Reference Values For Intracranial Pressure And Lumbar Cerebrospinal Fluid Pressure: A Systematic Review

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Abstract

Background

Although widely used in the evaluation of the diseased, normal intracranial pressure and lumbar cerebrospinal fluid pressure remains sparsely documented. Intracranial pressure is different from lumbar cerebrospinal fluid pressure. In addition, intracranial pressure differs considerably according to body position of the patient. Despite this, the current reference interval are used indistinguishable for intracranial and lumbar cerebrospinal fluid pressure, and body position dependent reference intervals does not exist. In this study, we aim to establish these reference intervals.

Method

A systematic search was conducted in MEDLINE, EMBASE, CENTRAL, and Web of Sciences. Methodological quality was assessed using an amended version of the Joanna Briggs Quality Appraisal Checklist. Intracranial pressure and lumbar cerebrospinal fluid pressure were independently evaluated and subdivided into body positions. Quantitative data were presented with mean ± SD, and 90% reference intervals.

Results

Thirty-six studies were included. Nine studies reported values for intracranial pressure, while 27 reported values for the lumbar cerebrospinal fluid pressure. Reference values for intracranial pressure were -5.9 to 8.3 mmHg in the upright position and 0.9 to 16.3 mmHg in supine position. Reference values for lumbar cerebrospinal fluid pressure were 7.2 to 16.8 mmHg and 5.7 to 15.5 mmHg in the lateral recumbent position and supine position, respectively.

Conclusions

This systematic review is the first to provide position-dependent reference values for intracranial pressure and lumbar cerebrospinal fluid pressure. Clinically applicable reference values for normal lumbar cerebrospinal fluid pressure was established, and were in accordance with previously used reference values. For intracranial pressure, this study strongly emphasizes the scarse normal material, and highlights the need for further research on the matter.

Background

Measurement and analysis of intracranial pressure (ICP) are used to inform treatments and management of numerous neurosurgical diseases, e.g., traumatic brain injury, acute intracranial hemorrhages, idiopathic intracranial hypertension, and hydrocephalus[1–4]. However, values for normal ICP measured intracranially remain sparsely documented, and the currently used reference interval (7 to 15 mmHg[5]) are based on studies in which lumbar cerebrospinal fluid opening pressure ($LCSF_{op}$) is used as a surrogate parameter for ICP or extrapolated from patients with a suspected ICP disorder[5–11].

In the 1920s and 30 s, it was assumed that ICP measured intracranially was equal to $LCSF_{op}$ measured at a lumbar spine level[12, 13]. This has, in recent years, been subject to much debate [14–18], and where some studies have documented similar values for intracranial measurements and lumbar measurements[14, 16], others find considerable differences between the two measurement-sites[15, 17, 18]. The comparison of these studies is hampered by differences in study design, particularly dissimilarities in body position during the measurement and included study participants[14–17, 19, 20].

It is well known that body position alters ICP[9, 19–22], e.g., ICP decrease in vertical position compared to horizontal position[9, 20, 22], and increase significantly with the body placed in lateral recumbent position compared to supine position[19, 23–25]. Based on this, it is highly likely that different reference intervals for ICP should be established for different body positions.

In this systematic review, we aim to 1) determine reference intervals for normal ICP and $LCSF_{op}$, and 2) examine if reference intervals for ICP depend on measurement-site and body position.

Methods

Prior to initiating this systematic review, the protocol was registered at PROSPERO (October 30, 2019, identification code: CRD42019143018). The review has been conducted in accordance with the PRISMA guidelines, and a completed PRISMA checklist is available in **Appendix 1**.

Eligibility criteria

All included studies had to provide 1) measurements conducted in humans, 2) original values for either ICP or $LCSF_{op,}$ and 3) ICP measured either intracranially (parenchymal, intraventricular, epidural, subdural, or subarachnoid) or $LCSF_{op}$ measured during a lumbar puncture. All age-groups were included.

