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# Comparative efficacy of volume expansion, inotropes and vasopressors in preterm neonates with probable transitional circulatory instability in the first week of life: a systematic review and network meta-analysis

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## ABSTRACT

**Background** There exists limited agreement on the recommendations for the treatment of transitional circulatory instability (TCI) in preterm neonates

**Objective** To compare the efficacy of various interventions used to treat TCI

**Methods** Medline and Embase were searched from inception to 21st July 2023. Two authors extracted the data independently. A Bayesian random effects network meta-analysis was used. Recommendations were formulated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.

**Interventions** Dopamine, dobutamine, epinephrine, hydrocortisone, vasopressin, milrinone, volume and placebo.

**Main outcome measures** Mortality, major brain injury (MBI) (intraventricular haemorrhage > grade 2 or cystic periventricular leukomalacia), necrotising enterocolitis (NEC) ≥stage 2 and treatment response (as defined by the author).

**Results** 15 Randomized Controlled Trials (RCTs) were included from the 1365 titles and abstracts screened. Clinical benefit or harm could not be ruled out for the critical outcome of mortality. For the outcome of MBI, epinephrine possibly decreased the risk when compared to dobutamine and milrinone (very low certainty). Epinephrine was possibly associated with a lesser risk of NEC when compared with dopamine, dobutamine, hydrocortisone and milrinone (very low certainty). Dopamine was possibly associated with a lesser risk of NEC when compared with dobutamine (very low certainty). Vasopressin possibly decreased the risk of NEC compared with dopamine, dobutamine, hydrocortisone and milrinone (very low certainty). Clinical benefit or harm could not be ruled out for the outcome response to treatment.

**Conclusions** Epinephrine may be used as the first-line drug in preterm neonates with TCI, the evidence certainty

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Transitional circulatory shock is one of the most common causes of cardiovascular instability in very preterm neonates in the first few days of postnatal life.

⇒ Severe isolated hypotension without any clinical or biochemical signs of hypoperfusion in the first few days of postnatal life is associated with severe grade intraventricular haemorrhage and other poor short-term outcomes.

### WHAT THIS STUDY ADDS

⇒ There are only a limited number of RCTs that have evaluated the efficacy and safety of various medications in transitional circulatory instability.

⇒ Epinephrine may be considered as the first-line drug of choice in preterm neonates with probable transitional circulatory instability, with the evidence certainty being very low.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This systematic review highlights the gaps in knowledge regarding the various aspects of transitional circulatory instability, thus fuelling future research into these arenas.

⇒ With the best available evidence in the literature as of now, this network meta-analysis might result in a shift in practice from using dopamine and dobutamine as first-line inotropic agents in transitional circulatory instability to epinephrine being used more frequently by the clinicians.

being very low. We suggest future trials evaluating the management of TCI with an emphasis on objective criteria to define it.

