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REVIEW ARTICLE

Outcomes of very preterm infants with hyperglycaemia treated with insulin: A systematic review and meta-analysis

Nital Patidar[1] | Chandra Prakash Rath[2,3] | Shripada Rao[3,4] | Sanjay Patole[2,4]

[1]Paediatrics, Armadale General Hospital, Armadale, Western Australia 6112, Australia

[2]Neonatology, King Edward Memorial Hospital, Subiaco, Western Australia 6008, Australia

[3]Neonatal, Perth Children's Hospital, Nedland, Western Australia 6009, Australia

[4]School of Medicine, University of Western Australia, Perth, Western Australia, Australia

Correspondence
Chandra Prakash Rath, Department of Neonatology, Perth Children's Hospital, Nedlands, WA 6008, Australia.
Email: chandra.rath@health.wa.gov.au

Abstract

Aim: To study the outcomes of very preterm infants with hyperglycaemia treated with Insulin.

Methods: This is a systematic review of randomised controlled trials (RCTs) and observational studies. PubMed, Medline, EMBASE, Cochrane Library, EMCARE and MedNar databases were searched in May 2022. Data were pooled separately for adjusted and unadjusted odds ratios (ORs) using random-effects model. Main outcome measures: Mortality and morbidities (e.g. Necrotising enterocolitis [NEC], retinopathy of prematurity [ROP]) in very preterm (<32 weeks) or very low birth weight infants (<1500 g) after treatment of hyperglycaemia with insulin.

Results: Sixteen studies with data from 5482 infants were included. Meta-analysis of unadjusted ORs from cohort studies showed that insulin treatment was significantly associated with increased mortality [OR 2.98 CI (1.03 to 8.58)], severe ROP [OR 2.23 CI (1.34 to 3.72)] and NEC [OR 2.19 CI (1.11 to 4)]. However, pooling of adjusted ORs did not show significant associations for any outcomes. The only included RCT found better weight gain in the insulin group, but no effect on mortality or morbidities. Certainty of evidence was 'Low' or 'Very low'.

Conclusion: Very low certainty evidence suggests that Insulin therapy may not improve outcomes of very preterm infants with hyperglycaemia.

KEYWORDS
hyperglycaemia, insulin, very preterm infants

1 | INTRODUCTION

Hyperglycaemia is common in very preterm and very low birth weight (VLBW) infants. The aetiology of hyperglycaemia is multifactorial and includes insulin resistance, decreased insulin production and immature control of gluconeogenesis.[1–3] Immaturity of beta cells and low GLUT 2 levels result in low Insulin production preterm infants.[4,5] A recent systematic review and meta-analysis concluded that hyperglycaemia is associated with higher odds of mortality, any-grade intraventricular haemorrhage (IVH), and any-stage retinopathy of prematurity (ROP) in very preterm infants.[6] Animal models have demonstrated that hyperglycaemia is associated with brain injury and retinal damage.[7,8] Hence one could hypothesize that treatment of hyperglycaemia with insulin infusion could be beneficial in very preterm infants, especially because they have physiological deficiency of endogenous insulin. However, insulin

Abbreviations: CIs, confidence intervals; CLD, chronic lung disease; IGF-I, insulin-like growth factor-I; IVH, intraventricular haemorrhage; LOS, late-onset sepsis; NEC, necrotising enterocolitis; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PRISMA, preferred reporting items for systematic reviews and meta-analysis; PVL, periventricular leukomalacia; RCTs, randomised controlled trials; ROP, retinopathy of prematurity; VLBW, very low birth weight.

therapy may result in hypoglycaemia, which, in turn, can worsen long-term developmental outcomes. The risks versus benefits of insulin therapy in hyperglycaemic very preterm infants remains uncertain. A Cochrane review (2011) of two small, randomised controlled trials (RCTs) concluded that evidence is insufficient to determine the effects of insulin therapy on mortality or major morbidities in preterm infants.[9] The other systematic review (2008) did not report on long-term outcomes and recommended against routine use of insulin infusion to promote growth.[10] Since then, many studies have been published evaluating short- and long-term outcomes associated with insulin infusion in preterm infants. Hence, we aimed to systematically review the evidence on insulin therapy and outcomes in very preterm or VLBW infants.