Patients with intracranial pathology that potentially could alter ICP dynamics (e.g., hydrocephalus, idiopathic intracranial hypertension, intracranial hemorrhage, arteriovenous malformation, intracranial tumor, intracranial abscesses or other significant space-occupying processes within the brain) were excluded.

Data search

On July 16st 2019, we conducted a search in MEDLINE Ovid (1946 to July 2019), Embase Ovid (1974 to July 2019), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library and Science Citation Index Expandex (1900 to July 2019), and Conference Proceeding Citation Index – Science (Web of Science) (1990 to July 2019). There was no restriction on the publication period. We included all peer-reviewed published studies without consideration for publication status or study design. The search was conducted in English, and studies with a non-English title or abstract were thus excluded. Non-English manuscripts, with an English title and abstract, were translated by a native speaker. The search strategy is attached in **Appendix 2**.

If published data in the included studies were insufficient, the authors were contacted in order to retrieve raw data. The systematic search was supplemented by a manual reference-search of included studies. Finally, an expert in the field (MJ) was asked to identify any obviously missing studies.

Study selection and data extraction

Four investigators (CSR, MHO, NHN, SHP) reviewed the studies for eligibility. Each study was assessed by two different investigators for the title, abstract and full-text screening. Discrepancies were initially resolved between the four investigators, and if this was not possible, an expert (MJ) had the deciding vote. The screening was conducted via Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Study design, demographics, and information regarding ICP-monitoring were extracted from each study.

Study data were extracted from Covidence by NHN and verified by MHO. Disagreements were resolved by discussion.

Quality assessment

The methodological study quality was independently assessed by two investigators (MHO, NHN). No intervention-based studies were included, and thus, traditional assessment methods for systematic reviews could not be used. Instead, a quality assessment method was created inspired by the Joanna Briggs Institute Critical Appraisal Tool[26]. Two parts of the tool were, however, irrelevant in the assessment of study type and therefore replaced; 1) *"Was the exposure measured in a valid and reliable way?"* was replaced with *"Was the measurement method described in details?"* and 2) *"Were the outcomes measured in a valid and reliable way?"* was replaced with *"Was the included population without current or previous intracranial pathology that could alter ICP dynamics?"*.

Data synthesis

All statistical analyses were performed in RStudio (R 3.6.2, R Development Core Team (2019), Vienna, Austria). Since all included studies were observational, and the primary purpose of this review was to determine a reference interval for ICP, a conventional meta-analysis was not applicable.

Instead, included studies were pooled into two groups, 1) studies in which ICP was measured, and 2) studies in which $LCSF_{op}$ was measured.

Raw data were assessed for normality and presented as mean ± standard deviation (SD), 95% confidence intervals (CI) and with coherent reference intervals (defined as 5th to 95th percentile)[5]. If statistical values other than SD were presented (e.g., 95% confidence intervals or reference intervals), SD was manually calculated based on the given statistical data according to the Cochrane Handbook of Systematic Reviews[27]. For studies where only the median and interquartile range (IQR) were presented, the median was directly transformed to a mean, while SD was estimated from IQR by SD = IQR/1.35, as recommended in the Cochrane Handbook of Systematic Reviews[27]. Finally, if pressure values were reported in other units (e.g., mmH_2O or cmH_2O) it was converted to mmHg.

Normal ICP and $LCSF_{op}$ were subdivided into different body positions stratified by study and presented in a forest plot, including mean values and 95% CI. The corresponding weighted reference intervals for the different body positions were subsequently presented in a table for ICP and $LCSF_{op}$. Reference intervals are presented in both mmHg and cmH_2O.

The different body positions were compared using a two-tailed Students t-test, and P-values were presented after Bonferroni correction. P-values < 0.05 were considered significant. The included studies provided insufficient data to perform a meaningful multivariate analysis adjusting for age, gender, monitoring equipment, neck position, and zeropoint for ICP measurement-site.

