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Early Recognition of Raised Intracranial Pressure in Craniosynostosis Using Optical Coherence Tomography

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Objective: Craniosynostosis can be associated with raised intracranial pressure (ICP), which can pose deleterious effects on the brain and vision if untreated. Estimating ICP in children is challenging, whilst gold standard direct intracranial measurement of ICP is invasive and carries risk. This systematic review aims to evaluate the role of optical coherence tomography (OCT), a noninvasive imaging technique, for detecting raised ICP in children with craniosynostosis.

Methods: The authors conducted a systematic review of the literature published from inception until 19 August, 2019 in the Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, and EMBASE. Eligible studies evaluated the role of OCT in detecting raised ICP in children aged 0 to 16 years with craniosynostosis. Main outcome measures were sensitivity and specificity of OCT parameters for raised ICP. Quality assessment was performed using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-sectional Studies.

Results: Out of 318 records identified, data meeting the inclusion criteria were obtained from 3 studies. The quality of 2 studies was poor whilst 1 was fair. Optical coherence tomography demonstrated higher sensitivity and specificity for detecting raised ICP compared to fundus examination, clinical history, radiological testing, and visual field testing.

Conclusions: This systematic review demonstrated a lack of quality evidence for OCT as a screening tool for children with craniosynostosis. Further research is required to clarify the strength of OCT in this role and to determine which OCT parameters are most appropriate.

Key Words: Craniosynostosis, intracranial hypertension, intracranial pressure, OCT, optical coherence tomography, systematic review

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Recognition of raised intracranial pressure (ICP) is crucial in children with craniosynostosis to enable timely surgical intervention. Raised intracranial pressure can cause visual impairment and death if untreated.[1] Prevalence of craniosynostosis is 3.1 to 6.4 in 10,000 live births and rising.[2] Nonsyndromic cases account for 65% of craniosynostosis and can be uni or multisutural - raised ICP affects 13% and 50% to 75% of such cases, respectively.[3,4] Twenty-one percent of cases are syndromic, which are associated with raised ICP in 30% to 40%[5,6] of syndromic cases; Apert[7] (71%), Crouzon[8] (65%) and Pfeiffer[8] (60%) syndromes are more commonly associated.

Estimating ICP in children is difficult. Direct intraparenchymal measurement represents the gold standard, but involves hospital admission and carries risks of infection, bleeding, and device failure.[6] Noninvasive methods such as ophthalmoscopy,[9] transorbital ultrasound,[10] and radiography[11] deliver inadequate sensitivity to be used for screening. An ideal solution would be a safe, noninvasive, and quantitative measure of ICP that can be repeated over time with good sensitivity and specificity.

Raised ICP can cause optic nerve swelling and secondary retinal changes. Detecting these changes early could help prevent visual damage. Optical coherence tomography (OCT) is a noninvasive imaging method that objectively generates ultra-high resolution 3-dimensional scans of the optic nerve and retina, in vivo, within seconds and with excellent repeatability.[12] The University of Leicester Ulverscroft Eye Unit has extensive experience in using handheld OCT – an adapted device suitable for children. Our unit has described the normal development of the optic nerve[13] and retina[14] in children. Our unit has also investigated a wide range of conditions using handheld OCT including nystagmus,[15] foveal hypoplasia,[16] optic nerve hypoplasia,[17] glaucoma,[18] microcephaly,[19] retinopathy of prematurity,[20] retinoblastoma,[21] and others.

Like craniosynostosis, cerebral malaria can also cause raised ICP. Our unit recently conducted a study in Queen Elizabeth Central Hospital, Blantyre, Malawi, in children with cerebral

malaria (n = 35; age range: 7–131 months; mean age 56.1 months), demonstrating that handheld OCT can detect changes associated with raised ICP.[22] Cerebrospinal fluid opening pressure was positively correlated with optic nerve parameters, including optic nerve head rim volume ($r = 0.582$; $P = 0.0002$), rim area ($r = 0.504$; $P = 0.002$) and superior peripapillary retinal nerve fiber layer (RNFL) thickness ($r = 0.479$; $P = 0.004$). Cerebrospinal fluid opening pressure was negatively correlated with cup parameters, including cup/disc ratio ($r = -0.498$; $P = 0.002$) and cup depth ($r = -0.432$; $P = 0.01$).