## INTRODUCTION

There are no uniform criteria to diagnose transitional circulatory instability (TCI) in preterm neonates and hence, its exact incidence has been difficult to quantify. TCI can present as isolated hypotension with or without clinical or biochemical parameters of hypoperfusion.[1] The treatment of isolated hypotension in these preterm neonates in the initial days of life is a contentious topic with studies showing differing outcomes.[2–6] Even, the mean arterial blood pressure (MAP) threshold to define hypotension in very preterm neonates (VPT) neonates varies significantly.[7] However, a significant proportion of VPT neonates are still treated with inotropes for hypotension in the initial days of life.[8 9] Some authors have used echocardiographic parameters of superior vena cava (SVC) blood flow, left ventricular output, right ventricular output and maximum mean velocity in the pulmonary artery as surrogate markers for assessing the adequacy of cardiac function and organ perfusion in VPT neonates.[10–13] The aetiopathogenesis of transitional shock is proposed to be multifactorial, which includes the failure of an immature myocardium to effectively respond to a sudden increase in the afterload immediately after birth (which occurs after the clamping of the umbilical cord, especially early cord clamping), raised pulmonary pressures secondary to conditions such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), corticosteroid deficiency and invasive mechanical ventilation.[1 14–18] Considering the ambiguity regarding the diagnosis of TCI, clinicians still treat VPT neonates with 'probable' TCI after ruling out the other aetiologies of shock such as hypovolaemia and sepsis.[19] Volume expansion with crystalloids, dopamine, dobutamine, epinephrine, vasopressin, hydrocortisone and milrinone is often used to treat probable TCI in preterm neonates.[19–21] There are three systematic reviews published until now on the efficacy of different inotropes in preterm neonates with shock.[22–24] While Bhayat *et al* in their systematic review had compared only dopamine and dobutamine, Dempsey *et al*.'s and Barrington *et al*.'s systematic reviews were predominantly narrative in nature.[22 23] Sarafidis *et al*. compared different inotropes in preterm neonates with shock in pairwise meta-analyses.[24] Most of the aforementioned systematic reviews included neonates with shock of varying aetiopathogenesis. Henceforth, we undertook this systematic review and network meta-analysis (NMA) with an aim to study the efficacy and safety of various interventions in preterm neonates with probable TCI.

## METHODS

The systematic review and NMA was registered in PROSPERO (CRD42023446535).

### Literature search

MEDLINE and Embase were searched from inception to 21st July 2023 by two authors blinded to each other using an online software (Rayyan QCRI, Doha). Disagreements were resolved by consensus. There were no language restrictions. Only Randomized Controlled Trials (RCTs) were included. Animal studies, descriptive reviews, case series and case reports were excluded. The literature search strategy is given in online supplemental table 1.

### Inclusion criteria

Patient population (P): Preterm neonates (born at less than 37 weeks' gestational age) and who were of <72 hours of postnatal age and diagnosed with TCI (as defined by the authors). RCTs which had enrolled preterm neonates in which the mean age of the cohort at the time of randomisation was less than 72 hours were also eligible for inclusion. RCTs that had evaluated other types of shock namely, hypovolaemic shock, septic shock and cardiogenic shock secondary to PDA, necrotising enterocolitis (NEC) and postcardiac surgery were excluded. RCTs that had included dexamethasone as an intervention were excluded.

Intervention (I)/comparators (C): Volume expansion, dopamine, dobutamine, epinephrine, hydrocortisone, milrinone, vasopressin and placebo.

Outcomes (O): The primary outcomes were mortality and major brain injury (MBI) (intraventricular haemorrhage >grade 2 or cystic periventricular leukomalacia). Secondary outcomes included response to treatment and NEC ≥stage 2.

### Data extraction and synthesis

Two authors extracted the data independently using a pre-specified proforma. The accuracy of the data was checked by a third author. A Bayesian NMA using the random effects model was used to synthesise data using the R-software (V.2023.06.0+421).[25] The packages 'gemtc' and 'BUGSnet' were used to perform the NMA. Network plots were used to depict the geometry of the networks. Intransitivity was assessed by tabulating the study characteristics and comparing them. Markov chain Monte Carlo simulation using vague priors with four chains, burn-in of 50 000 iterations, followed by 10 00 000 iterations and 10 000 adaptations was used. Model convergence was assessed using the Gelman-Rubin Potential Scale Reduction Factor. Node-splitting to assess inconsistency was attempted if the networks were sufficiently connected. The effect estimates of the NMA were expressed as risk ratio (RR) with 95% credible interval (CrI), depicted using forest plots and matrix plots. Surface under the cumulative ranking curve (SUCRA) was used to rank the interventions. Pairwise meta-analyses were used to assess the direct evidence from the RCTs which were expressed as RR with 95% CI and depicted using forest plots. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) recommendations were used to assess the certainty of evidence (CoE) of the

NMA effect estimates.[26] A clinical practice guideline was formulated using the GRADE framework.[27]

### Risk of bias

Cochrane risk of bias tool version 2.0 was used to assess the risk of bias of the included RCTs by two authors independently.[28] Disagreements were resolved by consensus.