Key Notes

- Neonatal hyperglycaemia is associated with mortality and morbidity in very preterm and very low birth weight infants.
- This systematic review suggests that Insulin therapy may not improve the outcomes of very preterm infants with hyperglycaemia.
- Randomised trials are needed to evaluate efficacy and safety of insulin therapy to prevent mortality and morbidity in very preterm infants with hyperglycaemia

2 | METHODS

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[11] It was registered on PROSPERO, the international prospective register of systematic reviews (CRD42022334370).

2.1 | Data sources and searches

The electronic databases PubMed, EMBASE (through OVID), EMCARE (through OVID), MEDLINE (through OVID), The Cochrane Library and Google Scholar were searched (since their inception until May 2022) independently by CR, NP and SR. The ClinicalTrials.gov website was searched to identify ongoing studies. Grey literature was searched on 'Opengrey' and 'Mednar' (http://mednar.com/mednar/desktop/en/search.html) databases.

PubMed was searched using the following broad keywords: ('Insulin'[Mesh Terms] OR 'insulin'[All Fields] OR 'insulin s'[All fields] OR 'insuline'[All Fields] OR 'insulin'[All Fields] OR 'insulinization [All Fields] OR insulinized'[All Fields] OR 'insulins'[MeSH Terms] OR 'insulins'[All Fields]) AND ('premature birth'[MeSH Terms] OR ('premature'[All Fields] AND 'birth'[All Fields]) OR 'premature birth'[All Fields] OR 'preterm'[All Fields]) AND ('hyperglycaemia'[All Fields] OR 'hyperglycemia'[MeSH Terms] OR 'hyperglycemia'[All Fields] OR 'hyperglycaemias'[All Fields] OR 'hyperglycemias'[All Fields] OR 'hyperglycemia s'[All Fields]). Similar terms were used for searching other databases. In addition to our electronic search strategy, CR and NP hand-searched referenced lists of relevant articles. There were no restrictions on the search with regards to the publication date or language.

2.2 | Study selection

We included the following types of studies: RCTs, quasi- RCTs, cohort and case-control studies that evaluated the association between insulin treatment of neonatal hyperglycaemia (treated and not treated) and clinical outcomes (present or absent).

Outcomes of interest included the following: (1) Mortality before hospital discharge, (2) IVH (any grade), (3) Severe IVH (grade III or IV based on Papille's classification[12]), (4) ROP (any stage), (5) Severe ROP defined as ≥stage 3 or requiring treatment, (6) Chronic lung disease (CLD) (need for respiratory support or oxygen at 36 weeks post-menstrual age), (7) Late-onset sepsis (LOS): Positive blood culture on a sample collected after 72 h of birth, (8) Periventricular leukomalacia (PVL), (9) Any-stage necrotising enterocolitis (NEC), (10) NEC ≥stage II (as per modified Bell's classification[13]), (11) Blindness, (12) Hearing impairment and (13) Long-term developmental outcomes based on validated tools.

2.3 | Data extraction and quality assessment

CR and NP independently screened the titles and abstracts to identify full texts, which can be included in the review. Full-text articles of the potentially eligible studies were read in detail by two reviewers to confirm their eligibility for inclusion. A standardised form was used to extract data. The incidence of the various clinical outcomes of interest in the two groups (Insulin treated vs insulin not treated) was abstracted. If the authors had reported odds ratios (ORs) or risk ratios (adjusted or unadjusted) for those outcomes, they were recorded. All authors were contacted to provide additional information; two acknowledged our request, of which one[14] provided additional information. For observational studies, the modified Newcastle-Ottawa Scale (NOS)[15] was used to assess the risk of bias across 8 domains. The quality of the RCTs was assessed using the Cochrane risk-of-bias tool.[16] The certainty of evidence was assessed using the GRADE methodology and classified into one of the four categories: high, moderate, low and very low.[17] In case of discrepancies, discussions were held with other two reviewers before reaching consensus.