Results

The search strategy identified a total of 2,515 studies. After the removal of duplicates, 1,790 studies remained. The abstract and title screening left 126 studies, and based on full-text screening, 44 studies were included (Fig. 1). Study characteristics are presented in Table 1.

Table 1
Characteristics of included studies

	Type of study	Type of population	Measurement place	No. of participant	Mean age or range	Included in analysis*
Albeck 1991[33]	Prospective, observational	Healthy	Lumbar	8	22–28	Yes
Albeck 1998[34]	Prospective, observational	Healthy	Lumbar	52	60	Yes
Andresen 2014[46]	Prospective, observational	Pseudo-healthy	Parenchymal	4	67	Yes
Avery 2010[63]	Prospective, observational	Pseudo-healthy	Lumbar	197	1–18	Yes
Avery 2014[70]	Case report, literature review	Pseudo-healthy	Lumbar	1	12	Yes
Beck 2017[66]	Prospective, observational	Pseudo-healthy	Lumbar	17	-	Yes
Blomquist 1986[73]	Prospective, observational	Pseudo-healthy	Lumbar	18	0–15	Yes
Bono 2003[67]	Prospective, observational	Pseudo-healthy	Lumbar	111	40	Yes
Bø 2010[69]	Prospective, observational	Pseudo-healthy	Lumbar	348	47	Yes
Chiari 2017[76]	Retrospective, observational	Pseudo-healthy	Parenchymal	41	43	Yes
Chapman 1990[21]	Prospective, observational	Pseudo-healthy	Ventricular	5	28	Yes
Corbett 1983[25]	Prospective, observational	Healthy	Lumbar	15	-	Yes
Eklund 2016[32]	Prospective, observational	Healthy	Lumbar	11	46	Yes
Ekstedt 1978[9]	Prospective, observational	Pseudo-healthy	Lumbar	100	-	Yes

* Studies were not included in the analysis, if they provided insufficient stastical data to calculate a mean and standard deviation

	Type of study	Type of population	Measurement place	No. of participant	Mean age or range	Included in analysis*
Ellis 1994[24]	Prospective, observational	Pseudo-healthy	Lumbar	33	8	Yes
Fleischman 2012[68]	Retrospective, observational	Pseudo-healthy	Lumbar	12118	54	Yes
Friden 1983[72]	Retrospective, observational	Pseudo-healthy	Lumbar	150	-	Yes
Gilland 1969[8]	Retrospective, observational	Healthy	Lumbar	15	25	Yes
Gilland 1974[7]	Prospective, observational	Healthy	Lumbar	31	23	Yes
Gonzalez 2017[62]	Prospective, case-control	Pseudo-healthy	Lumbar	28	41	No
Hannerz 1995[35]	Prospective, observational	Healthy	Lumbar	19	52	Yes
Kaiser 1986[60]	Prospective, observational	Pseudo-healthy	Lumbar	49	30 (24–41) weeks	Yes
Kawasaki 1998[61]	Retrospective, case-control	Pseudo-healthy	Lumbar	1	51	Yes
Lakke 1968[36]	Prospective, observational	Healthy	Lumbar	34	-	No
Langvatn 2019[77]	Retrospective, observational	Pseudo-healthy	Parenchymal	12	3	Yes
Lawley 2017[56]	Prospective, observational	Pseudo-healthy	Ventricular	8	35	Yes
Lee 2011[59]	Retrospective, observational	Pseudo-healthy	Lumbar	44	9	Yes
Lundberg 1960[57]	Prospective, case-control	Pseudo-healthy	Ventricular	1	45	No
Magneli 2016[54]	Prospective, case-control	Pseudo-healthy	Parenchymal	1	8	Yes

* Studies were not included in the analysis, if they provided insufficient stastical data to calculate a mean and standard deviation