The role of OCT in craniosynostosis has not yet been rigorously assessed by systematic review, nor has it been studied yet by our unit. The aim of this systematic review is to assess the available evidence supporting the role of OCT in managing craniosynostosis. Specifically, the sensitivity and specificity of OCT in the detection of raised ICP in craniosynostosis will be assessed.

OBJECTIVES

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

The secondary objectives are to explore the OCT parameters used per study and ICP ranges determined as normal and raised.

METHODS

Search Strategy

We entered medical subject headings terms for "raised intracranial pressure" and "optical coherence tomography" into the following search platforms: Cochrane Central Register of Controlled Trials (CENTRAL) (including the Cochrane Eyes and Vision Group (CEVG) Trials Register), Ovid MEDLINE (1946 to present), Ovid MEDLINE Inprocess and Other Nonindexed Citations, EMBASE Classic + Embase (1947 to present) and PubMed (1948 to present). Appendix 1 includes full details of keywords and medical subject headings terms used, http://links.lww.com/SCS/B771. We uploaded search results into EndNote X10 (Thomson Reuters, New York, NY) reference management software. No date or language restrictions were stipulated. We included Level IV evidence and above, that is, case series, case-control studies, cohort studies, randomized controlled trials and systematic reviews, as defined by the Oxford Centre for Evidence-based Medicine.[23]

Optical coherence tomography studies of children, defined as being aged 0 to 16 years, diagnosed with forms of craniosynostosis and raised ICP were included. Exclusion criteria are as follows:

1. studies with participants over 16 years old;
2. studies not pertaining to children with craniosynostosis;
3. studies not pertaining to diagnosis of raised ICP.

A 2-stage screening process was employed by 2 screeners (SRR and RJM). First, titles and abstracts were screened, followed by full papers. Screening questions are included in Appendix 2, http://links.lww.com/SCS/B771. The references of included papers were reviewed and investigators contacted to identify published and unpublished works. Unpublished works identified and recommended by experts were included if applicable. The systematic review protocol was registered with PROSPERO (CRD42019154254).

Outcome Measures

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

- Optic nerve parameters: cup depth, cup width, disc width, and cup to disc ratio;
- Rim parameters: RNFL thickness, rim volume, Bruch's membrane opening-minimum rim width, 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 were as follows:

- Other OCT parameters not listed above;
- ICP range determined as normal;
- ICP range determined as abnormal, that is, low or raised;
- Other surrogate estimates of ICP.
- Quality of life and adverse events were recorded and reported where applicable.

Data Collection and Analysis

Two-stage screening was performed by 2 screeners (SRR and RJM) whereby titles and abstracts were screened first, followed by full papers. Screening questions are included in Appendix 2, http://links.lww.com/SCS/B771. Data was extracted using a data extraction tool included in Appendix 3, http://links.lww.com/SCS/B771, adapted from the Cochrane Collaboration.[24] Quality assessment was performed using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies,[25] included in Appendix 4, http://links.lww.com/SCS/B771.

RESULTS

Figure 1 is a PRISMA flow diagram summarizing the screening process. Of 318 records identified, three papers were included for review. Supplementary Digital Content, Table 1, http://links.lww.com/SCS/B587 displays the main characteristics of the included studies. Appendix 5, http://links.lww.com/SCS/B771 is a table of excluded studies with reasons.

Quality Assessment

As per the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies,[25] the internal validity of the

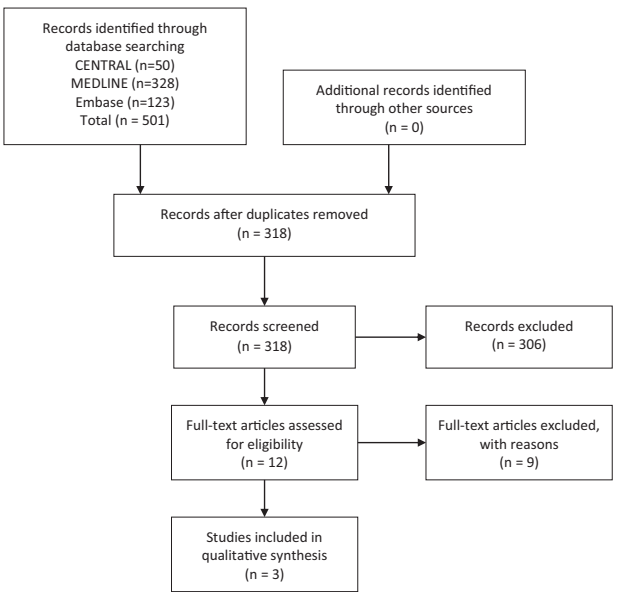

FIGURE 1. PRISMA study inclusion flow diagram.

