BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2023-077429 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 04-Jul-2023 |
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| Keywords: | ACCIDENT & EMERGENCY MEDICINE, Paediatric intensive & critical care < INTENSIVE & CRITICAL CARE, Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric orthopaedic & trauma surgery < PAEDIATRIC SURGERY, Calcium & bone < DIABETES & ENDOCRINOLOGY |
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# The Incidence of Admission Ionised Hypocalcaemia in Paediatric Major Trauma: Protocol for a Systematic Review and Meta-Analysis

## Registration

PROSPERO registration number: CRD42023425172

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## Support

There is no funding or sponsorship to declare.

## Abstract

Introduction

Hypocalcaemia forms part of the 'diamond of death' in major trauma, alongside hypothermia, acidosis, and coagulopathy. In adults, admission hypocalcaemia prior to transfusion is associated with increased mortality, increased blood transfusion requirements, and coagulopathy. Data in paediatric major trauma patients are limited. This systematic review and meta-analysis aims to describe and synthesise the available evidence relevant to paediatric trauma, admission hypocalcaemia, and outcome.

Methods and analysis

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline will be used to construct this review. A planned literature search for articles in the English language will be conducted from inception to the date of searches using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The grey literature will also be searched. Both title and abstract screening, and full-text screening will be done by two reviewers, with an adjudicating third reviewer. Heterogeneity will be assessed using $I^2$ test, and risk of bias will be assessed using the ROBINS-I tool. A meta-analysis will be undertaken using ratio measures (odds

ratio) and mean differences for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a *p*-value.

Ethical review and dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

Prospero registration number

CRD42023425172

**Strengths and limitations of this study**

- ⇒ The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.
- ⇒ This is a novel review that addresses an area of uncertainity in the current evidence base surrounding paediatric major trauma through systematic review and meta-analysis of published data and the grey-literature.
- ⇒ The review methodology is at risk of limitation by publication bias.

## Background

Major trauma is one of the leading causes of death in children in the United Kingdom (UK).[1][2] A key cause of potentially-survivable death from trauma is haemorrhage.[3] Uncontrollable haemorrhage may be related to the injury mechanism itself, or as a result of Trauma Induced Coagulopathy (TIC).[4] TIC is common, occurring in at least a quarter of haemorrhagic deaths, and has a number of proposed pathophysiological mechanisms, which generally involve injury and shock provoking a immunological, endothelial, and platelet response.[4] All forms of haemorrhage are further exacerbated by the 'lethal triad' of coagulopathy, hypothermia and acidosis.[5][6][7] More recently biochemical abnormalities such as hyperkalaemia and hypocalcaemia have been recognised to contribute to deaths from haemorrhage.[6][8] In particular, calcium's role is important for clot formation, vascular tone, and cardiac contractility, with hypocalcaemia contributing to coagulopathy and cardiovascular decompensation.[5][6]] As such the 'lethal triad' is now considered a 'diamond of death' with hypocalcaemia forming a key component of this deleterious combination.[5][6]] The early recognition and treatment of these components in the 'diamond of death' are essential for trauma resuscitation.[5][7][9]

## Rationale

The free form of calcium (ionised calcium (iCa)) is the physiologically relevant component of calcium in the blood.[10] iCa is measured on blood gases, which are often taken on arrival for major trauma patients, and there is good agreement between arterial and venous measurements.[11] Blood gas measurement will also record the pH and lactate, and can affect the availability of iCa.[12][13] Ionised hypocalcaemia (iHypoCa) in major trauma patients is multifactorial.[5][6][7][14] The infusion of citrated blood products is a recognised cause of hypocalcaemia in trauma due to calcium chelation with citrate.[6][15] There is also emerging evidence in adults that early hypocalcaemia may occur in trauma patients prior to the receipt of blood products containing citrate.[16][17][18][19] Potential pathophysiological mechanisms underpinning this include calcium binding by lactate, intracellular influx of calcium due to ischaemia and reperfusion, impaired calcium homeostasis secondary to trauma, and secondary to dilution by crystalloid fluid resuscitation.[5][6][7]] A systematic review and meta-analysis, which included a total of 1213 major trauma patients, 18 years or older, with a

document iCa level on admission explored the incidence and outcomes associated with admission iHypoCa.[20] Studies that involved patients in whom calcium concentration may have been confounded by prior blood transfusion were excluded.[20] Overall, the incidence of admission ionised hypocalcaemia (iHypoCa) was 56.2%, and iHypoCa was associated with: increased mortality, increased blood transfusion requirements, and coagulopathy.[16][17][18][19][20]] Evidence of admission iHypoCa and the association with adverse outcomes in adult trauma patients has led to the early measurement and replacement of calcium being recommended in adult trauma guidelines.[21][22] In paediatric major trauma data are limited. A search of PROSPERO did not find any similar planned systematic reviews or meta-analyses. Moreover, a preliminary search of the literature has found a few heterogenous studies, which indicate that admission iHypoCa may be less prevalent in children compared to adults.[23][24][25][26]

## Aims

The primary aim of this systematic review and meta-analysis is to explore the limited evidence related to the incidence of admission iHypoCa in paediatric major trauma patients. The review also aims to explore whether admission iHypoCa, compared to normocalcaemia, is associated with adverse clinical outcomes.