	Type of study	Type of population	Measurement place	No. of participant	Mean age or range	Included in analysis*
Mahr 2016[78]	Prospective, observational	Pseudo-healthy	Parenchymal	35	73	No
Malm 2011[5]	Prospective, observational	Healthy	Lumbar	40	70	Yes
Martin 1978[79]	Prospective, case-control	Pseudo-healthy	Intracranial	1	19	No
Pedersen 2018[41]	Retrospective, observational	Pseudo-healthy	Parenchymal	35	4–85	Yes
Petersen 2016[55]	Prospective, observational	Pseudo-healthy	Parenchymal and ventricular	11	44	Yes
Puhringer 1997[37]	Prospective, observational	Healthy	Lumbar	5	25–38	Yes
Purvin 2000[52]	Retrospecitve, case-control	Pseudo-healthy	Lumbar	-	-	No
Riedel 2020	Prospective, observational	Pseudo-healthy	Parenchymal	44	60	Yes
Schwartz 2013[58]	Prospective, observational	Pseudo-healthy	Lumbar	55	56	Yes
Shapiro 1980[29]	Prospective, observational	Healthy	Lumbar	23	0–55	Yes
Skau 2013[30]	Prospective, case-control	Healthy	Lumbar	20	-	Yes
Skipper 2019[31]	Retrospective, case-control	Healthy	Lumbar	24	33	No
Sugita 1985[64]	Prospective, case-control	Pseudo-healthy	Lumbar	3	38	No
Whiteley 2006[11]	Retrospective, observational	Pseudo-healthy	Lumbar	242	-	Yes
Wibroe 2016[65]	Prospective, observational	Pseudo-healthy	Lumbar	28	37	Yes

* Studies were not included in the analysis, if they provided insufficient stastical data to calculate a mean and standard deviation

The majority of studies reported a mean value with coherent SD or a mean value with either 95% CI or reference intervals, from which SD could be calculated (n = 32). In a few studies, only median and IQR were reported (n = 4). Studies that only reported a range or a mean, and where no further statistical data could be provided from the authors were omitted from analysis (n = 8). Thus, 36 studies remained in the data analysis.

Reference intervals for ICP and LCSF $_{op}$

Reference intervals differed significantly between body positions (e.g., lateral recumbent position $LCSF_{op}$ versus supine $LCSF_{op}$ ($P = 0.04$), and upright ICP versus supine ICP ($P < 0.01$)). Details are shown in Table 2 for both ICP and $LCSF_{op}$.

Table 2
Reference vales for intracranial pressure and lumbar cerebrospinal fluid pressure in different body positions

	No. of studies	**No. of participants**	**Mean (reference interval) [mmHg]**	**Mean (reference interval) [cmH_2O]**
ICP				
- supine	6	62	8.6 (0.9–16.3)	11.7 (1.2–22.2)
- upright	6	62	1.0 (-5.9–8.3)	1.3 (-8.7–11.2)
- daytime	2	45	-0.1 (-12.0–12.2)	-0.15 (-16.3–16.6)
- nighttime	3	57	6.3 (-15.8–28.2)	8.6 (-21.5–38.3)
CSF_{op}				
- supine	7	389	10.7 (5.7–15.5)	14.4 (7.5–21.1)
- lateral recumbent	21	13,359	11.9 (7.2–16.8)	16.3 (9.8–22.8)

Nine studies provided values for ICP measured intracranially. Reference intervals were subdivided into four groups based on body position: 1) supine position with a mean ICP of *8.6* mmHg (SD 4.7, reference interval 0.9 to 16.3 mmHg), 2) upright position with a mean ICP of 1.0 mmHg (SD 4.3, reference interval – 5.9 to 8.3 mmHg), 3) continuous daytime measurement with a mean ICP of -0.1 mmHg (SD 7.4, reference interval – 12.0 to 12.2 mmHg), and 4) continous nighttime measurement with a mean ICP of 6.3 mmHg (SD 13.3, reference interval – 15.8 to 28.2) (Fig. 2, Table 2).

