Glucagon for Neonatal Hypoglycaemia: Systematic Review and Meta-Analysis

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Abstract

Introduction: Glucagon is often used in neonatal hypoglycaemia, but its effects have not been systematically assessed. We undertook a systematic review to determine the efficacy and safety of glucagon treatment for neonatal hypoglycaemia. Methods: We searched MEDLINE, CINAHL, EMBASE, and CENTRAL from inception until May 2021. We included studies that reported one or more prespecified outcomes and compared glucagon with placebo or no glucagon. Studies were excluded if the majority (>70%) of participants were >1 month of age. Two authors independently extracted data. We used ROB-2/modified ROBINS-I to assess risk of bias, GRADE for certainty of evidence, and RevMan for meta-analysis. Results: 100 studies were screened, 37 reviewed in full, and seven single-arm non-randomised intervention studies, involving 348 infants, were included (no trials). Data were insufficient to undertake meta-analysis of the critical outcomes (time to blood glucose normalization, recurrent hypoglycaemia, neurocognitive impairment). In 3 studies, \geq80\% of neonates achieved normoglycaemia within 4 h of glucagon administration. However, recurrent hypoglycaemia was common (up to 55\%). Glucagon increased blood glucose concentration at 1–2 h by 2.3 mmol/L (95\% CI 2.1, 2.5) (low certainty evidence, 6 studies, $N = 323$). There were few data for other important clinical outcomes. Conclusion: There is a paucity of evidence about the efficacy and safety of glucagon for treatment of neonatal hypoglycaemia. Low certainty evidence suggests that glucagon may increase blood glucose by \sim 2.3 mmol/L but recurrent hypoglycaemia appears common. High-quality, randomized controlled trials are required to determine the role of glucagon in managing neonatal hypoglycaemia.

Introduction

Hypoglycaemia is the most common metabolic problem in neonates, with an incidence of 5–15\% of all births [1]. Safe and effective treatment is important due to the risk of long-term neurological sequelae [2]. Infants with severe or recurrent hypoglycaemia are usually treated with intravenous (IV) dextrose, but there is increasing evidence that rapid correction of blood glucose concentration (BGC) or to too high a level may contribute to neuronal injury after hypoglycaemia [3]. Further, some infants have ongoing episodes of hypoglycaemia despite dextrose treatment, most likely due to failure to adequately suppress insulin secretion, thereby inhibiting hepatic glucose output [4]. Thus, new treatment approaches are
needed that target the underlying pathophysiology and promote glycaemic stability [5].

Glucagon injection or infusion is one such potential treatment, which is sometimes used for refractory neonatal hypoglycaemia. Glucagon is a counterregulatory hormone of insulin, secreted from pancreatic α-cells into the blood stream in a pulsatile fashion in response to low BGC [6]. It promotes hepatic glycogenolysis and gluconeogenesis through induction of phosphoenolpyruvate carboxykinase, which is regulated by the ratio of glucagon to insulin [7]. In addition, glucagon promotes lipolysis in adipose tissue, releasing glycerol for gluconeogenesis and free fatty acids for ketogenesis [7]. Ketogenesis promotes euglycaemia not only by providing alternative fuels to reduce glucose oxidation in peripheral tissues, but also by providing cofactors, such as acetyl CoA and NADH, that support gluconeogenesis.

A systematic review in diabetic patients found that glucagon can be given by the nasal route with similar efficacy to intramuscular injection, but the overall effectiveness of glucagon was variable with failure of correction of hypoglycaemia in up to 15% of patients in some studies [8]. In neonates, the benefits and risks of glucagon have not been systematically evaluated, and there are concerns that glucagon may be less effective due to reduced glycogen stores and higher insulin concentrations [9]. The aim of this systematic review is to evaluate the effectiveness and safety of treatment with glucagon, including glucagon analogues, for improving short- and long-term outcomes in neonates born at ≥35 weeks’ gestation who require treatment for hypoglycaemia.