## RESULTS

Of the 1365 titles and abstracts screened after the removal of duplicates, a total of 14 RCTs[11 29–41] were included in the NMA and 1 in the narrative review.[42] The PRISMA flow is provided in online supplemental figure 1.

### Characteristics of included studies

Of the 14 RCTs, while 13 had included neonates with a mean gestational age of less than 29 weeks, 1 had included preterm neonates with a mean gestation of 31 weeks.[39] While seven RCTs compared dopamine versus dobutamine[31–33 38–41] and three RCTs compared dopamine versus volume institution,[11 30 34] for the comparisons: milrinone versus placebo,[35] dopamine versus vasopressin,[37] dopamine versus hydrocortisone[29] and dopamine versus epinephrine,[36] only single RCT was available. Except for one RCT,[40] all the other trials included preterm infants with low MAP. The single RCT which had not taken MAP as threshold used SVC flow as a parameter for diagnosing hypoperfusion.[40] Clinical features of hypoperfusion along with low MAP were considered by only one RCT. The characteristics of the included studies are given in online supplemental table 2.

### Primary outcomes

#### Mortality

For the primary outcome of mortality, clinical benefit or harm could not be ruled out for any of the comparisons of the interventions as the NMA effect estimates were statistically non-significant and the CoE was very low to low (figure 1, online supplemental figure 2, online supplemental table 3).

#### *Major brain injury*

Epinephrine was possibly associated with a lesser risk of MBI when compared with dobutamine (RR, 95% CrI: 0.14, 0.01 to 0.99, CoE: very low) and milrinone (RR, 95% CrI: 0.04, 0.00 to 0.97, CoE: very low). Clinical benefit or harm could not be ruled out for any of the other comparisons (figure 1, online supplemental figure 3, online supplemental table 4).

### Secondary outcomes

#### NEC ≥2

Likewise for the outcome of MBI, epinephrine was possibly associated with lesser risk of NEC ≥stage 2 when compared with dopamine (RR, 95% CrI: 0.00, 0.00 to 0.46, CoE: very low), dobutamine (RR, 95% CrI: 0.00, 0.00 to 0.11, CoE: very low), hydrocortisone (RR, 95% CrI: 0.00, 0.00 to 0.30, CoE: very low) and milrinone (RR, 95% CrI: 0.00, 0.00 to 0.82, CoE: very low). Further, dopamine was possibly associated with lesser risk of NEC ≥stage 2 when compared with dobutamine (RR, 95% CrI: 0.21, 0.04 to 0.75, CoE: very low). Vasopressin also possibly decreased the risk of NEC ≥stage 2 when compared with dopamine (RR, 95% CrI: 0.00, 0.00 to 0.45, CoE: low), dobutamine (RR, 95% CrI: 0.00, 0.00 to 0.10, CoE: very low), hydrocortisone (RR, 95% CrI: 0.00, 0.00 to 0.31, CoE: very low) and milrinone (RR, 95% CrI: 0.00, 0.00 to 0.73, CoE: very low). Clinical benefit or harm could not be ruled out for the other comparisons for this outcome. Epinephrine was ranked the best intervention according to SUCRA ranking (figure 2, online supplemental figure 4, online supplemental table 5).

#### Response to treatment

Moderate CoE indicated a trend towards dopamine being possibly associated with better treatment response when compared with dobutamine (RR, 95% CrI: 1.6 (0.98 to 3.54). Clinical benefit or harm could not be ruled out for any of the other comparisons (figure 2, online supplemental figure 5, online supplemental table 6).

The study by Phillipos *et al.* whose data could not be synthesised in the NMA was included in the narrative review. The authors compared dopamine versus epinephrine and concluded that epinephrine was possibly associated with better cardiac contractility (online supplemental table 2). The evidence to decision framework is given in online supplemental table 7.