## Methods

### Eligibility criteria

This proposed systematic review and meta-analysis will explore the incidence of iHypoCa in paediatric (<16 years old) major trauma patients (Injury Severity Score (ISS) >15) and explore whether admission iHypoCa (iCa <1.16 mmol/L), compared to normocalcaemia (iCa ≥ 1.16 mmol/L) is associated with a greater incidence of adverse outcomes.[12] The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) eligibility criteria are detailed in Table 1.

### Information sources

A planned literature search for articles in the English language will be conducted from inception to the search date using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The reference lists of all included studies, and the grey literature will also be searched.

### Search strategy

The search strategy can be found in online supplementary tables 2,3 and 4.

The search will also involve checking reference lists of retrieved articles, conference abstracts, and online study results. If data is incomplete, then corresponding authors will be contacted for additional information.

### Study records

The search strategy will be undertaken by a trained librarian. The combined abstracts from the search strategy will be independently screened by two reviewers to identify studies meeting inclusion criteria, any duplications will be removed manually. For abstracts meeting inclusion criteria, full texts will be retrieved and again be independently reviewed against the inclusion and exclusion criteria by two reviewers and an adjudicating third reviewer.

A standardised data sheet (Microsoft ® Excel for Mac, Version 16.72, 2023) will be used to extract data from included studies to facilitate data synthesis and assessment of quality and risk of bias.

Extracted data will be independently verified by the second reviewer, and any discrepancies again adjudicated by the third reviewer.

The following data items will be extracted:

1. Hospital setting
2. Study type
3. Country of treatment
4. Cohort size
5. Median [interquartile range (IQR)] severity of injury (ISS)
6. Abbreviated Injury Scale (AIS) score for injury regions
7. Ionised hypocalcaemia definitions
8. Incidence of admission iHypoCa (iCa <1.16 mmol/L) (yes/no)[12]
9. Definitions, and presence of, coagulopathy
10. The presence of hyperkalaemia (>5.5 mmol/L)(yes/no/not reported)[27]
11. The presence of hyperlactataemia (>2.0mmol/L) (yes/no/not reported)[28]
12. Haemodynamic instability (hypotension (based upon age specific Advanced Paediatric Life Support (APLS) values) or elevated Shock Index Paediatric Age-Adjusted (SIPA))(yes/no/not reported)[29][30][31]
13. Administration of calcium (yes/no/not reported)
14. Vasopressor requirements within the first 24 hours (yes/no/not reported)
15. Total blood product transfusion requirement during the first 24 hours (yes/no/not reported)
16. Activation of the major haemorrhage protocol within the first 24 hours (yes/no/not reported)
17. Requirement for invasive (operative or interventional radiology) intervention within 24 hours (yes/no/not reported)
18. Hospital length of stay (LOS) (days)
19. Paediatric Intensive Care Unit (PICU) LOS (days)
20. Early mortality within 24 hours and medium mortality during episode of hospital admission (>24 hours) or within 30 days (yes/no/not reported)

Outcomes and prioritisation

The primary outcome of this systematic review and meta-analysis is the overall incidence of admission iHypoCa. Secondary outcomes are the associations with physiological abnormalities, and adverse outcomes. Physiological abnormalities are classified dichotomously as the presence of hypotension (based upon age specific APLS values)[29] or elevated SIPA(0-6yrs >1.22, 7-12yrs > 1.00, 13-16yrs > 0.90)[30][31], hyperkalaemia (>5.5 mmol/L)[27], and hyperlactataemia (>2.0mmol/L)[28]. Adverse outcomes are classified dichotomously as the requirement for vasopressors, transfusion, activation of the major haemorrhage protocol, or invasive (operative or interventional radiology) intervention in the first 24 hours and mortality within 30 days. Hospital LOS, and PICU LOS in days are classified continuously.

Ratio measures (odds ratio) and mean differences will be used for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a *p*-value.