2.4 | Data synthesis

Meta-analysis was performed using the Review Manager V.5.4 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). We separately pooled the reported adjusted and

unadjusted ORs from included studies using the inverse variance method (Cochrane Handbook section 10.3.3). Subgroup analysis was carried out based on study design (RCT, cohort and case control). Random-effects model (DerSimonian and Laird) was used for meta-analysis since heterogeneity was expected. We used raw numbers to calculate unadjusted ORs prior to pooling if the published manuscripts of the included studies did not have information on ORs. For dichotomous outcomes, the pooled effect size estimates were presented as pooled ORs with 95% confidence intervals (CIs). Qualitative synthesis was done for studies where meta-analysis was not possible. Statistical heterogeneity was assessed using visual inspection of the forest plots and quantified using the I^2 statistic. The I^2 results were interpreted as follows: 0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; 75%–100%: considerable heterogeneity (Cochrane Handbook).[18] In some studies, the control arm was also treated with Insulin. Such studies were excluded if the control arm contamination was >30%.

3 | RESULTS

A PRISMA flow chart of screening and selection of studies is shown in Figure 1. The preliminary search yielded 1728 citations, out of which 16 articles were included in the systematic review.[14,19–33] The total sample size was 5482. The number of infants in individual studies ranged between 24 and 1441. The RCT had a sample size of 24 ELBW infants. The number of studies included in the meta-analysis for mortality, IVH, ROP, CLD, LOS, PVL, NEC, blindness, hearing impairment and long-term developmental outcomes were 7, 8, 6, 2, 4, 2, 3, 1, 2 and 3, respectively. Four out of the 16 studies were of case-control design,[19,20,26,28] 1 was RCT,[23] 10 were retrospective cohort studies[14,22,24,25,27,29–33] and one was a prospective cohort study[21] (Table S1). Blood glucose cut-off levels to initiate Insulin treatment varied between >9.9 and >16.66 mmol/L amongst studies. The definition of hyperglycaemia in the control arm ranged from >8.3 to >16.66 mmol/L and its management was mainly by decreasing glucose infusion rates (Table S1).

3.1 | Quality of included studies

The median (IQR) number of stars in the cohort and case-control studies as assessed by NOS was 8 (7–9) and 9 (8–9), respectively (Table S2 and S3). The included RCT had major concerns in the blinding domain during the risk-of-bias assessment (Figures S1 and S2).

Table S1 provides an overview of the results of individual studies. Pooling of unadjusted ORs from studies showed that insulin treatment was associated with increased odds of mortality, severe ROP and NEC (Figure 2, Figures S4 and S7, Table 1). However, pooling of adjusted ORs for mortality, severe ROP and moderate to severe disability did not find a significant association between insulin treatment and outcomes (Figure 3, Figures S5 and S17). There was no effect of insulin treatment on mortality, severe IVH, LOS and CLD in the RCT (Figure 2, Figures S3, S8 and S9, Table 1). The results of other meta-analyses are given in Table 1 and Figures S6 and S10–17.

Only four studies reported on hypoglycaemia, and its incidence varied between 0% to 12%.[21,23,25,30]

The weight at 36 weeks' gestation or discharge was not significantly different between the insulin treated group and controls.[24] Head circumference was also similar between the two groups.[23] There was no difference in the anthropometry measurements at 12 months between insulin treated and control groups.[25] One study showed significant weight gain in the insulin group at the end of the study period.[23]

Certainty of evidence was 'Low' or 'Very low' for all outcomes (Table S4).

4 | DISCUSSION

This systematic review, which included 16 studies (RCT: 1, Non-RCTs: 15) did not find any benefits of insulin therapy in very preterm infants with hyperglycaemia. Whilst the total sample size was 5482, the RCT had a very small sample size of 24 ELBW infants. Pooling of unadjusted ORs from non-RCTs showed that insulin therapy was associated with increased odds of mortality, severe ROP and NEC. However, these results are less reliable given that the confounding factors were not adjusted for. The evidence was inadequate for most of the outcomes as very few studies had reported adjusted ORs. The data from the RCT showed no significant benefit of insulin treatment on mortality, severe IVH, LOS and CLD.