### Risk of bias

While six studies had a low risk of overall bias,[11 34–37 40] six had some concerns.[29 30 32 33 38 41] Two studies had a high risk of bias.[31 39] The predominant reasons for the studies with some concerns were issues with the domains of randomisation and selective reporting. For the two studies with a high risk of overall bias, there were issues with the domains randomisation process, deviation from intended interventions and selective reporting (online supplemental table 8).

The CoE for the NMA effect estimates for the various outcomes is provided in online supplemental table 9.

## DISCUSSION

This systematic review and NMA was performed to generate evidence to formulate recommendations on management of TCI in preterm neonates in the initial days of life as guided by the GRADE working group. Of the 15 RCTs that were included in the systematic review, we could synthesise data from 14 trials which had enrolled 562 neonates.

The proposed pathophysiology of TCI is multifactorial, which includes poor myocardial contractility due to its immaturity and inability to suddenly adapt to an increased afterload after the umbilical cord has been clamped as well as due to the raised pulmonary pressures which is a frequent occurrence in preterm neonates

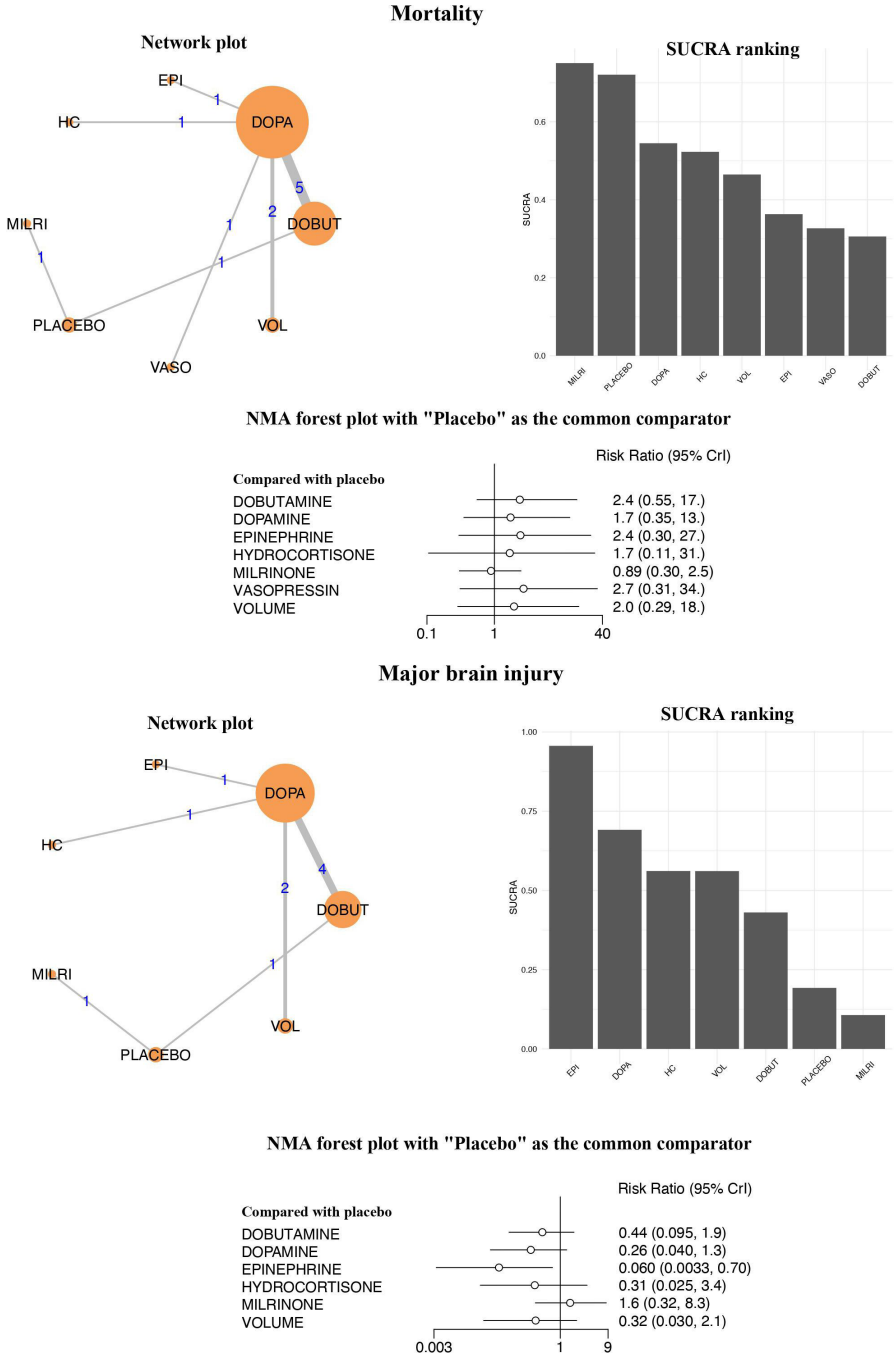