study by Swanson et al[26] was deemed as fair, whereas that of the studies by Dagi et al[27] and Driessen et al[28] was deemed as poor. Hence, the risk of bias for the study by Swanson et al[26] was deemed as moderate, whereas that of the studies by Dagi et al[27] and Driessen et al[28] was deemed as high. This is largely due to the fact that Swanson et al[26] compared OCT parameters to direct ICP measurements, whereas other studies compared OCT parameters to fundus examination – a subjective estimate of ICP.

Primary Outcome Measures

Optical coherence tomography was effective in detecting raised ICP or evidence thereof in all included studies. However, only Swanson et al[26] compared OCT parameters to direct ICP measurements, wherein they considered ICP greater than 15 mmHg as raised. On the other hand, Dagi et al[27] and Driessen et al[28] compared OCT parameters to papilledema detected on fundus examination. Spectral-domain OCT devices used in these studies included Spectralis[27,28] (axial resolution 3.9 μm; Heidelberg Engineering, Heidelberg, Germany) and iVue (axial resolution 5 μm; Haag-Streit, Wedel, Germany).[26] No study used handheld OCT. A qualitative review was performed without meta-analysis due to the absence of randomized controlled trials required for the latter. Supplementary Digital Content, Table 2, http://links.lww.com/SCS/B587 summarizes the OCT outcome measures of all included studies.

Secondary Outcome Measures

All included studies explored the association of secondary outcome measures with the gold standard, as displayed in Supplementary Digital Content, Table 3, http://links.lww.com/SCS/B587. Some of the alternative methods had either good sensitivity or good specificity, but none of the methods demonstrated as strong a combination of sensitivity and specificity as the OCT outcomes in Supplementary Digital Content, Table 2, http://links.lww.com/SCS/B587.

Quality of Life Outcomes and Adverse Events

No included study reported quality of life outcomes or adverse events.

DISCUSSION

This systematic review has highlighted a lack of quality evidence for the role of OCT in detecting raised ICP in craniosynostosis. Only 3 studies were identified and included, 2 of which were deemed as poor quality according to the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies.[25] This could be because conventional OCT, as used in these studies, is very challenging in conscious children and infants.

Optical Coherence Tomography as a Screening Tool

All included studies reported better association between OCT and ICP (or estimates by fundus examination) as compared to other conventional clinical methods, including clinical history, visual acuity, visual field testing, radiological examination, and fundus examination (where ICP measurement was used as the gold standard). Spectral-domain OCT devices used in these studies included Spectralis[27,28] (axial resolution 3.9 μm; Heidelberg Engineering, Heidelberg, Germany) and iVue (axial resolution 5 μm; Haag-Streit, Wedel, Germany).[26] The former was used in older, conscious patients[27,28] whilst the latter was used in younger children under general anaesthesia.[26]

With regards to feasibility, most children were cooperative with OCT examination and successfully imaged on first attempt. Driessen et al[28] reported that OCT imaging was unsuccessful in 6 patients (13.6%), whilst Dagi et al[27] reported that 11 children (16.9%) were excluded due to limited cooperation, severe nystagmus, poor scan quality or retinal degeneration – the full breakdown for reasons for exclusion was not provided. Swanson et al[26] successfully imaged all included patients, albeit under general anesthesia and hence were nonreliant on patient cooperation. In reality, if OCT is initially unsuccessful in a child, it is common practice to offer further appointments for reattempt. Furthermore, our unit has extensive experience with the more recently developed handheld OCT, where we have demonstrated excellent feasibility in awake infants.[12,13,15,16] Handheld OCT may, therefore, represent a good solution in this setting, but a high quality prospective study is required to clarify this.