The proposed pathophysiology of preterm hyperglycaemia includes inherent insulin deficiency and insulin resistance. Insulin stimulates hepatic production of Insulin-like growth factor-I (IGF-I), which plays a major role in foetal growth and organ development.[34] Early hyperglycaemia is associated with low IGF-I.[35] Lack of IGF-I has been associated with low brain volume,[36] subnormal neurodevelopment,[37] severe ROP,[38–40] NEC,[41] CLD[42] and impaired growth in VLBW infants. A small RCT reported that treatment of extremely preterm infants with recombinant IGF-I decreases the incidence of severe CLD and severe IVH.[43] Evaluation of the protective effect of IGF-I in animal NEC models has shown conflicting results.[44,45] Treatment with Insulin has been shown to improve IGF-I levels.[35] In this context, insulin therapy is expected to reduce hyperglycaemia associated morbidity and mortality. An animal study reported that insulin treatment of hyperglycaemic preterm lambs attenuated the increased mortality and morbidity, but not the decreased growth.[46] Whilst the data from the animal studies cannot be directly applied to complex clinical situations, they do suggest treatment with insulin may prevent some of the clinical adverse effects of hyperglycaemia.

The lack of effect of insulin treatment on clinical outcomes may partially be explained by insulin resistance, which is most pronounced in extremely premature neonates but reduces with