**Figure 1** Network geometry, SUCRA ranking and network meta-analysis forest plot with 'placebo' as the common comparator for the primary outcomes: mortality and major brain injury (intraventricular haemorrhage ≥grade 2 and/or cystic periventricular leukomalacia). NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve.

secondary to RDS.[43] Our NMA indicated that epinephrine was associated with decreased risk of MBI and NEC ≥stage 2 when compared with other medications. This could be attributed to many plausible reasons. The effect of epinephrine is dose dependent. While at a dose of 0.05–0.30 µg/kg/min, epinephrine is proposed to increase the cardiac contractility, decrease the systemic vascular resistance and the pulmonary arterial pressures, all of which mitigate the risk of transitional haemodynamic instability in preterm neonates immediately after birth.[19 20] It should be noted that epinephrine might possibly be associated with an increased risk of certain adverse events such as hyperglycaemia requiring insulin therapy and raised lactate levels which requires monitoring.[44] Our results are in disagreement with the study by Osborn *et al*.[10] This was a follow-up study of the RCT included in our NMA evaluating dopamine and dobutamine in neonates with low SVC flow.[40] In their long-term follow-up cohort study, Osborn *et al*. reported that infants treated with dopamine had a higher risk of disability as indicated by a lower Griffith's General Quotient.[10] The discrepancy between our results favouring dopamine