Methods

This systematic review was conducted following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [10]. The protocol was registered in PROSPERO (CRD42021248917). Ethical approval was not required as this review used only published data.

Search Strategy

MEDLINE, CINAHL, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched using relevant medical subject headings (MeSH), including glucagon, neonate, infant, infant newborn, infant premature, infant postmature, hypoglycemia, low blood glucose, and related key words with both their British and American spelling variants. The search was limited to studies involving human infants with abstracts. There were no language or publication date restrictions. Reference lists in eligible studies, review papers, and conference abstracts were hand searched to identify additional items. One author identified records through database searching and screened titles and abstracts for potential eligibility. Two authors then independently assessed the full text for eligibility using Rayyan (https://www.rayyan.ai/). Conflicts were resolved through discussion or consultation with a third author.

Eligibility Criteria

We included all published trials (randomized, non-randomized, historically controlled), before and after observational studies, and case-control studies of glucagon or glucagon analogues for treatment of hypoglycaemia, administered via any route (intramuscular, intranasal, or IV infusion), where the majority of neonates (>70%) were born at ≥35 weeks’ gestation, and if one or more of the critical or noncritical, important outcomes were reported for one or more comparison. Studies were excluded if the majority of subjects (>70%) received glucagon treatment at ≥1 month of age.

Outcomes

Clinically relevant outcomes were prespecified and rated by the authors as critical, or important but noncritical, according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines [11]. Outcomes were divided into four developmental epochs: neonatal (<1 month), early childhood (1–5 years), late childhood (6–11 years), and adolescence (12–18 years). The critical outcomes were time to blood glucose normalization after commencing glucagon therapy and recurrent hypoglycaemia (≥2 episode after initial correction of hypoglycaemia, as defined by authors) in the neonatal period and neurocognitive impairment in early or late childhood or adolescence (abnormal motor, sensory, or cognitive function).

The important, noncritical neonatal outcomes were highest BGC ≤2 h after first treatment administration, hyperglycaemia (during and <48 h after stopping therapy, as defined by authors), duration of IV fluids, duration of hospital admission, seizures, abnormal brain imaging, and any other event classified as “adverse” or “seriously adverse.” The change in BGC at 1–2 h after first treatment administration was included post hoc as an additional outcome, as it was frequently reported. Other important, noncritical outcomes at early or late childhood or adolescence were visual-motor impairment, executive dysfunction, epilepsy, low language achievement, emotional-behavioural difficulty, and abnormal brain imaging. Three comparisons were prespecified: (i) glucagon versus placebo or no glucagon; (ii) glucagon versus alternative pharmacological therapy for neonatal hypoglycaemia (e.g., diazoxide, corticosteroids); and (iii) between intervention comparisons: route and/or type of glucagon therapy.

Risk of Bias

Two authors independently assessed the risk of bias of studies for each outcome using the Cochrane Collaboration’s risk of bias tool for randomized trials [12] and a modified ROBINS-I tool for non-randomized intervention studies [2, 13]. The following bias domains were assessed: selection of participants, exposures, measurement of outcomes, missing data, and reporting of results. Discrepancies between authors were resolved through discussion or by consultation with a third author.

Data Extraction and Analysis

Two authors independently extracted data from the included studies using a prespecified data form. Year of publication, study...
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Included Studies
All seven included studies were single-arm non-randomized intervention studies or case series, of which four were prospective. Glucagon was administered via infusion in 4 studies and via bolus in 3 studies (Table 1). The studies were conducted in advanced economies, including England, the USA, Canada, Scotland, Japan, Israel, and Hungary. One study was conducted in the 1970s [17], one in the 1980s [18], two in the 1990s [19, 20], one in the 2000s [21], and two in the 2020s [22, 23]. All studies were performed in neonatal intensive care units.