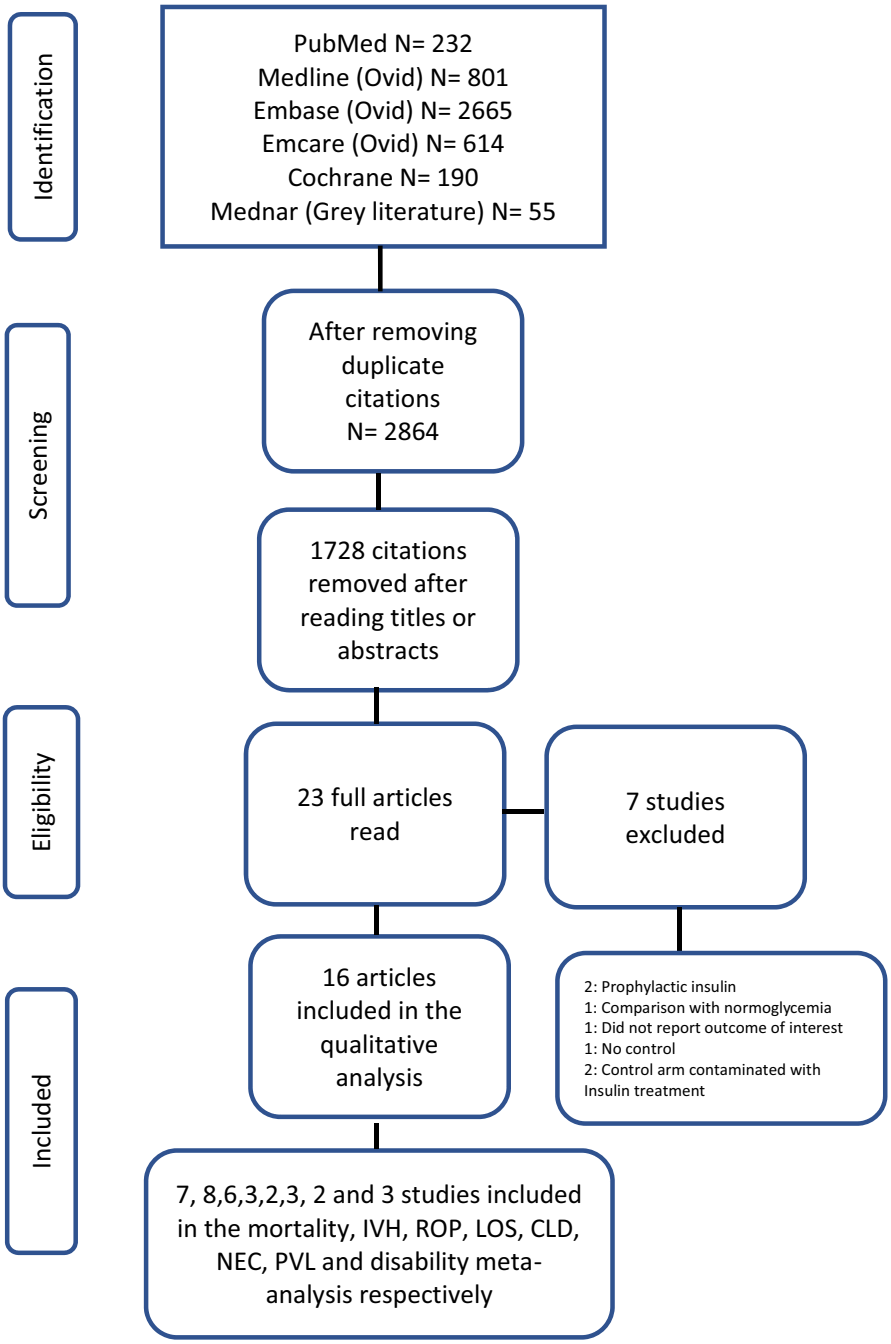

FIGURE 1 Flow chart for study selection (CLD, chronic lung disease; IVH, intraventricular haemorrhage; LOS, late inset sepsis; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity).

increased gestation.[47] Rise in IGF-I after insulin treatment may be delayed up to 28 days[35] and can result in suboptimal clinical benefits. It is possible that there are two distinct group of VLBW infants, an insulin deficient group that might respond to insulin treatment and the insulin resistant group that might not respond to the treatment.[3] The issue of insulin adsorption on to the infusion set surface needs to be acknowledged. It increases with decreasing flow and different materials have different adsorption capacities. In low-flow and low-concentration contexts, such as in preterm neonates, insulin loss to adsorption represents a significant proportion of daily insulin delivery, which needs to be accounted for.[48] In addition, the lack of effect of insulin may be attributed to delay in initiating treatment, higher glucose threshold for treatment initiation and selective insulin treatment. Surveys have shown a wide variation in the management of neonatal hyperglycaemia in terms of initial choice of treatment modality (decreased glucose infusion rate/insulin therapy), blood glucose cut-off to initiate insulin infusion and target blood glucose levels.[49–51]

Hypoglycaemia is a real concern during insulin therapy and frequent monitoring is warranted. In this review, four studies that reported incidence of hypoglycaemia did not find it to be a significant concern. A study by Alsweiler et al reported a 58% incidence of hypoglycaemia in the treatment arm.[52] The use of a relatively lower cut-off to initiate insulin infusion (>8.5 mmol/L) and targeting a tight glucose control (4–6 mmol/L) might have contributed to such high incidence of hypoglycaemia. Infrequent measurements can lead to