Risk of bias

Risk of bias will be assessed for all included studies. For any randomised controlled trials GRADE methodology will be used, and for observational studies, the ROBINS-I tool will be used.[32][33]

The risk of publication bias will be assessed with funnel plots as appropriate.[36]

Data synthesis

Data will be synthesised following PRISMA guidelines. Studies will be assessed clinically (PICO) and methodologically (study design, comparability, outcome ascertainment, and risk of bias). Given that current evidence is likely to be limited, the minimum number of studies is two. A preliminary search has identified four studies.[23][24][25][26]] The $I^2$ test will be conducted to determine if data are suitable for quantitative synthesis.[34]

Meta-analysis of effect estimates is intended and will be displayed using a forest plot. If there is limited evidence for pre-specified comparison, then the haemodynamic instability and vasopressor PICO groups may be combined. Definitions of hypocalcaemia will also be combined if required, providing values are iCa <1.16. Other elements are unlikely to be suitable as contingencies for combination. If different effect measures are used attempts will be made to transform the effect measures for meta-analysis.

A narrative synthesis and summary of effect measures (with the use of box-and-whisker plots) will be conducted if heterogeneity is deemed too substantial across studies to allow for meaningful meta-analysis or if there are major concerns about bias from the three reviewers.

Meta-analysis or narrative synthesis of elements will focus on the incidence of hypocalcaemia in paediatric trauma patients and trend towards adverse outcomes. Subgroup analysis may be undertaken for severe iHypoCa (iCa <1mmol/L).

**Patient and public involvement**

No patients will be directly involved in the design of this study and dissemination of findings to participants is not applicable.

**Ethics and Dissemination**

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

**Discussion**

The study has the advantage of using rigorous methodology in accordance with the Cochrane handbook and will be reported as per PRISMA guidelines. The methodology is at risk of publication bias.

As paediatric trauma remains a leading cause of death in the UK this study will add to the knowledge base on the management of paediatric major trauma. Given the different physiology of children compared to adults, children may be more vulnerable to the effects of iHypoCa and the results of studies involving adult major trauma patients may not be able to be extrapolated to a paediatric cohort.[35] This study aims to provide further knowledge on the incidence and association of admission hypocalcaemia in paediatric major trauma. Findings of a high incidence of hypocalcaemia, and adverse outcomes, may prompt the consideration of early calcium testing and early replacement for injured children.

**Acknowledgements**

The authors would like to acknowledge and thank Catherine Hancox and the Defence Medical Academic Library Team for their assistance with the search strategy.

## Tables

**Table 1. Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) Strategy for Inclusion and Exclusion**

| PICOS Strategy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| P – Population | Paediatric (<16yrs) major trauma patients (Injury Severity Score> 15) with a documented ionised calcium (iCa) level on admission. | iCa level taken after the administration of blood products. |
| I – Intervention | Hypocalcaemia on admission (iCa <1.16 mmol/L) | N/A |
| C – Comparator | Normocalcaemia on admission (iCa ≥1.16 mmol/L) | N/A |
| O – Outcome | Primary outcome, the incidence of admission ionised hypocalcaemia.<br><br>Secondary outcomes include the association with physiological abnormalities:<br>▪ Haemodynamic instability<br>▪ Hyperkalaemia<br>▪ Hyperlactataemia<br><br>and adverse outcomes:<br>▪ Vasopressor requirement within 24 hours<br>▪ Transfusion requirement within 24 hours<br>▪ Activation of the major haemorrhage protocol within 24 hours<br>▪ Requiring invasive (operative or interventional radiology) intervention within 24 hours<br>▪ Hospital length of stay<br>▪ PICU length of stay<br>▪ Early mortality within 24 hours and medium mortality during episode of hospital admission (>24 hours) or within 30 days | N/A |
| S – Study design | Clinical trials (randomised and non-randomised), observational studies (cohort and case-controlled) case | Systematic reviews.<br><br>Opinion articles. |

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| | reports, case series and literature reviews. | |

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**Online Supplementary Tables**

**Table 2. CINAHL search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma**

| Search ID# | Search Terms | Last Run Via | Results from 3rd July 2023 |
|---|---|---|---|
| **S29** | S25 AND S28 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 2 |
| **S28** | S26 OR S27 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 95,090 |
| **S27** | AB trauma | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 77,482 |
| **S26** | TI trauma | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 39,417 |
| **S25** | S23 OR S24 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 11 |
| **S24** | AB paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 2 |
| **S23** | TI paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 9 |
| **S22** | S3 AND S17 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 351 |
| **S21** | S3 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 0 |

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|---|---|---|---|
| **S20** | S18 OR S19 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 19 |
| **S19** | AB admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 18 |
| **S18** | TI admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1 |
| **S17** | S15 OR S16 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 835,597 |
| **S16** | AB outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 732,991 |
| **S15** | TI outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 213,098 |
| **S14** | S3 AND S9 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 0 |
| **S13** | S3 AND S6 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 2 |
| **S12** | S10 OR S11 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 83 |
| **S11** | AB normocalcaemia or normocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 78 |
| **S10** | TI normocalcaemia or normocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced | 8 |

| | | | |
|---|---|---|---|
| | | Search<br>Database - CINAHL | |
| **S9** | S7 OR S8 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,406 |
| **S8** | AB hospital arrival | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,349 |
| **S7** | TI hospital arrival | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 107 |
| **S6** | S4 OR S5 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,745 |
| **S5** | AB hypocalcaemia or hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,451 |
| **S4** | TI hypocalcaemia or hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 584 |
| **S3** | S1 OR S2 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,003 |
| **S2** | AB paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 805 |
| **S1** | TI paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 364 |

