Detection of Raised Intracranial Pressure in Craniosynostosis using Optical Coherence Tomography: A Systematic Review Protocol

Sohaib R Rufai
University of Leicester
Noor ul Owase Jeelani
Great Ormond Street Hospital For Children NHS Foundation Trust
Rebecca J McLean (rjm19@le.ac.uk)
University of Leicester

Protocol

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Abstract

Introduction

Craniosynostosis is characterised by the premature fusion of cranial sutures. This can be associated with raised intracranial pressure (ICP), which can lead to developmental delay, visual impairment and death. Treatment involves surgical expansion of the skull vault. There is no consensus over who to treat and when. Intracranial pressure is difficult to estimate in a child and existing methods possess sub-optimal diagnostic accuracy to be employed as screening tools. Here, we propose a systematic review protocol to examine the role of optical coherence tomography (OCT) in early detection of raised ICP in craniosynostosis.

Methods

Electronic searches in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase will identify studies featuring OCT in detecting raised ICP in children with craniosynostosis. Two independent researchers will identify studies for inclusion using a screening questionnaire. Quality will be assessed using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. The primary outcome measure is the sensitivity and specificity of OCT in detecting raised ICP in children with craniosynostosis. Secondary outcomes measures include the sensitivity and specificity of other surrogate measures for raised ICP, OCT parameters used and normal ranges for ICP reported. A formal narrative synthesis with descriptive statistics will be presented.

Discussion

The proposed study will be the first to examine the role of optical coherence tomography in the early recognition of raised intracranial pressure in craniosynostosis, thereby addressing an important clinical problem in paediatric ophthalmology and craniofacial surgery. This systematic review protocol provides transparency to the proposed methods and reduces the possibility of duplication. The proposed methods reflect those prescribed by the Cochrane Collaboration. Systematic review registration International Prospective Register for Systematic Reviews (PROSPERO) number CRD42019147693

Background

Craniosynostosis

“Craniosynostosis” is derived from Greek and translates to “fused skull”. It is characterised by the premature, pathological fusion of one or more cranial sutures.[1] Normally, during infancy, the skull vault expands to create adequate space for the growing brain. However, in craniosynostosis there is premature ossification of affected cranial sutures, causing distortion of skull shape and compensatory overgrowth at non-fused sutures.[1] This can cause raised intracranial pressure (ICP), which can lead to developmental

delay, blindness and death if untreated.[2] Craniosynostosis affects 3.1–6.4 in 10,000 live births and prevalence is rising.[3]

Craniosynostosis can be categorised as syndromic or non-syndromic. Non-syndromic craniosynostosis accounts for 65% of cases.[4] It can be uni- or multi-sutural, with raised ICP resulting in 13 and 50–75% of such cases, respectively.[5] Amongst syndromic cases, 21% fall within clinically recognised syndromes, while a further 9% have syndromes of unknown aetiology.[4] Overall, raised ICP affects 30–40% of syndromic craniosynostosis, with more common association in Apert's[6] (71%), Crouzon's[7] (65%) and Pfeiffer's[7] (60%) syndromes. The remaining aetiologies include clinically non-syndromic with identified mutations (3%) and secondary causes (2%), such as extreme prematurity.[4]

Treatment

Treatment involves surgical expansion of the skull vault, which aims to expand skull volume and reduce ICP. There is no clinical consensus over who should receive surgery and when this should be performed. In their landmark paper, Renier *et al*[2] recommended prophylactic surgery for all patients with multi-suture or syndromic craniosynostosis within the first 12 months of life, to avoid or reduce complications of raised ICP. This policy is still adopted by many clinicians worldwide.[8]

When surgical treatment is delayed, the sequelae of raised ICP increase in severity. However, many children may not be at risk of raised ICP and hence undergo unnecessary surgery carrying significant complication rates. A recent review of the literature for posterior cranial vault distraction surgery reported mean complication rate of 35.5% (range: 12.5% to 100%; S. D. 41%; n = 86 patients). The most common complications were cerebrospinal fluid (CSF) leak or dural injury, followed by wound infections, device exposures and device failure. Avoiding unnecessary surgery would help to minimise treatment burden for patients, families and healthcare providers. Moreover, where surgery is performed purely for cosmetic reasons in children with significant disfigurement but no risk of raised ICP, deferring the operation beyond the infancy period is safer and tends to deliver better outcomes.[9]

Intracranial pressure

Measuring or estimating ICP in children is very difficult. The gold standard method is direct intracranial ICP measurement, which involves hospital admission and general anaesthesia. This carries significant risks, including infection, bleeding, CSF leak and mechanical failure.[10] There is no universally agreed clinical consensus on timing, frequency and duration for accurate ICP measurement, or indeed what figure constitutes raised ICP. However, 11–15mmHg is generally considered normal.[2, 11]