Neonatal Period
Critical Outcomes
Time to blood glucose normalization after commencing glucagon treatment was reported by 3 studies but data were not in a form suitable for meta-analysis. Carter et al. [18] found that 20/25 (80%) of infants achieved normoglycaemia (BGC ≥4 mmol/L) within 3 h; Kasirer et al. [23] found that 145/158 (92%) infants achieved normoglycaemia (BGC ≥2.6 mmol/L) within 2 h, and Nakamura et al. [20] found that 14/15 (93%) infants achieved normoglycaemia (BGC ≥2.2 mmol/L) within 4 h. There was serious risk of bias for this outcome (Table 2).

Recurrent hypoglycaemia (≥1 episode after initial correction of hypoglycaemia) was reported by 2 studies, but data were not in a form suitable for meta-analysis [18, 21]. Carter et al. [18] found that 9/25 (36%) infants had recurrent hypoglycaemia, defined as BGC <4 mmol/L after reaching BGC of >4 mmol/L; Miralles et al. [21] found that 30/55 (55%) infants had recurrent hypoglycaemia, defined as BGC <2.6 mmol/L after reaching BGC of ≥2.6 mmol/L. There was serious risk of bias for this outcome (Table 2).

Important, Noncritical Outcomes
Highest BGC ≤2 h after first treatment administration of glucagon was reported only by Godin et al. [22]; mean (SD) of maximum plasma glucose concentration (GC) at 20–60 min after standard dose glucagon (≤0.2 mg/kg) was 4.7 (1.1) mmol/L and 4.5 (0.8) mmol/L after high dose glucagon (>0.2 mg/kg). There was serious risk of bias for this outcome (Table 2). Hyperglycaemia was reported only by Carter et al. [18]; 5/25 (20%) of infants developed hyperglycaemia (BGC >10 mmol/L) during treatment with glucagon. The hyperglycaemia resolved with a reduction in the glucagon infusion rate. There was moderate risk of bias for this outcome (Table 2). The presence of seizures in the neonatal period was reported only by Carter et al. [18]; seizures occurred in 4/25 (16%)
infants, but it was unclear whether this was before or after glucagon administration. There was moderate risk of bias for this outcome (Table 2). The change in BGC at 1–2 h post-glucagon was reported by 6 studies (N = 323) [17, 19–23]. Meta-analysis showed that glucagon treatment may be associated with a mean (95% CI) increase in BGC or plasma GC of 2.3 (2.1, 2.5) mmol/L (Fig. 2). There was serious risk of bias for this outcome (Table 2) and the overall certainty of evidence was low (downgraded for risk of bias, upgraded for large exposure effect). There was no evidence that the route of administration influenced the effect of glucagon on BGC at 1–2 h (Fig. 2). Data were not available for other subgroup analyses. No data were available for duration of IV fluids, duration of hospital admission, abnormal brain imaging, and adverse events.

**Early Childhood**

**Critical Outcomes**

Two studies reported data related to neurocognitive function, but data were not suitable for meta-analysis [18, 20]. Carter et al. [18] reported that 3/23 (13%) infants were developmentally delayed at follow-up, but the age at assessment was not specified. Nakamura et al. [20] reported that 5/15 (33%) cases developed major handicaps in the first 3 years, but further details were not provided. There was serious risk of bias for this outcome (Table 2).

**Important, Noncritical Outcomes**

Visual-motor impairment was not directly assessed in any studies, although Carter et al. [18] reported that 4/20 (20%) infants had squints at follow-up. There was moderate risk of bias for this outcome. No data were available for executive dysfunction, epilepsy, low language achieve-
### Table 1. Characteristics of included studies