**Table 3. MEDLINE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma**

| Search ID# | Search Terms | Last Run Via | Results from 3rd July 2023 |
|---|---|---|---|

| | | | |
|---|---|---|---|
| S30 | S26 AND S29 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 5 |
| S29 | S27 OR S28 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 276,599 |
| S28 | AB trauma | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 245,191 |
| S27 | TI trauma | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 87,100 |
| S26 | S24 OR S25 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 38 |
| S25 | AB paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 22 |
| S24 | TI paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 18 |
| S23 | S6 AND S22 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 4 |
| S22 | S3 AND S17 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 746 |
| S21 | S3 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 0 |
| S20 | S18 OR S19 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 72 |
| S19 | AB admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 71 |
| S18 | TI admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 4 |
| S17 | S15 OR S16 | Interface - EBSCOhost Research Databases | 2,179,197 |

| | | | |
|---|---|---|---|
| | | Search Screen - Advanced Search<br>Database - MEDLINE | |
| S16 | AB outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 2,053,450 |
| S15 | TI outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 450,999 |
| S14 | S3 AND S9 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 0 |
| S13 | S3 AND S6 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 5 |
| S12 | S10 OR S11 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 870 |
| S11 | AB normocalcaemia or normocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 837 |
| S10 | TI normocalcaemia or normocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 52 |
| S9 | S7 OR S8 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 80,231 |
| S8 | AB hospital arrival or hospital admission | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 76,431 |
| S7 | TI hospital arrival or hospital admission | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 8,797 |
| S6 | S4 OR S5 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 11,987 |
| S5 | AB hypocalcaemia or hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 10,707 |
| S4 | TI hypocalcaemia or hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 3,153 |

| | | | |
|---|---|---|---|
| S3 | S1 OR S2 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 2,051 |
| S2 | AB paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 1,764 |
| S1 | TI paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 649 |

**Table 4. EMBASE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma**

| # | Query | Results from 3rd July 2023 |
|---|---|---|
| 1 | (paediatric trauma patients or pediatric trauma patients).m_titl. | 384 |
| 2 | (paediatric trauma patients or pediatric trauma patients).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 1,172 |
| 3 | limit 2 to abstracts | 1,155 |
| 4 | 1 or 3 | 1,172 |
| 5 | (hypocalcaemia or hypocalcemia).m_titl. | 3,811 |
| 6 | (hypocalcaemia or hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 31,406 |
| 7 | limit 6 to abstracts | 26,928 |
| 8 | 5 or 7 | 27,890 |
| 9 | (hospital arrival or hospital admission).m_titl. | 4,381 |
| 10 | (hospital arrival or hospital admission).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 292,976 |
| 11 | limit 10 to abstracts | 245,800 |
| 12 | 9 or 11 | 246,388 |
| 13 | (normocalcaemia or normocalcemia).m_titl. | 63 |
| 14 | (normocalcaemia or normocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 1,223 |
| 15 | limit 14 to abstracts | 1,213 |

| | | |
|---|---|---|
| 16 | 13 or 15 | 1,223 |
| 17 | 4 and 8 and 12 | 1 |
| 18 | 4 and 8 | 6 |
| 19 | (paediatric hypocalcaemia or pediatric hypocalcemia).m_titl. | 2 |
| 20 | (paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 4 |
| 21 | limit 20 to abstracts | 2 |
| 22 | 19 or 21 | 4 |
| 23 | (admission hypocalcaemia or admission hypocalcemia).m_titl. | 2 |
| 24 | (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 11 |
| 25 | limit 24 to abstracts | 11 |
| 26 | 23 or 25 | 11 |
| 27 | 4 and 16 | 0 |

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | Page 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | Page 1 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | Page 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | N/A |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | Page 1 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | Page 2 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | Page 3 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | Page 3 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | Page 3 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | Page 3 |
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | Page 3 |

| | | | |
|---|---|---|---|
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | Page 3 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | Page 3 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | Page 3 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | Page 4 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | Page 4 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | Page 4 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

BMJ Open

# The Incidence of Admission Ionised Hypocalcaemia in Paediatric Major Trauma: Protocol for a Systematic Review and Meta-Analysis