Currently, there are various non-invasive methods to estimate ICP, including ophthalmoscopy[12], transorbital ultrasound[13] and radiography[14]. However, these methods display inadequate diagnostic

accuracy to be used as screening tools. Visual evoked potentials (VEP) measure the amplitude and latency time of the averaged encephalographic response to visual stimuli. Axonal injury, associated with raised ICP, is associated with reduction of amplitude or prolongation of the latency period.[5, 9] Limitations of VEP include the requirement for good cooperation + general anaesthesia, plus high variability in normal subjects.[15]

Optical coherence tomography

Raised ICP can cause optic nerve swelling and retinal changes. Optical coherence tomography (OCT) is a non-invasive imaging modality that produces ultra-high resolution, three-dimensional, *in vivo* images of the optic nerve and retina within seconds.[16] Normal development of the optic nerve[17] and fovea[18] in children has been recently described using OCT. Paediatric ophthalmological conditions investigated with OCT include retinopathy of prematurity and other retinal disorders, nystagmus, central nervous diseases, intraocular tumours and trauma.[18]

OCT may play an important role in screening and management for craniosynostosis, but it has not yet been rigorously assessed by systematic review. The proposed systematic review protocol aims to address this.

Aims

The primary aim of the proposed systematic review is to assess the sensitivity and specificity of OCT in the detection of raised ICP in children with craniosynostosis causing raised ICP.

The secondary aims are as follows: i) to explore the sensitivity and specificity of surrogate measures for raised ICP employed by the included studies; ii) to identify the OCT parameters used per study; to identify the ICP ranges determined as normal and raised per study, where applicable.

Methods/design

The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P)[19] checklist has been adhered to in the production of this protocol.

Eligibility criteria

The Population, Intervention, Comparison, Outcome and Study design (PICOS) strategy[20] has been used to determine the eligibility criteria for this systematic review, summarised in Table 1.

Table 1: Eligibility criteria.

PICOS strategy[20]	Inclusion criteria	Exclusion criteria
P - Population	Studies of children, defined as being aged 0-16 years, diagnosed with forms of craniosynostosis and raised ICP.	i) Studies with participants over 16 years old; ii) Studies not pertaining to children with craniosynostosis; iii) Studies not pertaining to diagnosis of raised ICP.
I - Intervention	Studies using OCT to detect raised ICP in children with craniosynostosis.	Any studies that do not feature OCT.
C - Comparator	Studies which have used a control group, such as healthy age matched children, will be included. However, absence of a comparator will not lead to exclusion of studies, as it may be deemed unethical to deprive one arm of a comparative study of the intervention (OCT) when it may lead to a better clinical outcome in such a dangerous situation of raised ICP.	N/A
O - Outcome	Sensitivity and specificity of any OCT measure(s); ± Surrogate measure(s) for raised ICP.	Studies that do not report OCT measures.
S - Study design	All Level IV evidence and above, i.e. case series, case-control studies, randomised controlled trials (RCTs) and systematic reviews, as defined by the Oxford CEBM.[21]	Level 5 evidence, i.e. expert opinion without explicit critical appraisal.

***Legend**: PICOS = Population, Intervention, Comparison, Outcome and Study design; ICP = intracranial pressure; OCT = optical coherence tomography; CEBM: Centre for Evidence-based Medicine.*

Types of outcome measures

The primary outcome measure will be sensitivity and specificity for OCT parameters in the detection of raised ICP. The OCT parameters may include any combination of the following:

- Optic nerve parameters: cup depth, cup width, disc width and cup to disc ratio;
- Rim parameters: retinal nerve fibre layer (RNFL) thickness, rim volume, Bruch's membrane opening-minimum rim width (BMO-MRW), Bruch's membrane orientation, full peripapillary analysis;

- Retinal parameters: macular and perimacular retinal thickness, foveal pit width, depth and area, plus segmentation of all retinal layers.

The secondary outcome measures are as follows:

- Other surrogate estimates of ICP;
- Other OCT parameters not listed above;
- ICP range determined as normal;
- ICP range determined as raised.

Quality of life outcomes

Quality of life outcomes and patient satisfaction measure by patient surveys will be included, however such studies are unlikely in the paediatric population, especially in preverbal children.

Adverse events

OCT is a safe and non-invasive imaging technique that uses low-coherence light. The process of OCT imaging cannot directly produce adverse events.

Follow-up

There shall be no stipulation of a minimum follow-up period for inclusion of studies. This is because in many cases, the decision to perform radical treatment (i.e. surgery) may be made quickly on the basis of any indication that ICP is raised. Hence, stipulating a minimum follow-up period may risk excluding valuable data.

