomes yielded similar effect estimates, multivariable adjustment was not performed for significant secondary outcomes, and longer-term neurodevelopmental outcomes were not assessed. Adequately powered multicentre studies with long-term follow-up are needed to confirm these findings, assess generalisability, and clarify the impact of ICR on longer-term outcomes.

CONCLUSION

In this randomized trial of very preterm neonates requiring delivery-room resuscitation, ICR was associated with more stable early cardiopulmonary transition and improved short-term clinical outcomes, without an increase in maternal adverse events. These findings support the feasibility and safety of performing ICR in a resource-limited setting and suggest potential early clinical advantages for vulnerable preterm infants.

Abbreviations

- BPD
Bronchopulmonary Dysplasia
- CCC
Conventional Cord Clamping
- CPAP

Continuous Positive Airway Pressure
● FFP
Fresh Frozen Plasma
● ICR
Intact Cord Resuscitation
● IQR
Interquartile Range
● IUGR
Intrauterine Growth Restriction
● IVH
Intraventricular Haemorrhage
● MSAF
Meconium–Stained Amniotic Fluid
● NEC
Necrotising Enterocolitis
● NICU
Neonatal Intensive Care Unit
● NRP
Neonatal Resuscitation Program
● PPH
Postpartum Haemorrhage
● PROM
Premature Rupture of Membranes
● PRBC
Packed Red Blood Cells
● RCT
Randomized Controlled Trial
● ROP
Retinopathy of Prematurity
● SD
Standard Deviation
● VD
Vaginal Delivery
● WHO
World Health Organization

Declarations

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ORCiD ID:

Dr. Kushal Mandal: https://orcid.org/0009-0007-5270-4375.

Dr. Arindam Ghosh: http://orcid.org/0000-0003-0367-1080.

Dr. Ayan Das: https://orcid.org/0009-0005-9253-8645.

Dr. Arun Kumarendu Singh: http://orcid.org/0000-0002-0157-4300

Dr. Dipankar Jana: http://orcid.org/0000-0001-7010-7979.