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2023-077429.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 13-Oct-2023 |
| Complete List of Authors: | Hibberd, Owen; Cambridge University, Emergency and Urgent Care Research in Cambridge (EUReCa), PACE Section, Department of Medicine, Cambridge University, UK<br>Price, James ; Cambridge University, Emergency and Urgent Care Research in Cambridge (EUReCa), PACE Section, Department of Medicine, Cambridge University, UK; East Anglian Air Ambulance, Department of Research, Audit, Innovation, & Development (RAID)<br>Harris, T; Queen Mary University of London Blizard Institute<br>Barnard, Ed; Cambridge University, Emergency and Urgent Care Research in Cambridge (EUReCa), PACE Section, Department of Medicine, Cambridge University, UK; Royal Centre for Defence Medicine, Academic Department of Military Emergency Medicine |
| Primary Subject Heading: | Paediatrics |
| Secondary Subject Heading: | Emergency medicine, Intensive care, Surgery |
| Keywords: | ACCIDENT & EMERGENCY MEDICINE, Paediatric intensive & critical care < INTENSIVE & CRITICAL CARE, Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric orthopaedic & trauma surgery < PAEDIATRIC SURGERY, Calcium & bone < DIABETES & ENDOCRINOLOGY |
| | |

## Abstract

Introduction

Hypocalcaemia forms part of the 'diamond of death' in major trauma, alongside hypothermia, acidosis, and coagulopathy. In adults, admission hypocalcaemia prior to transfusion is associated with increased mortality, increased blood transfusion requirements, and coagulopathy. Data in paediatric major trauma patients are limited. This systematic review and meta-analysis aims to describe and synthesise the available evidence relevant to paediatric trauma, admission hypocalcaemia, and outcome.

Methods and analysis

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline will be used to construct this review. A planned literature search for articles in the English language will be conducted from inception to the date of searches using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The grey literature will also be searched. Both title and abstract screening, and full-text screening will be done by two reviewers, with an adjudicating third reviewer. Heterogeneity will be assessed using $I^2$ test, and risk of bias will be assessed using the ROBINS-I tool. A meta-analysis will be undertaken using ratio measures (odds ratio) and mean differences for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a *p*-value.

Ethical review and dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

Prospero registration number

CRD42023425172


**Strengths and limitations of this study**

- ⇒ The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.
- ⇒ This is a novel review that addresses an area of uncertainity in the current evidence base surrounding paediatric major trauma through systematic review and meta-analysis of published data and the grey-literature.
- ⇒ The review methodology is at risk of limitation by publication bias. Where appropriate this will be assessed using funnel plots.

## Background

Major trauma is one of the leading causes of death in children in the United Kingdom (UK).[1][2] A key cause of potentially-survivable death from trauma is haemorrhage.[3] Uncontrollable haemorrhage may be related to the injury mechanism itself, or as a result of Trauma Induced Coagulopathy (TIC).[4] TIC is common, occurring in at least a quarter of haemorrhagic deaths, and has a number of proposed pathophysiological mechanisms, which generally involve injury and shock provoking a immunological, endothelial, and platelet response.[4] All forms of haemorrhage are further exacerbated by the 'lethal triad' of coagulopathy, hypothermia and acidosis.[5][6][7] More recently biochemical abnormalities such as hyperkalaemia and hypocalcaemia have been recognised

to contribute to deaths from haemorrhage.[6][8] In particular, calcium's role is important for clot formation, vascular tone, and cardiac contractility, with hypocalcaemia contributing to coagulopathy and cardiovascular decompensation.[5][6]] As such the 'lethal triad' is now considered a 'diamond of death' with hypocalcaemia forming a key component of this deleterious combination.[5][6]] The early recognition and treatment of these components in the 'diamond of death' are essential for trauma resuscitation.[5][7][9]

**Rationale**

The free form of calcium (ionised calcium (iCa)) is the physiologically relevant component of calcium in the blood.[10] iCa is measured on blood gases, which are often taken on arrival for major trauma patients, and there is good agreement between arterial and venous measurements.[11] Blood gas measurement will also record the pH and lactate, and can affect the availability of iCa.[12][13] Ionised hypocalcaemia (iHypoCa) in major trauma patients is multifactorial.[5][6][7][14] The infusion of citrated blood products is a recognised cause of hypocalcaemia in trauma due to calcium chelation with citrate.[6][15] There is also emerging evidence in adults that early hypocalcaemia may occur in trauma patients prior to the receipt of blood products containing citrate.[16][17][18][19] Potential pathophysiological mechanisms underpinning this include calcium binding by lactate, intracellular influx of calcium due to ischaemia and reperfusion, impaired calcium homeostasis secondary to trauma, and secondary to dilution by crystalloid fluid resuscitation.[5][6][7] A systematic review and meta-analysis, which included a total of 1213 major trauma patients, 18 years or older, with a document iCa level on admission explored the incidence and outcomes associated with admission iHypoCa.[20] Studies that involved patients in whom calcium concentration may have been confounded by prior blood transfusion were excluded.[20] Overall, the incidence of admission ionised hypocalcaemia (iHypoCa) was 56.2%, and iHypoCa was associated with: increased mortality, increased blood transfusion requirements, and coagulopathy.[16][17][18][19][20] Evidence of admission iHypoCa and the association with adverse outcomes in adult trauma patients has led to the early measurement and replacement of calcium being recommended in adult trauma guidelines.[21][22] In paediatric major trauma data are limited. Given the different physiology of children compared to adults, children may be more vulnerable to the effects of iHypoCa and the results of studies involving adult major trauma patients may not be able to be extrapolated to a paediatric cohort.[23] A search of PROSPERO did not find any similar planned systematic reviews or meta-analyses. Moreover, a preliminary search of the literature has found a few heterogenous studies, which indicate that admission iHypoCa may be less prevalent in children compared to adults.[24][25][26][27]