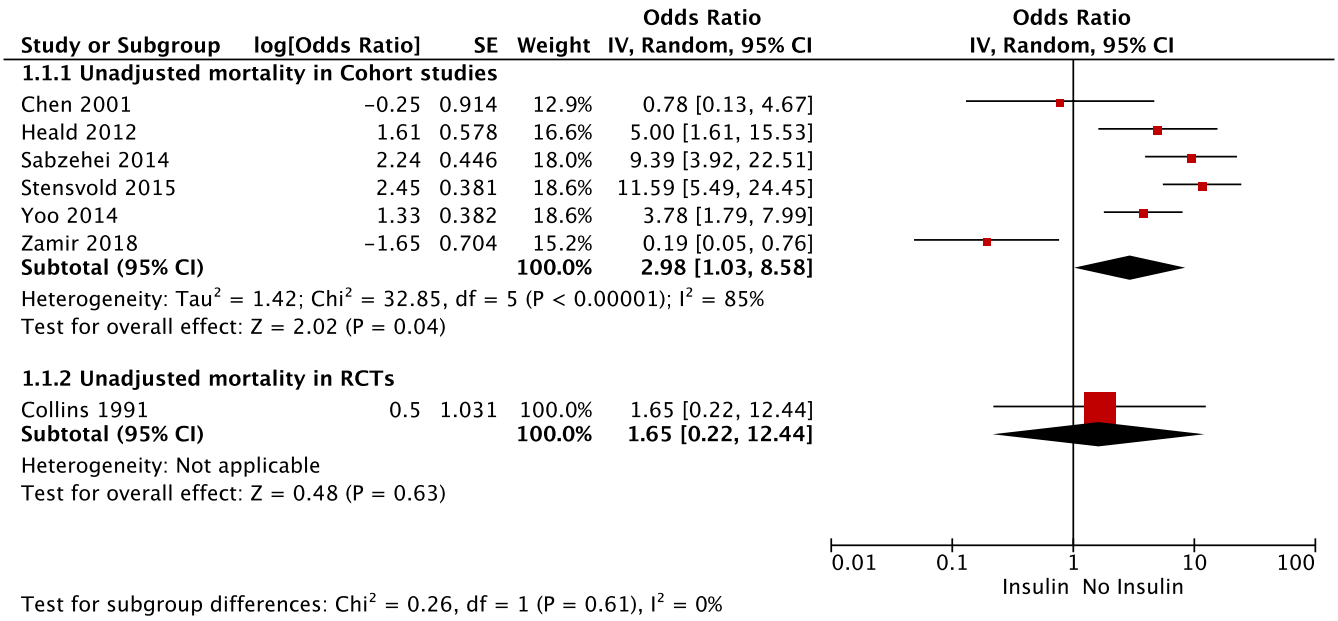

FIGURE 2 Forest plot showing the association between insulin and unadjusted mortality (CI, confidence interval; IV, inverse variance; SE, standard error).

TABLE 1 Pooled OR (95% CI), heterogeneity (I^2 and *p*-value of the outcomes).

Outcome		Reference numbers of studies included	Total number of studies included	Pooled OR (95% CI)	I^2 (%)	*p* Value
Mortality (unadjusted)	Cohort	14,24,25,29,30,32	6	2.98 (1.03 to 8.58)	85	0.04
	RCT	23	1	1.65 (0.22 to 12.44)	–	0.63
Mortality (adjusted)	Cohort	25,32	2	0.56 (0.17 to 1.88)	54	0.35
Severe IVH (unadjusted)	Cohort	14,21,24,25,29,30	6	1.33 (0.57 to 3.11)	61	0.51
	CC	20	1	2.29 (1.28 to 4.12)	–	0.006
	RCT	23	1	0.60 (0.08 to 4.45)	–	0.62
Severe ROP (unadjusted)	Cohort	25,27,29,30	4	2.23 (1.34 to 3.72)	14	0.002
	CC	28	1	5.21 (2.84 to 9.56)	–	0.006
Severe ROP (adjusted)	Cohort	25,27	2	0.97 (012 to 8.06)	67	0.98
	CC	28	1	1.26 (0.77 to 2.06)	–	0.36
Any-stage ROP (unadjusted)	Cohort	29	1	1.22 (0.22 to 6.78)	–	0.82
	CC	19	1	6.24 (0.29 to 132.17)	–	0.24
LOS (unadjusted)	Cohort	14,29,30	3	1.68 (0.94 to 2.98)	0	0.08
	RCT	23	1	0.24 (0.04 to 1.36)	–	0.11
NEC (unadjusted)	Cohort	25,30,31	3	2.19 (1.11 to 4.31)	0	0.02
CLD (unadjusted)	Cohort	30	1	1.48 (0.82 to 2.69)	–	0.19
	RCT	23	1	0.67 (0.11 to 3.93)	–	0.65
PVL (unadjusted)	Cohort	14,30	2	0.64 (0.25 to 1.62)	0	0.35
CP (unadjusted)	Cohort	25,30	2	1.54 (0.74 to 3.23)	0	0.25
Hearing impairment (unadjusted)	Cohort	25,30	2	5.32 (0.55 to 51.11)	23	0.15
Blindness (unadjusted)	Cohort	25	1	22.76 (0.86 to 604.71)	–	0.06
Severe motor disability (unadjusted)	Cohort	30	1	1.00 (0.26 to 3.81)	–	1.00
Severe cognitive disability (unadjusted)	Cohort	25,30	2	1.25 (0.22 to 6.95)	0	0.80
Moderate to severe disability (unadjusted)	Cohort	31	1	0.69 (0.13 to 3.66)	–	0.66
Moderate to severe disability (adjusted)	Cohort	31	1	0.06 (0.00 to 1.80)	–	0.10

Abbreviations: CC, case-control study; CLD, chronic lung disease; CP, cerebral palsy; IVH, intraventricular haemorrhage; LOS, late-onset sepsis; NEC, necrotising enterocolitis; OR, odds ratio; PVL, periventricular leukomalacia; RCT, randomised controlled trial; ROP, retinopathy of prematurity.