Information sources

Record characteristics

Records from all years will be considered for inclusion. Published and unpublished records will be considered. There will be no language restrictions stipulated. For any non-English records, language interpretation will be requested from the University of Leicester Centre for Translation and Interpreting Studies.

Electronic searches

The following electronic platforms will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL) (including the Cochrane Eyes and Vision Group (CEVG) Trials Register)
- Ovid MEDLINE(R) (1946 to present)
- Ovid MEDLINE In-Process and Other Non-Indexed Citations
- EMBASE Classic+Embase (1947 to present)

Searching other resources

The references of included papers will be searched and the investigators contacted to identify published and unpublished works. Unpublished works identified and recommended by experts will also be included.

Search strategy

Medical subject headings (MeSH) terms for ‘raised intracranial pressure’ and ‘optical coherence tomography’ were entered into the search platforms listed below. Appendix 1 includes full details of keywords and MeSH terms to be used.

Study records

Data management

Data will be uploaded and managed using EndNote X10 (Thomson Reuters, New York, NY) reference management software.

Selection of studies

A two-stage screening process will be employed by two independent screeners (SRR and RJM). First, titles and abstracts will be screened, followed by full papers. Screening questions are included in Appendix 2. If any discrepancy arises between the papers selected for inclusion, arbitration will be performed by the third arbitrator (NUOJ).

Data collection process

Data will be extracted using a data extraction tool included in Appendix 3, adapted from the Cochrane Collaboration.[22]

Data items, outcomes and prioritisation

The following data items will be sought from included papers:

- Study characteristics
    - Author(s)
    - Year
    - Study design
    - Study location
    - Number of patients
    - Mean age
    - Age range
- Primary outcome measures
    - OCT Parameter(s)
        - Sensitivity (%)
        - Specificity (%)
- Secondary outcome measures, where available:
    - Surrogate measure(s) of raised ICP
        - Sensitivity (%)
        - Specificity (%)
    - ICP range determined as normal (mmHg)
    - ICP range determined as raised (mmHg)
    - Quality of life outcomes
    - Adverse events

Extraction and reporting of primary outcome measures will be prioritised as they address the primary research question posed by this review.

Risk of bias in individual studies

Risk of bias assessment will be performed at the study level using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[23], included in Appendix 4.

Data analysis

Scoping searches suggest that no relevant RCTs have been conducted in this area. It is anticipated that only observational studies will be returned by this systematic review. Hence, the proposed analysis will represent a qualitative review aiming to summarise the available evidence and to inform future research

in this area. A narrative synthesis will be performed, whereby we will investigate similarities and differences between the identified studies and assess the strength of the evidence identified. Sensitivity and specificity analyses for OCT in detecting raised ICP, plus that of other surrogate measures will be extracted and reported descriptively. We will interpret the results based on the strength of the evidence. Meta-analysis will not be performed because, to our knowledge, no randomised controlled trials have been conducted on this subject.

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[24] will be used to assess the strength of the body of evidence returned by this systematic review, where applicable.

Discussion

This systematic review protocol represents the first to examine the role of OCT in the detection of raised ICP in children with craniosynostosis through rigorous systematic review. The PRISMA-P checklist[19] has been adhered to during the production of this protocol. Two independent screeners shall execute the search and select papers for inclusion, with third arbitration where required. The resulting systematic review should help to clarify the suitability of OCT as a non-invasive screening tool for raised ICP in craniosynostosis. The findings of this systematic review will be disseminated through presentation at relevant meetings and peer-reviewed publication.

Abbreviations

BMO-MRW = Bruch's membrane opening-minimum rim width

CEBM = Centre for Evidence-based Medicine

CENTRAL = Cochrane Central Register of Controlled Trials

CEVG = Cochrane Eyes and Vision Group

CSF = Cerebrospinal fluid

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation

ICP = Intracranial pressure

MeSH = Medical subject headings

NIH = National Institutes of Health

OCT = Optical coherence tomography

PICOS = Population, Intervention, Comparison, Outcome and Study

PRISMA-P = Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

PROSPERO = Prospective Register for Systematic Reviews

RCT = Randomised controlled trial

RNFL = Retinal nerve fibre layer

VEP = Visual evoked potentials

Declarations

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Authors' contributions:

SRR: Concept, methodology, manuscript writing, final approval.

NUOJ: Supervision, concept, critical revision, final approval.

RJM: Supervision, methodology, critical revision, final approval, guarantor of review.

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Ethics approval and consent to participate: Ethics approval and consent to participate are not required for the proposed systematic review as no primary data will be collected.

Availability of data and material: Available on reasonable request, following completion of this study

Consent to publish: Not applicable or required

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Supplementary Files

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