**Aims**

The primary aim of this systematic review and meta-analysis is to explore the limited evidence related to the incidence of admission iHypoCa in paediatric major trauma patients. The review also aims to explore whether admission iHypoCa, compared to normocalcaemia, is associated with adverse clinical outcomes.

**Methods**

Eligibility criteria

This proposed systematic review and meta-analysis will explore the incidence of iHypoCa in paediatric (<18 years old) major trauma patients (Injury Severity Score (ISS) >15) and explore whether admission iHypoCa (iCa <1.16 mmol/L), compared to normocalcaemia (iCa ≥ 1.16 mmol/L) is associated with a greater incidence of adverse outcomes.[12] An iCa of <1.16 mmol/L was chosen to reflect different levels of hypocalcaemia thresholds across the literature and facilitate inclusion of all relevant studies.[24][25][26] The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) eligibility criteria are detailed in Table 1.

Information sources

A planned literature search for articles in the English language will be conducted from inception to the search date using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The reference lists of all included studies, and the grey literature will also be searched.

Search strategy

The search strategy can be found in online supplementary tables 1,2 and 3.

The search will also involve checking reference lists of retrieved articles, conference abstracts, and online study results. If data is incomplete, then corresponding authors will be contacted for additional information.

Study records

The search strategy will be undertaken by a trained librarian and information specialist. The combined abstracts from the search strategy will be independently screened by two reviewers to identify studies meeting inclusion criteria, any duplications will be removed manually. For abstracts meeting inclusion criteria, full texts will be retrieved and again be independently reviewed against the inclusion and exclusion criteria by two reviewers and an adjudicating third reviewer.

A standardised data sheet (Microsoft ® Excel for Mac, Version 16.72, 2023) will be used to extract data from included studies to facilitate data synthesis and assessment of quality and risk of bias. Extracted data will be independently verified by the second reviewer, and any discrepancies again adjudicated by the third reviewer.

The following data items will be extracted:

1. Hospital setting
2. Study type
3. Country of treatment
4. Cohort size
5. Injury severity score (ISS)
6. Abbreviated Injury Scale (AIS) score for injury regions
7. Ionised hypocalcaemia definitions
8. Incidence of admission iHypoCa (iCa <1.16 mmol/L)[12]
9. Definitions, and presence of, coagulopathy
10. The presence of hyperkalaemia (>5.5 mmol/L)[28]
11. The presence of hyperlactataemia (>2.0mmol/L)[29]
12. Haemodynamic instability (hypotension (based upon age specific Advanced Paediatric Life Support (APLS) values) or elevated Shock Index Paediatric Age-Adjusted (SIPA))[30][31][32]
13. Administration of exogenous calcium
14. Vasoactive medication requirements within the first 24 hours
15. Total blood product transfusion requirement during the first 24 hours
16. Activation of the major haemorrhage protocol within the first 24 hours
17. Requirement for invasive (operative or interventional radiology) intervention within 24 hours
18. Hospital length of stay (LOS) (days)
19. Paediatric Intensive Care Unit (PICU) LOS (days)
20. Early mortality within 24 hours and medium mortality during episode of hospital admission (>24 hours) or within 30 days

Outcomes and prioritisation

The primary outcome of this systematic review and meta-analysis is the overall incidence of admission iHypoCa. Secondary outcomes are the associations with physiological abnormalities, and adverse outcomes. Physiological abnormalities are classified dichotomously as the presence of hypotension (based upon age specific APLS values)[30] or elevated SIPA(0-6yrs >1.22, 7-12yrs > 1.00, 13-16yrs > 0.90),[31][32] hyperkalaemia (>5.5 mmol/L),[28] and hyperlactataemia (>2.0mmol/L).[29] Adverse outcomes are classified dichotomously as the requirement for vasopressors, transfusion, activation of the major haemorrhage protocol, or invasive (operative or interventional radiology) intervention in the first 24 hours and mortality within 30 days. Hospital LOS, and PICU LOS in days are classified continuously.