Swanson et al[26] and Dagi et al[27] reported better sensitivity and specificity for OCT as compared to other clinical methods, but Driessen et al[28] did not perform sensitivity and specificity analyses. Rather, Driessen et al[28] demonstrated that funduscopic anomaly showed a significantly increased total retinal thickness as compared to patients with normal fundus examination (Mann Whitney U test, $P < 0.001$). Crucially, all included studies highlighted the objective and quantitative nature of OCT for evaluating optic nerve and/or retinal parameters, in contrast to the subjective nature of clinical history, fundus examination and visual field testing.

There was no standardization of OCT parameters used across the included studies. Dagi et al[27] used RNFL thickness as their sole OCT parameter, whereas Driessen et al[28] used total retinal thickness as their sole parameter. Swanson et al[26] used a combination of maximal RNFL thickness, maximal retinal thickness, and maximal anterior retinal projection. Further studies are required to establish which parameters should be used in the assessment of raised ICP in craniosynostosis.

Other Clinical Screening Methods

Clinical history, visual acuity, visual field testing, radiological examination, and fundus examination were all poor screening methods for raised ICP in the included studies. Although specificity for raised ICP was good in all but historical evidence in the study by Dagi et al,[27] sensitivity was too low to qualify any of these methods as screening tools. This is consistent with previous literature.[29] Interestingly, Dagi et al[27] reported that historical evidence of raised ICP had good sensitivity but poor specificity.

Such investigations may represent useful adjuncts to overall clinical assessment. For instance, Swanson et al[26] found that papilledema found on fundus examination was 100% specific (95% confidence interval 85%–100%) for raised ICP and hence should prompt urgent referral for neurosurgical intervention on these grounds alone. Abnormal signs on radiological examination also demonstrated good specificity and represent an objective investigation.[26] Visual acuity and visual field testing are subjective and difficult for young children with craniosynostosis, particularly those with associated cognitive impairment.

Transorbital ultrasound has also been evaluated as a potential screening method.[30,31] Raised ICP can increase optic nerve sheath diameter, hence elevation above age-controlled diameters may predict raised ICP. However, Driessen et al[10] demonstrated that transorbital ultrasound delivers sensitivity of only 11% for detecting raised ICP in children with craniosynostosis, excluding this method as a potential screening tool. Visual evoked potentials testing involves measuring the amplitude and latency time of the averaged encephalographic response to a visual stimulus; reduction of amplitude or prolongation of the latency period represent axonal injury and correlate with elevated ICP.[4,29] However, visual evoked potentials testing demands good cooperation and displays high variability in normal subjects.[32]

Intracranial Pressure Measurement

Swanson et al[26] employed an intraoperative single ICP measurement protocol consistent with other published methods, but lacked the 24- to 48-hour duration or surveillance for multiple B-type waves reported in other protocols, which may represent the gold standard.[1,33,34] They attempted to mitigate confounding perioperative factors. However, children with craniosynostosis and associated upper airway obstruction may have increased ICP during sleep,[35] which will not be detected during general anesthesia as the child is intubated. Hence, no included study has used the current gold standard measure for ICP.

Strengths and Limitations

To our knowledge, this study represents the first systematic review of the role of OCT in detecting raised ICP in craniosynostosis. A rigorous search strategy was employed, screening was executed by 2 screeners (SRR and RJM) as per Cochrane Collaboration guidance and the data extraction sheet was adapted from the Cochrane Collaboration, with no language restrictions.[24] Both screeners returned the same studies for inclusion, obviating the need for arbitration.

This study has a number of limitations. No randomized controlled trials were returned by the systematic search, rather only Level IV evidence was identified, as defined by the Oxford Centre for Evidence-based Medicine.[23] Hence, it was not possible to perform conventional meta-analysis with a consistent comparator across the studies. Out of the 3 included studies, 2 used fundus examination as the gold standard, which is demonstrably an unreliable indicator of raised ICP due to poor sensitivity, hence both were deemed to be at a high risk of bias. Publication bias assessment was not possible in the available studies.

CONCLUSIONS

This systematic review has revealed a lack of quality evidence for the role of OCT in detecting raised ICP in craniosynostosis. High quality evidence is required to validate and/or recommend OCT as an effective screening tool in craniosynostosis, as has been demonstrated in other studies of pediatric conditions affecting the eye. Further research is required to ascertain which OCT parameters are most appropriate for identifying raised ICP.

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