Diagnostic accuracy of intraocular pressure measurement for the detection of raised intracranial pressure: meta-analysis

A systematic review

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Object. Because clinical examination and imaging may be unreliable indicators of intracranial hypertension, intraocular pressure (IOP) measurement has been proposed as a noninvasive method of diagnosis. The authors conducted a systematic review and meta-analysis to determine the correlation between IOP and intracranial pressure (ICP) and the diagnostic accuracy of IOP measurement for detection of intracranial hypertension.

Methods. The authors searched bibliographic databases (Ovid MEDLINE, Ovid EMBASE, and the Cochrane Central Register of Controlled Trials) from 1950 to March 2013, references of included studies, and conference abstracts for studies comparing IOP and invasive ICP measurement. Two independent reviewers screened abstracts, reviewed full-text articles, and extracted data. Correlation coefficients, sensitivity, specificity, and positive and negative likelihood ratios were calculated using DerSimonian and Laird methods and bivariate random effects models. The Y statistic was used as a measure of heterogeneity.

Results. Among 355 identified citations, 12 studies that enrolled 546 patients were included in the meta-analysis. The pooled correlation coefficient between IOP and ICP was 0.44 (95% CI 0.26–0.63, F² = 97.7%, p < 0.001). The summary sensitivity and specificity for IOP for diagnosing intracranial hypertension were 81% (95% CI 26%–98%, F² = 95.2%, p < 0.01) and 95% (95% CI 43%–100%, F² = 97.7%, p < 0.01), respectively. The summary positive and negative likelihood ratios were 14.8 (95% CI 0.5–417.7) and 0.2 (95% CI 0.02–1.7), respectively. When ICP and IOP measurements were taken within 1 hour of another, correlation between the measures improved.

Conclusions. Although a modest aggregate correlation was found between IOP and ICP, the pooled diagnostic accuracy suggests that IOP measurement may be of clinical utility in the detection of intracranial hypertension. Given the significant heterogeneity between included studies, further investigation is required prior to the adoption of IOP in the evaluation of intracranial hypertension into routine practice.

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Key Words • intracranial pressure • intracranial hypertension • intraocular pressure • meta-analysis • systematic review • diagnostic accuracy

Intracranial hypertension represents a life-threatening emergency. Left untreated, intracranial hypertension may lead to progressive cerebral ischemia, herniation, and death. Alternatively, the early diagnosis and treatment of intracranial hypertension improves patient survival. Recognizing intracranial hypertension is often difficult, however, as clinical examination and imaging are unreliable measures of intracranial pressure (ICP).

While the delayed diagnosis of intracranial hypertension results in ongoing brain injury, the liberal placement of invasive ICP monitors is associated with significant iatrogenic morbidity due to intraparenchymal hemorrhage and bacterial colonization.

The accurate noninvasive measurement of ICP would allow early recognition of intracranial hypertension while sparing patients with normal ICP from the risks associated with invasive monitoring. The long-recognized indirect transmission of ICP to the orbit via the intervening venous anatomy has resulted in the proposal of various methods of noninvasive ICP measurement. Intraocular pressure (IOP) measurement, as opposed to

Abbreviations used in this paper: ED = emergency department; ICP = intracranial pressure; ICU = intensive care unit; IOP = intraocular pressure; LP = lumbar puncture; QUADAS = Quality Assessment of Diagnostic Accuracy Studies.
Intraocular and intracranial pressure: a meta-analysis

alternative surrogate ICP measures such as optic nerve sheath diameter or central retinal venous pressure, may be obtained rapidly at the bedside with the use of widely available handheld tonometers by clinicians without specialized training.

The accuracy of IOP measurement in the noninvasive diagnosis of intracranial hypertension has been the subject of multiple previous studies. As these often small, disparate reports have produced conflicting results, IOP measurement in the evaluation of patients suspected of intracranial hypertension has yet to be adopted into clinical practice. We therefore conducted a systematic review and meta-analysis to determine the correlation between IOP and ICP and the diagnostic accuracy of IOP measurement for detecting raised ICP among patients with suspected intracranial hypertension. We also sought to determine whether heterogeneity among these pooled estimates could be explained by various patient- or study-level covariates to guide future research.

