INPLASY PROTOCOL

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Conflicts of interest:
There is no conflict of interest.

Long-term neurodevelopment outcomes of regional versus general anesthesia for infants undergoing inguinal herniorrhaphy. A protocol for systematic review and meta-analysis

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Review question / Objective: **P: infants undergoing inguinal herniorrhaphy; I: regional anesthesia; C: general anesthesia; O: long-term neurodevelopment outcomes; S: randomised controlled trials.**
Condition being studied: **Inguinal hernia (IH) is a common developmental defect in infants and children. IH requires early surgical repair to reduce the risk of incarceration, intestinal obstruction, and gonadal infarction. With improved anesthetic techniques and pediatric care management protocols, more infants with IH are presenting for surgery in early infancy. However, in addition to surgical complications, there is a concern that anesthetic agents may produce direct toxic effect on brain development of infants even after growing up. Whether regional anesthesia (RA) offers better long-term neurodevelopment outcomes compared to general anesthesia (GA) to infants undergoing inguinal herniorrhaphy is still under heated debate.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 June 2020 and was last updated on 17 June 2020 (registration number INPLASY202060064).

INTRODUCTION

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METHODS

Search strategy: The Medical Subject Headings (MeSH), text words, and word variants for "infants" ,"inguinal herniorrhaphy", "inguinal hernioplasty", "repair of inguinal hernia", "inguinal hernia repair", "regional anesthesia", "regional nerve block", "general anesthesia", "anaesthesia", "neurodevelopment" ,"neurological development" and various combinations will be used in the searches. This search strategy will be modified to be suitable for other certain electronic databases.

Participant or population: Infants who underwent inguinal herniorrhaphy with regional or general anesthesia within 60 weeks postpartum will be included.

Intervention: Regional anesthesia, including spinal, epidural, caudal, and local infiltration anesthesia

Comparator: General anesthesia, including various combinations of techniques of airway management and anesthetic agents (for analgesia, sedation, and nerve muscle block) with or without regional analgesia which are left to the discretion of anesthesiologists.

Study designs to be included: RCTs.

Eligibility criteria: (1) Infants who underwent inguinal herniorrhaphy with regional or general anesthesia within 60 weeks postpartum in the eligible studies; (2)Infants were randomly assigned into RA or GA group in the eligible studies; (3) Long-term neurodevelopment outcomes were assessed in the eligible studies; (4) Available full text or abstract with complete data in English; and (4) Sufficient data to extract weighted mean differences (WMDs), odds ratios (ORs) and respective 95% confidence intervals (CIs).

Information sources: A systematic search of MEDLINE, EMBASE, PubMed, the Cochrane Central Register of Controlled Trials, clinicaltrials.gov and controlledtrials.com will be performed. The US 'Society for Pediatric Research' and the European Society for Pediatric Research and Pediatric Anesthesia databases will be also searched. The relative references, academic conferences and network resources in the included literature will be further screened to find out the potential eligible ones. When multiple reports describing the same sample were published, the most recent or complete report will be included. All RCTs published in electronic databases before May 20, 2020 with language restricted in English will be included in this review study.

Main outcome(s): Long-term neurodevelopmental state at two- and five-year follow-up as reflected in the Bayley and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) scales of infants development (mental developmental index/psycho-motor developmental index, MDI/PDI) following surgeries. (1) The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) has cognitive, language, and motor scales assessments. The main outcome for the analysis at 2-year follow-up will be prespecified to be the composite cognitive score of the Bayley-III. (2) The main outcome at 5-year follow-up will be measured by full-scale intelligence quotient (FSIQ) on the WPPSI, Third Edition (WPPSI-III).

Additional outcome(s): (1) satisfactory intraoperative infants immobility which allows satisfactory completion of the operation; (2) duration of surgery; (3) any anesthetic failure (including anesthetic agent failure and anesthetic placement failure); (4) the supplement of postoperative

analgesia; (5) postoperative apnoea; (6) postoperative bradycardia.

Data management: EndNote X8 (Clarivate Analytics) software will be applied to manage all citations, as well as for duplicates screening.

Quality assessment / Risk of bias analysis: The methodological quality will be evaluated by two reviewers according to the Review Manager software version 5.3 (RevMan 5.3) 'Risk of Bias' assessment tool in terms of selection bias (method of randomization and allocation concealment), information bias (masking of outcome adjudicators), and bias in the analysis (intention to treat analysis and completeness of follow-up). Risk of bias for each study will be calculated using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and be graded into 3 levels, including 'High Risk', 'Low Risk', and 'Unclear'. Disagreement between two independent reviewers will be solved by discussion and consulting the expert in Evidence-Based Medicine (EBM). The 'Risk of Bias' table and graph will be drawn by RevMan 5.3.

Strategy of data synthesis: The RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) will be employed for statistical analysis. Continuous outcomes (sores of Bayley-III and WPPSI-III scale, duration of surgery) will be expressed as the weighted mean differences (WMDs) and relative 95% confidence intervals (CIs). Dichotomous outcomes (satisfactory intraoperative infants immobility, any anesthetic failure, the supplement of postoperative analgesia, postoperative apnoea, postoperative bradycardia) will be expressed as the odds ratios (ORs) with 95% CIs. Statistical significance will be set at P.

Subgroup analysis: Subgroup analyses will be performed to explore possible sources of heterogeneity. Subgroup analyses will be conducted based on sex, age, region, race, the use of preoperative sedatives, full-term pregnancy or premature and history of apnoea in the preoperative period.

Sensibility analysis: The sensitivity analysis will be performed to ensure the stability of measure effects of primary outcomes by removing one by one those studies with high risk of bias in terms of sample size, study design, heterogeneity qualities, and with non-informative prior distributions for the heterogeneity parameters. Non-robust results of primary outcomes identified by sensitivity analysis will be added to a descriptive analysis.

Language: Only articles originally written in English or translated into English will be considered.

Country(ies) involved: China.

Keywords: regional anesthesia; general anesthesia; neurodevelopment outcomes; inguinal herniorrhaphy; meta-analysis; protocol.

Contributions of each author:

Author 1 - Tao Yuan - Author 1 designed the research, identified the feasibility of the study, and drafted the manuscript.

Author 2 - Wenming Yang - The author designed the research, identified the feasibility of the study, and contributed equally to draft the manuscript with author 1.

Author 3 - Lei Yang - The author contributed to the study design, the development of the selection criteria, and the risk of bias assessment strategy and approved the final version of the manuscript.

Author 4 - Xueting Liu - The author provided methodological advice and statistical expertise, and approved the final version of the manuscript.

Author 5 - Lie Yang - The author contributed to study design and read, provided feedback and approved the final version of the manuscript.

Author 6 - Yu Li - The author planned and designed the research, identified the feasibility of the study, provided methodological advice, polished and revised the manuscript, and approved the final version of the manuscript.