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Figures

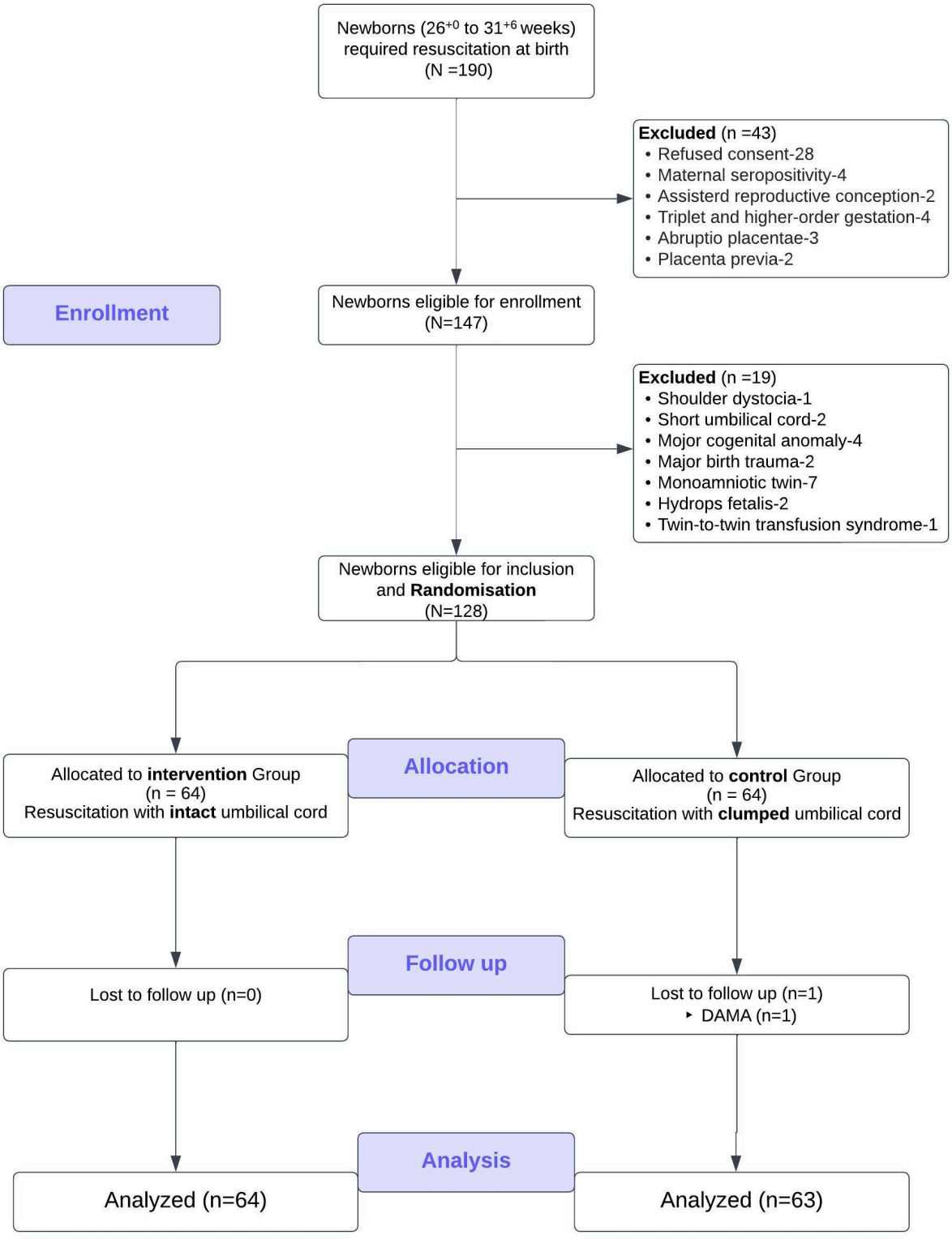


Figure 1

CONSORT flow diagram detailing participants' recruitment and randomization. (**Abbreviation**: DAMA =Discharge against medical advice)

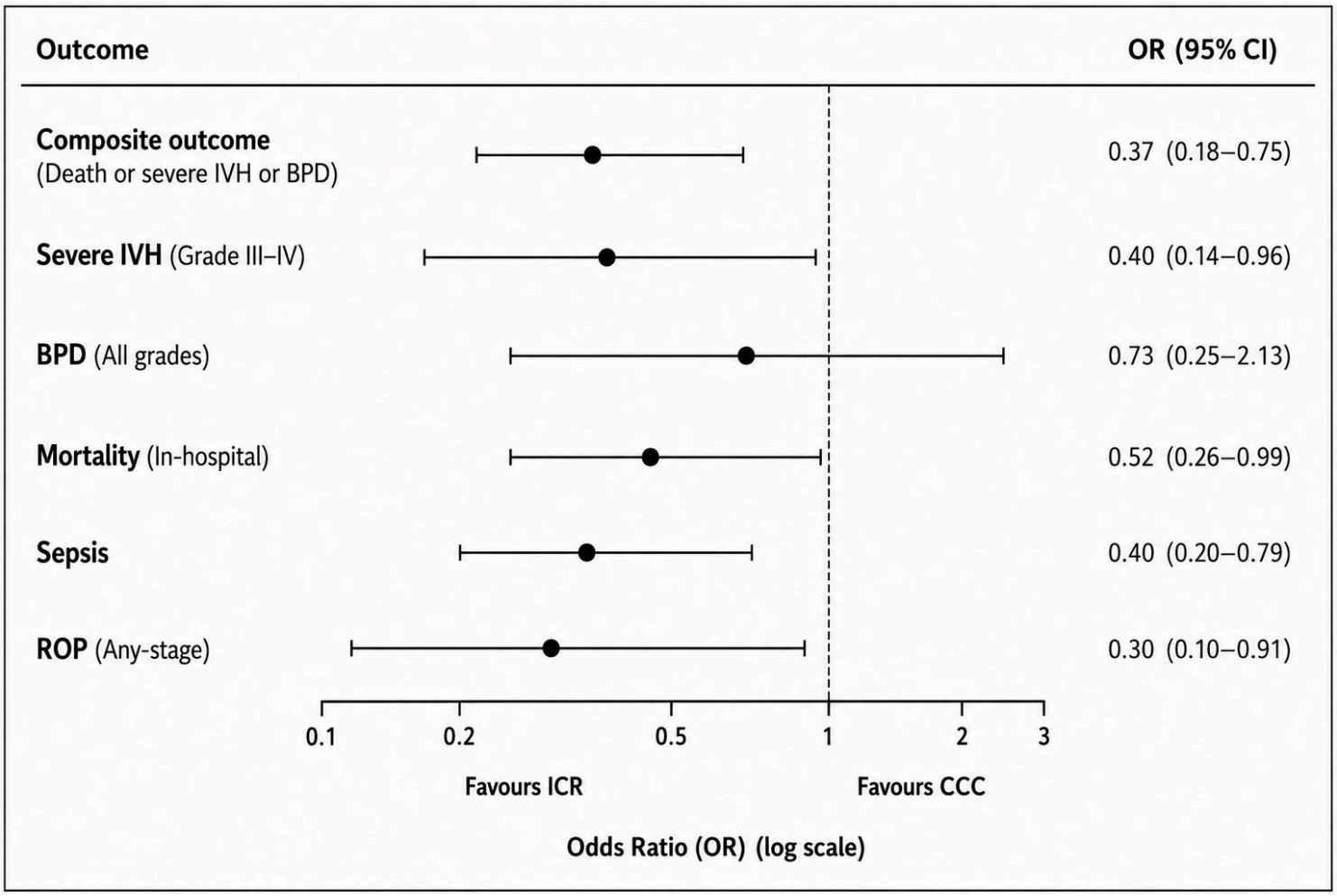


Figure 2

Forest plot summarising the effect estimates for major neonatal outcomes. Odds ratios (ORs) with 95% confidence intervals (CIs) are shown on a logarithmic scale. (**Abbreviations:** ICR = intact cord resuscitation; CCC = conventional cord clamping; BPD = bronchopulmonary dysplasia; IVH = intraventricular haemorrhage; ROP = retinopathy of prematurity)

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