Ratio measures (odds ratio) and mean differences will be used for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a *p*-value.

Risk of bias

Risk of bias will be assessed for all included studies. For any randomised controlled trials GRADE methodology will be used, and for observational studies, the ROBINS-I tool will be used.[33][34]

The risk of publication bias will be assessed with funnel plots as appropriate.[35]

Data synthesis

Data will be synthesised following PRISMA guidelines. Studies will be assessed clinically (PICO) and methodologically (study design, comparability, outcome ascertainment, and risk of bias). Given that current evidence is likely to be limited, the minimum number of studies is two. A preliminary search has identified four studies.[24][25][26][27] The I2 test will be conducted to determine if data are suitable for quantitative synthesis.[36]

Meta-analysis of effect estimates is intended and will be displayed using a forest plot. If there is limited evidence for pre-specified comparison, then the haemodynamic instability and vasopressor PICO groups may be combined. Definitions of hypocalcaemia will also be combined if required, providing values are iCa <1.16 mmol/L. Other elements are unlikely to be suitable as contingencies for combination. If different effect measures are used attempts will be made to transform the effect measures for meta-analysis.

A narrative synthesis and summary of effect measures (with the use of box-and-whisker plots) will be conducted if heterogeneity is deemed too substantial across studies to allow for meaningful meta-analysis or if there are major concerns about bias from the three reviewers.

Meta-analysis or narrative synthesis of elements will focus on the incidence of hypocalcaemia in paediatric trauma patients and trend towards adverse outcomes. Subgroup analysis may be undertaken for severe iHypoCa (iCa <1.0 mmol/L).

Patient and public involvement

None

**Ethics and Dissemination**

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

**Contributorship statement**

OH conceptualised the protocol. OH, JP, TH, and EB all contributed to the design, data interpretation, critical revision and final approval of the protocol.

**Competing interests**

None

**Funding**

None

**Acknowledgements**

The authors would like to acknowledge and thank Catherine Hancox and the Defence Medical Academic Library Team for their assistance with the search strategy.

**Tables**

**Table 1. Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) Strategy for Inclusion and Exclusion**

| PICOS Strategy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| P – Population | Paediatric (<18yrs) major trauma patients (Injury Severity Score> 15) with a documented ionised calcium (iCa) level on admission. | iCa level taken after the administration of blood products in the Emergency Department. |
| I – Intervention | Hypocalcaemia on admission (iCa <1.16 mmol/L) | N/A |
| C – Comparator | Normocalcaemia on admission (iCa ≥1.16 mmol/L) | N/A |
| O – Outcome | Primary outcome, the incidence of admission ionised hypocalcaemia.<br><br>Secondary outcomes include the association with physiological abnormalities:<br>▪ Haemodynamic instability<br>▪ Hyperkalaemia<br>▪ Hyperlactataemia<br>▪ pH abnormalities<br>▪ Coagulopathy<br><br>and adverse outcomes:<br>▪ Vasopressor requirement within 24 hours | N/A |

| | | |
|---|---|---|
| | ▪ Transfusion requirement within 24 hours<br>▪ Activation of the major haemorrhage protocol within 24 hours<br>▪ Requiring invasive (operative or interventional radiology) intervention within 24 hours<br>▪ Hospital length of stay<br>▪ PICU length of stay<br>▪ Early mortality within 24 hours and medium mortality during episode of hospital admission (>24 hours) or within 30 days | |
| S – Study design | Clinical trials (randomised and non-randomised), observational studies (cohort and case-controlled) case reports, case series and literature reviews. | Systematic reviews.<br><br>Opinion articles. |

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**Online Supplementary Tables**

**Supplementary Table 1. CINAHL search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma**

| Search ID# | Search Terms | Last Run Via | Results from 3rd July 2023 |
|---|---|---|---|
| **S29** | S25 AND S28 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 2 |
| **S28** | S26 OR S27 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 95,090 |
| **S27** | AB trauma | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 77,482 |
| **S26** | TI trauma | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 39,417 |
| **S25** | S23 OR S24 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 11 |
| **S24** | AB paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 2 |
| **S23** | TI paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 9 |
| **S22** | S3 AND S17 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 351 |
| **S21** | S3 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 0 |
| **S20** | S18 OR S19 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 19 |
| **S19** | AB admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 18 |

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|---|---|---|---|
| **S18** | TI admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1 |
| **S17** | S15 OR S16 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 835,597 |
| **S16** | AB outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 732,991 |
| **S15** | TI outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 213,098 |
| **S14** | S3 AND S9 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 0 |
| **S13** | S3 AND S6 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 2 |
| **S12** | S10 OR S11 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 83 |
| **S11** | AB normocalcaemia or normocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 78 |
| **S10** | TI normocalcaemia or normocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 8 |
| **S9** | S7 OR S8 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,406 |
| **S8** | AB hospital arrival | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,349 |
| **S7** | TI hospital arrival | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 107 |
| **S6** | S4 OR S5 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL | 1,745 |
| **S5** | AB hypocalcaemia | Interface - EBSCOhost Research Databases | 1,451 |