| Study          | Country    | Setting and eligibility                                           | Sample size | Definition of hypoglycaemia                                      | Glucagon route and regimen                                      | Gestation length | FGR or SGA | Age at entry (range) | Comments                                                                                           |
|----------------|------------|------------------------------------------------------------------|-------------|------------------------------------------------------------------|------------------------------------------------------------------|------------------|-------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Mestyan et al. [17] | Hungary    | Referral neonatal unit SGA neonates with hypoglycaemia Prospective | 7           | Term: BGC <1.7 mmol/L preterm: BGC <1.1 mmol/L                   | Continuous IV infusion 0.2 μg/kg/min for 4 h                       | 3 term, 4 preterm; no other information                          | All SGA       | 3–18 h               | Given the year of publication, preterm infants were assumed to be ≥35 weeks' gestation
Seven non-hypoglycaemic infants were also studied but there was no direct comparison with hypoglycaemic infants |
| Carter et al. [18] | Scotland    | Admitted to NICU with birthweight <5th centile, ongoing hypoglycaemia despite IV dextrose infusion 12.5% at ≥6.5 mg/kg/min and frequent high energy milk feeds Prospective | 25          | BGC <2 mmol/L                                                     | Continuous IV infusion commencing 0.5 mg/day, increasing up to 20 mg/day | 33–40 weeks (range), 9 preterm                                  | All SGA       | 15.7 h (mean)        | Mothers of three infants were taking β blockers
Nine infants required glucagon infusion >0.5 mg/kg
Mean duration of treatment 81 h
Two infants died from unrelated causes
Two cases of thrombocytopenia, one case of hyponatremia, one case of necrotising enterocolitis |
| Hawdon et al. [19] | England    | Admitted to NICU for recurrent hypoglycaemia (≥2 BGC <2.6 mmol/L in 1 day) Prospective | 11          | BGC <2.6 mmol/L                                                  | Single IV bolus 0.2 mg/kg                                         | 36.3 weeks (mean)                                              | 6 SGA        | 24 h (median)         | Ten infants were on IV glucose before the start of the study at GDR ≥5 mg/kg/min |
| Nakamura et al. [20] | Japan     | Admitted to NICU with ongoing hypoglycaemia despite IV dextrose infusion >12% and GDR > 9 mg/kg/min Prospective | 15          | BGC <2.2 mmol/L                                                  | Continuous IV infusion commencing 0.5 mg/day, increasing up to 2.4 mg/day | 36.7 weeks (mean)                                              | 11 SGA       | 37.5 h (mean)         | Three cases had neonatal asphyxia, one had a chromosomal disorder and one had Potter syndrome
Male to female ratio 11:4
Three infants required glucagon infusion >0.5 mg/day |
| Miralles et al. [21] | Canada     | Admitted to NICU, received glucagon and had ≥1 BGC before and after starting treatment All on IV dextrose infusion (mean GDR 8.8 mg/kg/min) Prospective | 55          | BGC <2.6 mmol/L                                                  | Continuous IV infusion 1 mg/day                                   | 36 weeks (mean)                                                | 25 FGR       | 4.5 days (mean)       | Thirty-two infants had recurrent hypoglycaemia for >24 h before receiving glucagon
Six infants received glucagon infusions >1 mg/day
Four patients died of causes unrelated to hypoglycaemia |
Table 1 (continued)

| Study          | Country | Setting and eligibility                                                                 | Sample size | Definition of hypoglycaemia | Glucagon route and regimen | Gestation length | FGR or SGA | Age at entry | Comments                                                                 |
|----------------|---------|----------------------------------------------------------------------------------------|-------------|-----------------------------|---------------------------|-----------------|-------------|---------------|---------------------------------------------------------------------------|
| Godin et al.   | USA     | Admitted to NICU, received glucagon and had PGC within 60 min before and 20–60 min after treatment Less than one-third were on IV dextrose Retrospective | 31          | PGC <2.8 mmol/L              | Single IV bolus ≤0.2 mg/kg | No data (mean PMA at study 38.7 weeks) | No data 30.5 days (mean) | Two infants had congenital hyperinsulinism, two had hypopituitarism     |
| Kasirer et al. | Israel  | Well-baby nursery; all neonates screened for hypoglycaemia within 2 h of birth Not on IV dextrose at time of study Exclusions: SGA, birthweight <3 kg, gestation <36 weeks, major congenital anomalies, proven infection Retrospective | 158         | BGC <2.8 mmol/L              | Single IM bolus 1 mg given if initial BGC <1.7 mmol/L or repeat <2.2 mmol/L despite feeding | 38.7 weeks (mean) | No SGA 4 h (mean) | Universal screening policy Five infants were transferred to NICU immediately after IM glucagon due to symptoms or severe hypoglycaemia (BGC <1.1 mmol/L) and were commenced on IV  dextrose |