Twenty-seven studies provided values for $LCSF_{op}$ measured by lumbar puncture. $LCSF_{op}$ was subdivided into two groups: 1) the supine position with a mean $LCSF_{op}$ of 10.7 mmHg (SD 3.0, reference interval 5.7 to 15.5 mmHg), and 2) the lateral recumbent position with a mean $LCSF_{op}$ of 11.9 mmHg (SD 2.9,

reference interval 7.2 to 16.8 mmHg) (Fig. 2, Table 2). There was a statistical difference between ICP values in the supine position and $LCSF_{op}$ values in the supine position (P = 0.03).

There was no statistical difference between reference intervals for $LCSF_{op}$ based solely on the healthy population compared to reference intervals for $LCSF_{op}$ based solely on the pseudo-healthy population. The difference between healthy individuals and pseudo-healthy individuals in lateral recumbent position was 1.4 mmHg (P = 0.34), and in supine position 1.0 mmHg (P = 0.73).

Quality of included studies

The overall methodological quality of the study designs was moderate. Out of seven, the average score of the included studies was 4.5.

None of the studies in which ICP was measured were based on completely healthy individuals, and in only two studies, the primary aim was to determine reference intervals for ICP. For the studies in which ICP was measured, the overall methodological study quality was moderate (average study quality = 4/7).

In the group of $LCSF_{op}$, the overall study quality was generally higher (average study quality = 5/7) and a few studies included completely healthy individuals (n = 13)[5, 6, 34–36, 7, 24, 28–33]. In general, studies with $LCSF_{op}$ consisted of a significantly higher number of study participants (Table 1).

Discussion

This systematic review aimed to establish reference intervals for normal ICP and $LCSF_{op}$. Through an extensive literature search, 44 studies examining either ICP or $LCSF_{op}$ in pseudo-normal or normal participants were identified, and of these, 36 provided sufficient pressure values and statistical data to calculate reference intervals. Nine studies reported ICP values, while 27 reported $LCSF_{op}$ values. The overall study quality was moderate. For ICP, the study material were scarce, and the reference intervals were based on a small sample size. Data on $LCSF_{op}$ were, in comparison, comprehensive in both lateral recumbent position and supine position. Finally, the reference intervals for both ICP and $LCSF_{op}$ were found to differ significantly between body positions, demonstrating the need for position-dependent reference intervals.

The literature further indicates that age, weight, neck position, zeropoint for measurement-site, and monitoring equipment is of great importance in measurement of ICP and $LCSF_{op}$ [10, 24, 37–42]. Especially zeropoint is of uttermost importance when measuring ICP in upright position. In supine and lateral recumbent position, zeropoint matters to the extend that it has to be in the midline of the patient which is a clinical standard in most neurological and neurosurgical departments. However, only nine of the included studies described the zeropoint of measurements. In terms of the studies reporting on measurement in upright position two out of six studies reported on zeropoint. Thus, for the purpose in

this systematic review, data in the included studies were too scarcely reported for meaningful analysis, and thus the reference values were not corrected for the above mentioned factors.

The measured intracranial pressure is clearly dependent on the zero point of the measurements. In supine and lateral recumbent position, it is less imporant as long as it is in the midline of the patient. However, in Nine of the study reported on zero point,

Reference intervals for ICP

Due to the still invasive nature of obtaining ICP, it is ethically unacceptable to examine ICP in healthy normal individuals. Several non-invasive ICP measuring methods have been developed, and though they can be useful to estimate interpatient ICP differences, e.g., during follow-up, none are currently accurate enough to measure ICP values[43, 44].

The studies in this review included pseudo-normal patients[21, 45–47], and we identified no published studies of ICP on completely healthy participants. In the last decade, a new telemetric monitoring technique has become available, allowing for ICP measurements for several months after implantation[48–50]. This has resulted in ICP measurements in groups outside of the traditional patient-categories with suspected ICP disorders. Andresen et al. implanted a telemetric ICP monitor in patients who had a small demarcated intracranial tumor surgically removed, thus establishing a pseudo-normal cohort[45]. Though this cohort is not completely healthy, long-term measurements via the telemetric ICP monitor provide ICP values at a time when intracranial conditions, including ICP, can be considered normal. This is an improvement to previous research, which have been mainly based on patients undergoing diagnostic evaluation for a suspected ICP disorder[21, 39, 51, 52]. Future research to establish normal ICP, until quantitative non-invasive technology is developed, could benefit from this telemetric monitoring technique and, hopefully, expand the material on ICP values obtained in pseudo-normal humans.