Methods

This meta-analysis was conducted in accordance with guidelines for the performance of diagnostic accuracy systematic reviews and reported in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement.

Search Strategy

We searched electronic bibliographic databases (Ovid MEDLINE, Ovid EMBASE, and the Cochrane Central Register of Controlled Trials [CENTRAL]) between 1950 and March 2013, and reference lists of included articles. Keywords used in the search strategy were “brain injury,” “intraocular pressure,” “intracranial hypertension,” “intracranial pressure,” “tonometry,” “intraventricular catheter,” and “cerebrospinal fluid pressure.” To identify additional citations, we also searched conference proceedings from the American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), and Canadian Neurologic Federation of Neurological Surgeons (CFNS) from 2009 to 2013. One reviewer performed the search (D.Y.), while another assessed the results (J.L.).

Study Selection

Two reviewers (D.Y. and J.L.) independently screened identified abstracts and articles in duplicate. Studies describing IOP and ICP in their title or abstract were retrieved for full text review. We used the following inclusion criteria: 1) study participants underwent measurement of both IOP and ICP; and 2) a Pearson, Spearman, Lin, or linear regression analysis-derived correlation coefficient or a 2 by 2 contingency table could be formulated from the available data for the calculation of sensitivity and specificity. Studies meeting inclusion criteria were incorporated into the analysis irrespective of the setting of the study, age of participants, patients’ intracranial pathology, publication status of the trial, or written language of the report. Reports involving only patients with known intraocular pathology were excluded.

Data Extraction

Two reviewers (D.Y. and J.L.) independently extracted data from included studies in duplicate. Disagreement was resolved by consensus. We extracted the following data: 1) patient demographics, including pathology responsible for suspected intracranial hypertension, mean age, sex, mean IOP, mean ICP, and prevalence of intracranial hypertension; 2) study design and setting; 3) thresholds used to define intracranial hypertension and elevated IOP; 4) number of IOP and ICP measurements performed; 5) number of centers involved; 6) method of invasive ICP measurement; 7) device used to measure IOP; 8) relative timing of IOP and ICP measurement; and 9) publication year. Outcomes extracted included the correlation coefficient between IOP and ICP and its variance, and the number of true and false positive and negative observations between IOP and invasive ICP measurement as the reference standard for the presence of intracranial hypertension.

Quality Assessment

The methodological quality of the studies included in the meta-analysis was graded independently by two reviewers (D.Y. and J.L.) with the Quality Assessment Of Diagnostic Accuracy Studies (QUADAS) tool. Question 12 of the QUADAS tool (interpretation of test results) was excluded as both IOP and ICP measurement are automated and therefore do not require subjective interpretation. Thus, a component analysis according to the QUADAS tool was performed and illustrated as a proportional bar graph for each of the 13 individual applicable criteria. Disagreement between the two reviewers was resolved by consensus.

Statistical Analysis

In recognition of interstudy variability, correlation coefficients were pooled using a DerSimonian and Laird random effects model. When not reported, measures of dispersion were calculated based upon the studies’ sample size. Fisher transformation was not performed on correlation coefficients prior to aggregation due to the associated risk of an overestimation of correlation in the summary estimate. Heterogeneity among trials was assessed using the I² test with values of 25%, 50%, and 75% classified as low, moderate, and high degrees of heterogeneity, respectively. Meta-regression was conducted according to study characteristics (quality, timing of IOP and ICP measurement, and method of invasive ICP assessment). Publication bias was assessed via Egger precision-weighted linear regression.