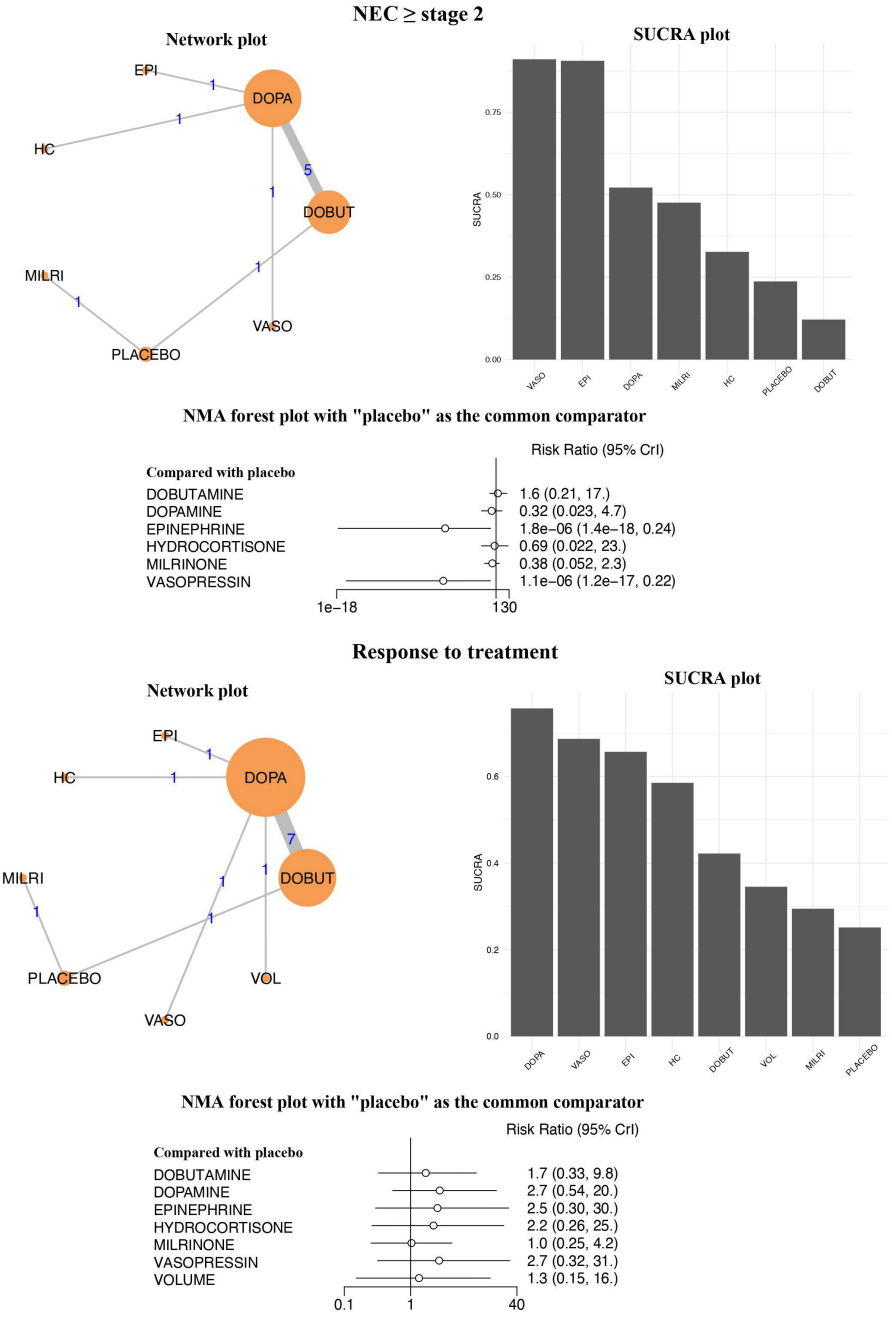


**Figure 2** Network geometry, SUCRA ranking and network meta-analysis forest plot with 'placebo' as the common comparator for the secondary outcomes: necrotising enterocolitis (NEC) ≥stage 2 and response to treatment. NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve.

when compared with dobutamine and Osborn *et al*.'s could be attributed to the fact that the Osborn *et al*. study defined TCI based on SVC flow which was different from the definitions used in the other RCTs. Also, we could evaluate only short-term outcomes as reported in the included RCTs. None of the included RCTs had evaluated long-term neurodevelopmental outcomes a priori.

Though vasopressin is not a well-researched drug in the neonatal population, its use in septic shock, nitric oxide refractory persistent pulmonary hypertension and postcardiac surgery has been on the rise in the past few years.[45 46] Our NMA indicated that vasopressin decreases the risk of NEC ≥stage 2 when compared with multiple other inotropes. This finding is in contrast with reports of vasopressin being associated with NEC in preterm neonates. Our results could be explained by various plausible reasons. Like epinephrine, vasopressin has differing actions based on the dosage used. Several human studies have also shown that vasopressin is not associated with an increased risk of NEC.[37 47 48] Further, several animal studies have shown that vasopressin when used at a lower dosage selectively improves blood flow and hence perfusion to vital organs including the splanchnic circulation.[49–52] Vasopressin decreases the pulmonary vascular resistance and increases the preload, thereby improving the right ventricular contractility and the systemic blood

flow.[46] But we caution that only one RCT trial had evaluated vasopressin for TCI, and hence further studies are required.