In this review, we found a reference interval for ICP in the supine position from 0.9 to 16.3 mmHg, based on six studies with a total of 62 participants[21, 45, 51, 53–55]. The reference intervals are based on a small sample size and differ substantially in their findings of normal ICP, and do, therefore, not represent a clinically applicable reference interval.

Since most humans, and in terms of patients specifically idiopathic intracranial hypertension and normal pressure hydrocephalus patients, spend the majority of their lives in the upright (vertical) position, a reference interval for this specific position is needed for interpretting diagnostic long-term ICP monitoring. Based on six studies with a total of 62 participants[21, 39, 45, 53–55], this review found a reference intervals for ICP in the upright position from − 6.2 to 8.0 mmHg. Though too wide to serve as a clinically applicable reference interval, the data show that negative ICP values can be normal in an upright position[45, 56].

For daytime ICP, the established reference intervals were likewise based on a limited number of studies (n = 2) and study participants (n = 45)[42, 57]. Furthermore, there are large interpersonal differences in the amount of time spend in an upright position during the day. These factors proberly result in the wide reference interval from − 12.0 to 12.2 mmHg. As with the reference interval for ICP in the upright position, this does not serve as a practical tool in clinical decision making.

For nighttime, we were able to establish a reference interval from − 15.8 to 28.2 mmHg. Besides a limited number of studies (n = 3) and participants (n = 57) addressing the matter[42, 57, 58], body position during sleep may vary considerably among patients. Furthermore, the degree of sleep apnoe has also been found to highly impact ICP[42]. Combined, this could potentially cause significant variations in measured ICP and, result in the very wide and clinical unuseful reference interval. Unfortunately, the included studies did not provide information on body position nor sleep apnoe coherent to ICP values.

Reference intervals for $LCSF_{op}$

The majority of included studies on $LCSF_{op}$ (81%) performed pressure measurement in a lateral recumbent position[6, 7, 34–36, 41, 59–64, 8, 65–70, 10, 23, 29–33], thus establishing a reference interval in this position from 7.2 to 16.8 mmHg. There were no significant difference between the reference intervals in healthy indidviduals versus pseudo-healthy individuals. The establish reference interval is similar to the reference of 7 to 15 mmHg routinely used in clinical practice[5, 18, 23, 24, 45].

Seven studies obtained $LCSF_{op}$ values in supine position[5, 8, 24, 28, 59, 71, 72], resulting in a reference interval from 5.7 to 15.5 mmHg. Participants in three out of the seven studies were completely healthy[5, 24, 28]. There was no significant difference between reference intervals in healthy indidviduals versus pseudo-healthy individuals.

When comparing supine $LCSF_{op}$ to supine ICP, we found a difference between the means corresponding to 2.1 mmHg (P = 0.03). These results suggest that supine $LCSF_{op}$ is not optimal as a surrogate marker of supine ICP. To our knowledge, there are no studies that comparing simultaneously measured supine ICP with supine $LCSF_{op}$.

Posture-dependent pressure differences

Postural-dependent pressure changes have mainly been evaluated in studies investigating ICP[19, 54]. Andresen et al. compared lumbar recumbent position to supine position in 31 patients with intracranial ICP monitoring and found that ICP increased approximately 5 mmHg in the lateral recumbent position, thus a significantly higher difference than found between LCSFop in recumbent position versus supine position in this review[19]. This postural-related difference in ICP may be caused by spine flexion and, in particular, flexion of the neck during lateral recumbent position in the study by Andresen et al[19]. A flexed neck could theoretically compress the jugular veins, thus hindering the venous return to the heart from the

head, thereby increasing ICP[40, 73–75]. Many studies have emphasized the importance of a neutral neck during the measurement of $LCSF_{op}$[23, 24, 40, 73].