Summary estimates of sensitivity and specificity were obtained through a bivariate random effects model. Individual and summary estimates of sensitivity and specificity were illustrated through a hierarchical summary receiver operating characteristic plot with the x- and y-axes representing the index test’s sensitivity, and 1 – specificity, respectively. Pretest and posttest probabilities were obtained.
through Fagan’s nomogram. Statistical analysis was performed through metan, midas (http://fmwww.bc.edu/repec/bocode/m/midas.html), and metandi (http://ideas.repec.org/c/boc/bocode/s456932.html) modules of Stata version 12.0 software (STATA Corp.).

Results

The database search yielded 355 studies, of which 326 were excluded following screening of titles and abstracts (Fig. 1). The remaining 29 studies were retrieved. Seventeen studies where excluded after full text review due to a lack of either IOP or invasive ICP measurement (12 studies), duplicate publications of results reported in greater detail elsewhere (3 studies), or the indirect measurement of IOP (2 studies). The remaining 12 studies enrolling 546 participants identified in our literature search were included in our meta-analysis (Table 1).2,4,5,11,15,16,19,24,25,31,32,35,36 Although all of these 12 studies contributed to the calculation of a pooled estimated correlation coefficient, only 4 presented outcomes required for the calculation of summary diagnostic accuracy estimates (Table 2).16,19,25,36

Study Characteristics

The characteristics of the studies included in our analysis are presented in Table 1. Patients were recruited from outpatient neurology clinics,11,15,19,31,32 the emergency department (ED),25 and intensive care units (ICUs).2,4,5,16,24,35,36 Participants were adult patients with the exception of 1 study performed in a pediatric ICU setting.36 In half of the included studies, invasive ICP measurement was obtained through lumbar puncture (LP)11,15,19,25,31,32 while the remainder measured ICP through intracranial monitors.2,4,5,16,24,35,36 The interval between IOP and ICP measurement ranged from simultaneous measurements2,4,5,16,24,35,36 to up to 5 hours.11 Among studies reporting diagnostic accuracy estimates, the thresholds for assigning elevated IOP and intracranial hypertension were defined as a measurement greater than 20 cm H2O.16,25,32,36

Assessment of the Risk of Bias

The average QUADAS score was 8 out of a potential 13 points (range 6–11), reflecting the overall modest quality of included studies (Fig. 2). Spectrum bias was the most pertinent source of systematic error in the included studies. This source of systematic error arises from study populations whose spectrum of diseased and nondiseased states is not reflective of the test’s intended patient population, resulting in falsely elevated measures of “rule-in” or “rule-out” performance.29 While studies performed in an outpatient setting enrolled participants with an extremely low index of suspicion of intracranial hypertension that would not have otherwise warranted invasive ICP measurement (as reflected by the absence of patients with intracranial hypertension in 1 study), others recruited study participants who were comatose, meeting criteria for brain death on clinical examination.2 Review bias was present in the majority of studies, as only 1 design involved the blinding of investigators to the results of both index and reference test results.32 Given the limited subjective interpretation involved in either IOP or invasive ICP measurement, the presence of diagnostic

![Flow chart of study identification, exclusion, and inclusion in the meta-analysis.](image-url)
review bias among included studies is unlikely to be a significant contributor of bias in the measured correlation coefficients. Lastly, given the known temporal variation present in ICP, particularly among those patients with intracranial hypertension, the asynchronous measurement of IOP and ICP in the majority of included studies represents a significant potential source of disease progression bias.2,11,15,19,25,28,31,32

Pooled Estimates of Correlation Between IOP and ICP

The summary correlation coefficient obtained through a DerSimonian and Laird random effects model aggregating outcomes from 12 studies was 0.44 (95% CI 0.26–0.63; Fig. 3).2,4,5,11,15,16,19,24,25,31,32,35,36 A high degree of heterogeneity was present between studies ($I^2$ = 97.7%, $p < 0.0001$).