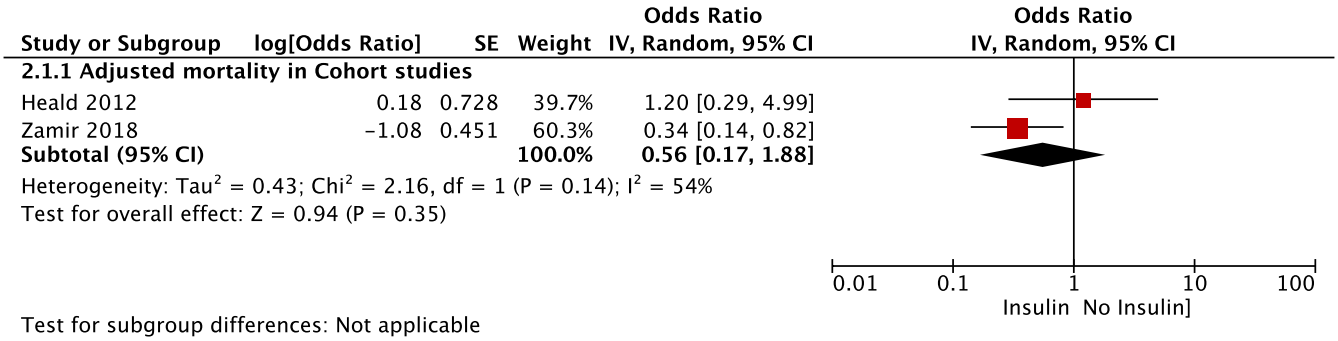

FIGURE 3 Forest plot showing the association between insulin and adjusted mortality.

delayed diagnosis of hypoglycaemia with detrimental neurodevelopmental consequences. In that context, it is reassuring to know that the recently published REACT trial found continuous monitoring of blood glucose levels is feasible and reduce the risk of exposure to prolonged and severe episodes of hyperglycaemia and hypoglycaemia in preterm infants.[53] Similarly, computer model based approach can provide safe and effective blood glucose control without increasing the risk of hypoglycaemia.[54] The latest Cochrane review has highlighted the need for further clinical trials of continuous glucose monitoring in preterm infants.[55]

Important challenges whilst designing RCTs of insulin therapy for hyperglycaemia are having a consensus on the definition of hyperglycaemia, cut-off point of blood glucose level for the commencement of insulin infusion, target blood glucose levels and the frequency of measurement. Another important challenge whilst conducting RCTs of insulin therapy is the management of hyperglycaemia in the control arm. Whilst the ideal trial design should not allow the use of insulin in the control arm, it may not be feasible if the glucose levels are very high and if clinicians believe that insulin therapy is necessary for them. The CONSORT guidelines recommend the use of both 'Intention to treat' and 'per-protocol' analyses in such situations.[56,57]

The included studies in our systematic review used various cut-offs of glucose levels for commencing insulin. In addition, some of the included studies tried reducing the glucose delivery rate before initiating insulin whereas in other studies insulin was started at clinician's discretion. Clinicians tend to start insulin at a higher glucose cut-offs, which might lead to selection bias. The control arm was also not uniform in terms of definition of hyperglycaemia and its management. All the above factors would have contributed to clinical and statistical heterogeneity. Other limitation of our review was the lack of data from some studies in a format suitable for pooling, especially for adjusted ORs. Future observational studies should endeavour to report ORs after adjusting for confounders. Publication bias could not be assessed owing to the small number of included studies in the meta-analysis. Given these limitations, the certainty of evidence was deemed low and hence the results need to be interpreted with caution.

The strengths of our review include its rigorous methodology, and separate pooling of adjusted and unadjusted ORs. Another important strength of the included studies (and hence the systematic review) was the absence of contamination of the control arm with rescue insulin therapy.

5 | CONCLUSIONS

Very low certainty of evidence suggests that Insulin therapy may not improve the outcomes of very preterm infants with hyperglycaemia. Well designed and adequately powered RCTs are needed.

AUTHOR CONTRIBUTIONS

CR conceptualised, designed the study and registered in the systematic review database. CR, NP and SR did data collection, data analysis and interpretation. NP contacted all the authors. CR and NP drafted the article. SP and SR did critical review and overall supervision. All authors discussed the results and contributed to the final manuscript.

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No funding was secured for this study.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

ORCID

Chandra Prakash Rath https://orcid.org/0000-0001-7584-1996

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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