Though statistically significant, the mean $LCSF_{op}$ difference of 1.2 mmHg between the lateral recumbent position and supine position hardly has any clinical implications (Fig. 2). This relatively small difference might be explained by $LCSF_{op}$ in the lateral recumbent position having been measured with the neck in a neutral position. Unfortunately, the significant change in $LCSF_{op}$ caused by neck position alone has not previously been subject to much debate. Thus, only six of the included studies examining $LCSF_{op}$ documented that $LCSF_{op}$ was obtained simultaneously with a neutral neck position[6, 24, 29, 32, 35, 68]. To establish an accurate reference interval of $LCSF_{op,}$ the neck should be held in a neutral position during all $LCSF_{op}$ measurements.

Conclusions

In this systematic review, we aimed to establish reference intervals for ICP and $LCSF_{op}$.

The data on ICP was not sufficient to establish clinically applicable reference intervals for either supine position, upright position, daytime, or nighttime. Negative ICP in upright position do however seem to be normal. For $LCSF_{op}$ we estimated clinically applicable reference intervals in both lateral recumbent position (6.3 to 15.9 mmHg) and supine position (5.3 to 15.1 mmHg). This systematic review highlights the need for future research within the field of reference intervals for ICP.

Declarations

Ethics approcal and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datased used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare thay they have no competing interests.

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Authors' contributions

NHN MHO, SSP, CSR, MJ designed the study.

NHN, MHO, SSP, CSR screened and extracted data from studies.

NHN and MHO drafted the manuscript.

All authors reviewed the manuscript.

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References

1. Sæhle T, Eide PK. Intracranial pressure monitoring in pediatric and adult patients with hydrocephalus and tentative shunt failure: a single-center experience over 10 years in 146 patients. J Neurosurg [Internet]. 2015;122:1076–86. Available from: http://thejns.org/doi/10.3171/2014.12.JNS141029
2. Schuhmann MU, Sood S, McAllister JP, Jaeger M, Ham SD, Czosnyka Z, et al. Value of overnight monitoring of intracranial pressure in hydrocephalic children. Pediatr Neurosurg. 2008;44:269–79.
3. Czosnyka Z, Czosnyka M. Long-term monitoring of intracranial pressure in normal pressure hydrocephalus and other CSF disorders. Acta Neurochir (Wien). Acta Neurochirurgica; 2017;159:1979–80.
4. Lilja-Cyron A, Kelsen J, Andresen M, Fugleholm K, Juhler M. Feasibility of Telemetric Intracranial Pressure Monitoring in the Neuro Intensive Care Unit. J Neurotrauma. 2018;35:1578–86.
5. Malm J, Jacobsson J, Birgander R, Eklund A. Reference values for CSF outflow resistance and intracranial pressure in healthy elderly. Neurology [Internet]. 2011;76:903–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2002373
6. Gilland O, Tourtellotte WW, O'Tauma L, Henderson WC. Normal cerebrospinal fluid pressure. J Neurosurg. 1974;40:587–93.
7. Gilland O. Normal cerebrospinal-fluid pressure. NEJM. 1969;
8. Ekstedt J. CSF hydrodynamic studies in man. II. Normal hydrodynamic variables related to CSF pressure and flow. J Neurol Neurosurg Psychiatry. 1978;41:345–53.
9. Loman J, Myerson A, Goldman D. Effects of alterations in posture on the cerebrospinal fluid pressure. Arch Neurol Psychiatry. 1935;33:1279–95.