BGC, blood glucose concentration; GDR, glucose delivery rate; IV, intravenous; PGC, plasma glucose concentration; PMA, post-menstrual age.
Glucagon has been recommended for the treatment of persisting neonatal hypoglycaemia by several professional bodies [24, 25], but our systematic review identified a paucity of evidence to support these guidelines. We found evidence of low certainty that glucagon may increase GCs by \( \sim 2.3 \text{ mmol/L} \) within 1–2 h of administration, and in individual studies most infants (\( \geq 80\% \)) achieved normoglycaemia within 2–4 h. However, the recurrence rate of hypoglycaemia was high (up to 55%) even with ongoing infusions. There was insufficient evidence to determine the time course of blood glucose response after glucagon; the effect on short-term clinical outcomes; and the long-term benefit and safety of glucagon therapy. High-quality, randomized controlled trials are needed to determine the clinical effectiveness and safety of glucagon for treatment of neonatal hypoglycaemia, including dose, route, and treatment regimen.

The central role of glucagon in facilitating postnatal metabolic transition provides a strong physiological rationale for the use of exogenous glucagon in treating neonates with hypoglycaemia that is refractory to first-line measures such as additional feeding and buccal dextrose gel [3]. It is surprising that no high-quality controlled trials of glucagon therapy in neonates were identified in this review, and this remains a critical knowledge gap.

While low certainty evidence suggests that glucagon may raise BGC in many infants, several concerns remain, especially the metabolic transition and safety of glucagon administration. The course of metabolic transition alters the course of treatment, and glucagon administration alters the course of metabolic transition. The central role of glucagon in facilitating postnatal metabolic transition provides a strong physiological rationale for the use of exogenous glucagon in treating neonates with hypoglycaemia that is refractory to first-line measures such as additional feeding and buccal dextrose gel [3]. It is surprising that no high-quality controlled trials of glucagon therapy in neonates were identified in this review, and this remains a critical knowledge gap.

Table 2. Risk of bias of included studies

| Outcome                                                                 | Mestyan et al. [17] | Carter et al. [18] | Hawdon et al. [19] | Nakamura et al. [20] | Miralles et al. [21] | Godin et al. [22] | Kasirer et al. [23] | Overall risk of bias for outcome |
|------------------------------------------------------------------------|----------------------|--------------------|--------------------|----------------------|----------------------|----------------------|----------------------|----------------------------------|
| Time to blood glucose normalization\*                                   | No data              | Moderate\*          | No data            | No data              | No data              | No data              | No data              | Serious\*                        |
| Recurrent hypoglycaemia (\( \geq 1 \) episode after initial correction of hypoglycaemia, as defined by authors)\*) | No data              | Moderate\*          | No data            | No data              | No data              | No data              | No data              | Serious\*                        |
| Highest BGC \( \leq 2 \text{ h} \) after first treatment administration | No data              | No data             | No data            | No data              | No data              | No data              | No data              | Serious\*                        |
| Hyperglycaemia (during and up to 48 h after stopping therapy)          | No data              | No data             | No data            | No data              | No data              | No data              | No data              | Serious\*                        |
| Seizures in the neonatal (\( \leq 1 \text{ month} \) period)           | No data              | No data             | No data            | No data              | No data              | No data              | No data              | Moderate\*                       |
| Change in BGC at 1–2 h post-glucagon administration\*                  | Moderate\*           | No data             | Moderate\*         | Serious\*            | No data              | No data              | No data              | Serious\*                        |
| Neurocognitive impairment in Early childhood (1–5 years)\*              | No data              | Moderate\*          | No data            | No data              | No data              | No data              | No data              | Serious\*                        |
| Visual-motor impairment in Early childhood (1–5 years)\*                | No data              | Moderate\*          | No data            | No data              | No data              | No data              | No data              | Moderate\*                       |