Dopamine and dobutamine have been the most commonly used first-line inotropes to treat TCI.[22] Hence, there are many RCTs comparing these two medications. The results of our NMA indicate that dopamine might be associated with a decreased risk of NEC ≥stage 2 when compared with dobutamine. However, clinical benefit or harm could not be ruled out for any of the other outcomes evaluated. Rios *et al*. in their survey on trends in the use of inotropes for neonatal hypotension reported a steady decrease in the usage of both of these medications over a 10-year period.[53] The authors also reported increasing usage of epinephrine and hydrocortisone in neonates with shock. Dopamine is proposed to increase the pulmonary vascular pressure more when compared with the systemic vascular pressure at similar doses.[54 55] This could have a negative impact on preterm neonates immediately after birth who are prone to TCI. Further, Martins-Filho *et al*. in their retrospective cohort study spanning 8 years studied VLBW neonates and compared two groups who were treated with either dopamine or dobutamine for TCI.[56] The authors concluded that after adjusting for baseline sickness, dopamine was associated with an increased risk of mortality within the first week and dobutamine with an increased risk of pulmonary haemorrhage. We did not evaluate the outcome of pulmonary haemorrhage. Also, the association of dopamine with mortality was not observed in our NMA. This could be because all the RCTs included in our NMA were underpowered to detect any difference in the outcome of mortality. In our NMA, clinical benefit or harm could not be ruled out for most of the other interventions such as milrinone, hydrocortisone and volume expansion.

There are no objective criteria for diagnosing TCI in preterm neonates. Most clinicians rely solely on the MAP threshold for initiating treatment. Only three RCTs included in our NMA had used surrogate markers of organ perfusion such as SVC flow to diagnose TCI.[11 34 40] The recent systematic review also indicated that there is insufficient evidence for the use of SVC flow to predict adverse outcomes.[57] Some authors have used near-infrared spectroscopy to correlate MAP with organ perfusion.[58 59] Diagnosis and treatment of TCI guided by these parameters need further research.

There were several limitations to this NMA. The network geometry for all the outcomes was sparse and hence, an inconsistency assessment could not be performed. Further, there is a possibility of clinical intransitivity related to the definitions of TCI and the outcome response to treatment, the varying dosage of inotropes used and the open-label use of volume expansion. All of these could have influenced the NMA effect estimates. Also, there is a paucity of literature with respect to this PICO and hence the evidence certainty for most of the outcomes was very low to low. Finally, though we had done a systematic literature search of the two important databases namely MEDLINE and Embase, we did not search others such as clinical trial registries, Web of Science and Cochrane CENTRAL.

## CONCLUSION

There are only a limited number of RCTs that have evaluated the efficacy and safety of various medications in TCI. The evidence base available as of the present was evaluated through the GRADE framework. We suggest that epinephrine may be used as the first-line drug of choice in preterm neonates with probable TCI, CoE being very low. We suggest further research on the aspect of objectively defining TCI and comparing the safety and efficacy of the various drugs in treating TCI.

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**Contributors** VVR, GK, AKP, ASA, PS, MS, SK, DS and KM conceptualised this systematic review, network meta-analysis and CPG. AKP formulated the literature search strategy and was involved in the data curation. GK and VVR did the literature search, data curation and data analysis. VVR produced the initial draft. ASA, PS, MS, SK, KM and DS provided further intellectual inputs and revised the initial draft. DS, GK, VVR, ASA, PS, MS, SK and KM were involved in the formulation of recommendations based on the GRADE framework. All the authors approved the final version of the manuscript submitted for peer review. KM is the guarantor of this study who accepts full responsibility for this work and the conduct of the study. KM has full access to the data and had controlled the decision to publish this work.

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