Meta-regression revealed a significant association between the timing of IOP and ICP measurement and aggregation correlation coefficients ($p < 0.03$; Table 3). Measurements taken greater than 1 hour apart showed no correlation (0.02, 95% CI −0.12 to 0.16) while those taken within an hour significantly correlated with one another (0.56, 95% CI 0.38–0.75). Conversely, study quality and the method of invasive ICP measurement were not significantly associated with summary correlation coefficients. Egger’s test for small study effects was statistically significant ($p < 0.02$), reflecting possible publication bias due to an absence of published studies reporting a negative correlation between IOP and ICP.

Pooled Estimates of Diagnostic Accuracy of IOP Versus ICP for Identification of Intracranial Hypertension

When the outcomes of the 4 studies reporting measures of diagnostic accuracy were pooled, summary estimates of sensitivity and specificity were 81% (95% CI 26%–98%) and 95% (95% CI 43%–100%), respectively (Fig. 4).16,19,24,25,36 A high degree of variability between studies was noted in individual estimates of both sensitivity and specificity, as reflected by $I^2$ values of 95% and 98%, respectively. The aggregate diagnostic odds ratio was 74.5 (95% CI 0.4–15,166.8) while the positive and negative likelihood ratios of IOP measurement in the diagnosis of intracranial hypertension were 14.8 (95% CI 0.5–417.7) and 0.2 (95% CI 0.02–1.7), respectively. With a pretest probability of 35% based on the accuracy of current guidelines for invasive ICP monitoring, the positive posttest probability of intracranial hypertension with the use of IOP measurement was 89%, while the corresponding negative posttest probability was 10% (Fig. 5).

### Discussion

The indirect transmission of ICP to the orbit via the intervening cavernous sinus, superior ophthalmic vein,
and episcleral veins was first recognized in 1925 when Baurmann observed that central retinal vein distension varied with ICP.1 Subsequent animal studies performed in Rhesus monkeys and canines confirmed a linear association between IOP and ICP.18,26 The difficulty involved in the measurement of IOP at the bedside restricted its clinical application in the diagnosis of intracranial hypertension. The recent advent of handheld tonometers that allow rapid measurement of IOP by health care providers without subspecialty training in ophthalmology has renewed interest in IOP as a noninvasive means of intracranial hypertension diagnosis.22,33 Despite the initial promise of preclinical reports, studies of the utility of IOP in the determination of ICP in humans have reported conflicting results. To clarify the clinical role of IOP in the diagnosis of intracranial hypertension, we have performed the only meta-analysis to date on this subject.

The pooled correlation coefficient demonstrated an association between IOP and ICP (0.44, 95% CI 0.26–0.63). However, the broad confidence interval and high degree of heterogeneity associated with the summary estimate prevent a definitive conclusion on the clinical application of IOP for assessment of ICP. Our meta-analysis suggests that the variability in the summary estimates of correlation likely reflects the disparate methods used in individual studies. The asynchronous measurement of IOP and ICP contributed to the loss of association between the two measures and represented a significant potential source of disease progression bias. The improved correlation ob-

![Fig. 2. Quality assessment of studies included in the meta-analysis. Values on the x axis represent percentages of studies.](image)