No data were available for the following prespecified outcomes: duration of intravenous fluids; duration of hospital admission; epilepsy in early or later childhood or adolescence; abnormal brain imaging in the neonatal period or in early or late childhood or adolescence; executive dysfunction in early or late childhood or adolescence; low language/literacy in early or late childhood or adolescence; low numeracy in late childhood or adolescence; emotional-behavioural difficulty. \* At risk of bias due to selection of participants. \* At risk of bias due to missing data. \* At risk of bias in ascertainment of exposures. \* At risk of reporting bias. \* Critical outcome. ** Post hoc outcome.
insulin concentrations are high, and this may explain glucagon unresponsiveness in some infants. Further research is required to understand the influence of other metabolites and hormones on glucagon action. Thus, although there is a good physiological rationale for using glucagon to treat neonatal hypoglycaemia, current evidence is far from complete.

It is interesting that the BGC response to glucagon within 1–2 h of administration did not appear to be influenced by route of administration, and that there was no apparent advantage in using a higher dose of IV bolus. In healthy adults, the half-life of glucagon ranges from 0.1 to 0.3 h with IV bolus and 0.3–0.4 h with IM injection [27]. Pharmacokinetics has not been well studied in neonates, and it is possible that the plasma half-life is longer due to reduced renal clearance, making route of administration less important. There is some evidence in adults that plasma concentrations are highest when glucagon is given by subcutaneous injection [27], but this has not been studied in neonates. Similarly, no data are available in infants on intranasal administration. This warrants further investigation as intranasal glucagon has been shown to have similar efficacy to IM and subcutaneous routes for treatment of hypoglycaemia in adults and is preferred by relatives [28]. Aqueous glucagon analogues, such as dasiglucagon, are increasingly being used in diabetes patients because they do not require reconstitution [29], but have also not been studied in neonates. Thus, in addition to the need for further data on clinical efficacy and safety, pharmacological studies of glucagon in neonates are needed, especially route and frequency of administration.

**Limitations**

The main limitation of this systematic review was the lack of data for analysis of the prespecified critical outcomes and the absence of randomized trials. All of the included studies were single-arm non-randomized intervention studies or case series, a design that has high risk of bias, especially selection, measurement and reporting bias [30]. As BGC normally increases in the first 2–3 days after birth, in the absence of a control group, it is difficult

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**Fig. 2.** Change in BGC or PGC 1–2 h after glucagon treatment. GC, glucose concentration; IV, inverse variance (fixed effects); SE, standard error of the mean; PGC, plasma glucose concentration.
Recommendations for Research

High-quality evidence supports the use of buccal dextrose gel as first-line treatment for neonatal hypoglycaemia, but there is a paucity of evidence to guide practice when dextrose gel fails [3]. Appropriately controlled randomized trials are urgently needed to assess the efficacy and safety of glucagon for treatment of neonatal hypoglycaemia and to determine its role in relation to other management strategies. Bolus doses of glucagon (IM, subcutaneous, or intranasal) could be used to reduce NICU admission, stabilize BGC while arranging NICU transfer and decrease the intensity of secondary interventions, for example, duration of IV dextrose. Continuous infusions may have an adjunctive role in persistent hypoglycaemia. Understanding the mechanisms that lead to recurrent hypoglycaemia during and after glucagon treatment and how this can be prevented will be important. Placebo or sham comparators are needed to provide strong evidence and could be implemented in many situations with carefully designed protocols. Further investigation is required to determine the optimal dose, route, and treatment regimen in neonates, including interactions with clinical risk factors.

Conflict of Interest Statement

The authors have no conflicts of interest relating to this manuscript.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

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Author Contributions

Protocol development: all authors; literature search and assessing for eligibility: E.P.G.W. and C.J.D.M.; data extraction: W.P.G.W., J.A., S.M.H., and C.J.D.M.; analysis: E.P.G.W. and C.J.D.M.; critical review and approval of the manuscript: all authors.

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