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|---|---|---|---|
| | or hypocalcemia | Search Screen - Advanced Search Database - CINAHL | |
| **S4** | TI hypocalcaemia or hypocalcemia | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 584 |
| **S3** | S1 OR S2 | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 1,003 |
| **S2** | AB paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 805 |
| **S1** | TI paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL | 364 |

**Supplementary Table 2. MEDLINE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma**

| Search ID# | Search Terms | Last Run Via | Results from 3rd July 2023 |
|---|---|---|---|
| S30 | S26 AND S29 | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 5 |
| S29 | S27 OR S28 | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 276,599 |
| S28 | AB trauma | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 245,191 |
| S27 | TI trauma | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 87,100 |
| S26 | S24 OR S25 | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 38 |
| S25 | AB paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 22 |
| S24 | TI paediatric hypocalcaemia or pediatric hypocalcemia | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 18 |

| | | | |
|---|---|---|---|
| S23 | S6 AND S22 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 4 |
| S22 | S3 AND S17 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 746 |
| S21 | S3 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 0 |
| S20 | S18 OR S19 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 72 |
| S19 | AB admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 71 |
| S18 | TI admission hypocalcaemia or admission hypocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 4 |
| S17 | S15 OR S16 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 2,179,197 |
| S16 | AB outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 2,053,450 |
| S15 | TI outcomes | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 450,999 |
| S14 | S3 AND S9 AND S12 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 0 |
| S13 | S3 AND S6 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 5 |
| S12 | S10 OR S11 | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 870 |
| S11 | AB normocalcaemia or normocalcemia | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 837 |
| S10 | TI normocalcaemi | Interface - EBSCOhost Research Databases | 52 |

| | | | |
|---|---|---|---|
| | a or normocalcemia | Search Screen - Advanced Search Database - MEDLINE | |
| S9 | S7 OR S8 | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 80,231 |
| S8 | AB hospital arrival or hospital admission | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 76,431 |
| S7 | TI hospital arrival or hospital admission | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 8,797 |
| S6 | S4 OR S5 | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 11,987 |
| S5 | AB hypocalcaemia or hypocalcemia | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 10,707 |
| S4 | TI hypocalcaemia or hypocalcemia | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 3,153 |
| S3 | S1 OR S2 | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 2,051 |
| S2 | AB paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 1,764 |
| S1 | TI paediatric trauma patients or pediatric trauma patients | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 649 |

**Supplementary Table 3. EMBASE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma**

| # | Query | Results from 3rd July 2023 |
|---|---|---|
| 1 | (paediatric trauma patients or pediatric trauma patients).m_titl. | 384 |
| 2 | (paediatric trauma patients or pediatric trauma patients).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 1,172 |

| | | |
|---|---|---|
| 3 | limit 2 to abstracts | 1,155 |
| 4 | 1 or 3 | 1,172 |
| 5 | (hypocalcaemia or hypocalcemia).m_titl. | 3,811 |
| 6 | (hypocalcaemia or hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 31,406 |
| 7 | limit 6 to abstracts | 26,928 |
| 8 | 5 or 7 | 27,890 |
| 9 | (hospital arrival or hospital admission).m_titl. | 4,381 |
| 10 | (hospital arrival or hospital admission).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 292,976 |
| 11 | limit 10 to abstracts | 245,800 |
| 12 | 9 or 11 | 246,388 |
| 13 | (normocalcaemia or normocalcemia).m_titl. | 63 |
| 14 | (normocalcaemia or normocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 1,223 |
| 15 | limit 14 to abstracts | 1,213 |
| 16 | 13 or 15 | 1,223 |
| 17 | 4 and 8 and 12 | 1 |
| 18 | 4 and 8 | 6 |
| 19 | (paediatric hypocalcaemia or pediatric hypocalcemia).m_titl. | 2 |
| 20 | (paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 4 |
| 21 | limit 20 to abstracts | 2 |
| 22 | 19 or 21 | 4 |
| 23 | (admission hypocalcaemia or admission hypocalcemia).m_titl. | 2 |
| 24 | (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 11 |
| 25 | limit 24 to abstracts | 11 |
| 26 | 23 or 25 | 11 |
| 27 | 4 and 16 | 0 |

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | Page 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | Page 1 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | Page 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | N/A |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | Page 1 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | Page 2 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | Page 3 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | Page 3 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | Page 3 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | Page 3 |
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | Page 3 |

| | | | |
|---|---|---|---|
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | Page 3 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | Page 3 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | Page 3 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | Page 4 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | Page 4 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | Page 4 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*