<table>
<thead>
<tr>
<th>Study</th>
<th>Correlation Coefficient (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czarnik et al., 2009</td>
<td>0.23 (0.14, 0.31)</td>
<td>9.87</td>
</tr>
<tr>
<td>Han et al., 2008</td>
<td>0.07 (-0.20, 0.33)</td>
<td>8.37</td>
</tr>
<tr>
<td>Kirk et al., 2011</td>
<td>-0.00 (-0.18, 0.17)</td>
<td>9.28</td>
</tr>
<tr>
<td>Lashutka et al., 2004</td>
<td>0.83 (0.74, 0.89)</td>
<td>9.93</td>
</tr>
<tr>
<td>Li et al., 2012</td>
<td>0.32 (0.16, 0.47)</td>
<td>9.42</td>
</tr>
<tr>
<td>Morgan et al., 2012</td>
<td>0.05 (-0.67, 0.76)</td>
<td>4.05</td>
</tr>
<tr>
<td>Muchnik et al., 2012</td>
<td>0.23 (-0.13, 0.54)</td>
<td>7.62</td>
</tr>
<tr>
<td>Sajjadi et al., 2006</td>
<td>0.95 (0.92, 0.97)</td>
<td>10.06</td>
</tr>
<tr>
<td>Sheeran et al., 2000</td>
<td>0.46 (0.19, 0.88)</td>
<td>7.48</td>
</tr>
<tr>
<td>Spentzas et al., 2010</td>
<td>0.75 (0.69, 0.80)</td>
<td>10.00</td>
</tr>
<tr>
<td>Blank &amp; Spring, 1988</td>
<td>0.07 (-0.67, 0.74)</td>
<td>4.12</td>
</tr>
<tr>
<td>Fen et al., 2011</td>
<td>0.76 (0.64, 0.84)</td>
<td>9.79</td>
</tr>
<tr>
<td>Overall (I² = 97.7%, p = 0.000)</td>
<td>0.44 (0.26, 0.63)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

![Fig. 3. Forest plot of the correlation between IOP and ICP. The dashed line indicates the pooled correlation coefficient between IOP and ICP.](image)
Intraocular and intracranial pressure: a meta-analysis

served when studies using measurements taken beyond 1 hour were excluded (0.56, 95% CI 0.38–0.75) imply that the pooled estimate of all studies is an underestimate of the true association between ICP and IOP.

Given the potentially ominous clinical consequences of failing to recognize intracranial hypertension, a high sensitivity is required of a noninvasive test of intracranial hypertension. The pooled estimate of sensitivity (81%, 95% CI 26%–98%) limits the clinical application of IOP in screening for intracranial hypertension. Conversely, while the pooled specificity of 95% (95% CI 43%–100%) indicates that IOP may provide a useful means of ruling in the diagnosis of intracranial hypertension, the relatively high specificity suggests that a lower threshold value for a positive result may improve the clinical utility of IOP measurement in detecting intracranial hypertension. As with the aggregate estimate of correlation, the implications of the pooled sensitivity and specificity estimates are limited by their imprecision due to the relatively small number of studies with disparate designs contributing to the estimate. In addition, the pooled estimates of diagnostic accuracy were subject to spectrum bias as a result of the wide-ranging prevalence of intracranial hypertension (29% to 68%) among participants of individual studies. Despite the promising pooled estimates of diagnostic accuracy of IOP in the detection of intracranial hypertension, given the large associated CIs, the results of this meta-analysis do not, at this time, support the routine clinical adoption of IOP in the screening for intracranial hypertension.

Even in light of the above-mentioned limitations, among those patients in whom clinical equipoise exists regarding the placement of an invasive ICP monitor, IOP measurement may still improve upon current clin-

### Table 3: Meta-regression: estimated influence of study characteristics on correlation coefficient

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>Correlation Coefficient (95% CI)</th>
<th>F (%)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>quality*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9</td>
<td>0.47 (0.24–0.70)</td>
<td>92</td>
<td>0.95</td>
</tr>
<tr>
<td>≥9</td>
<td>0.42 (0.12–0.73)</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>method of ICP measurement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LP</td>
<td>0.44 (0.26–0.63)</td>
<td>98</td>
<td>0.77</td>
</tr>
<tr>
<td>ICP monitor</td>
<td>0.49 (0.23–0.75)</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>timing of IOP &amp; ICP measurement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 hr</td>
<td>0.56 (0.38–0.75)</td>
<td>98</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>&gt;1 hr</td>
<td>0.02 (−0.12 to 0.16)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Quality as measured by the QUADAS tool on a 13-point scale.
† The p value was obtained by joint test on the basis of Knapp-Hartung modification.


10. Fischer RA: On the “probable error” of a coefficient of correlation deduced from a small sample. Metron 1:3–32, 1921


30. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH: Bivariate analysis of sensitivity and speci-

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