10. Whiteley W, Al-Shahi R, Warlow CP, Zeidler M, Lueck CJ. CSF opening pressure: Reference interval and the effect of body mass index. Neurology. 2006;67:1690–1.
11. Ekstedt J. CSF hydrodynamic studies in man. J Neurol Neurosurg Psychiatry. 1977;40:105–19.
12. Hodgson JS. Combined ventricular and lumbar puncture in the diagnosis of brain tumor. J Am Med Assoc. 1928;90:1524–6.
13. Smyth GE, Henderson WR. Observations on the cerebrospinal fluid pressure on simultaneous ventricular and lumbar punctures. J Neurol Neurosurg Psychiatry [Internet]. 1938;1:226–38. Available from: https://jnnp.bmj.com/lookup/doi/10.1136/jnnp.1.3.226
14. Speck V, Staykov D, Huttner HB, Sauer R, Schwab S, Bardutzky J. Lumbar catheter for monitoring of intracranial pressure in patients with post-hemorrhagic communicating hydrocephalus. Neurocrit Care. 2011;14:208–15.
15. Eide PK, Brean A. Lumbar cerebrospinal fluid pressure waves versus intracranial pressure waves in idiopathic normal pressure hydrocephalus. Br J Neurosurg. 2006;20:407–14.
16. Lenfeldt N, Koskinen LOD, Bergenheim AT, Malm J, Eklund A. CSF pressure assessed by lumbar puncture agrees with intracranial pressure. Neurology. 2007;68:155–8.
17. Warden KF, Alizai AM, Trobe JD, Hoff JT. Short-term continuous intraparenchymal intracranial pressure monitoring in presumed idiopathic intracranial hypertension. J Neuro-Ophthalmology. 2011;31:202–5.
18. Eide PK, Due-Tønnessen B, Helseth E, Lundar T. Assessment of intracranial pressure volume relationships in childhood: The lumbar infusion test versus intracranial pressure monitoring. Child's Nerv Syst. 2001;17:382–90.
19. Andresen M, Hadi A, Petersen LG, Juhler M. Effect of postural changes on ICP in healthy and ill subjects. Acta Neurochir (Wien). 2014;157:109–13.
20. Poca MA, Sahuquillo J, Topczewski T, Lastra R, Font ML, Corral E. Posture-induced changes in intracranial pressure: A comparative study in patients with and without a cerebrospinal fluid block at the craniovertebral junction. Neurosurgery. 2006;58:899–906.
21. Chapman PH, Cosman ER, Arnold MA, Portnoy HD, Sklar F. The relationship between ventricular fluid pressure and body position in normal subjects and subjects with shunts: A telemetric study. Neurosurgery. 1990;26:181–9.
22. Barami K, Sood S, Ham SD, Canady AI. Postural changes in intracranial pressure in chronically shunted patients. Pediatr Neurosurg. 2000;33:64–9.
23. Ellis R. Lumbar cerebrospinal fluid opening pressure measured in a flexed lateral decubitus position in children. Pediatrics. 1994;24.
24. Corbett JJ, Mehta MP. Cerebrospinal fluid pressure in normal obese subjects and patients with pseudotumor cerebri. Neurology. 1983;33:1386–8.
25. Wilson TJ. Textbook of Child Neurology. J Neurol Neurosurg Psychiatry. 1980;43:1050–1.
26. The Joanna Briggs Institute. Joanna Briggs Institute Reviewer's Manual. Joanna Briggs Inst. 2014.

27. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Cochrane Database Syst. Rev. 2011.

28. Eklund A, Jóhannesson G, Johansson E, Holmlund P, Qvarlander S, Ambarki K, et al. The pressure difference between eye and brain changes with posture. Ann Neurol. 2016;80:269–76.

29. Albeck MJ, Borgesen SE, Gjerris F, Schmidt JF, Sorensen PS. Intracranial pressure and cerebrospinal fluid outflow conductance in healthy subjects. J Neurosurg [Internet]. 1991;74:597–600. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2002373

30. Albeck MJ, Skak C, Nielsen PR, Olsen KS, Børgesen SE, Gjerris F. Age dependency of resistance to cerebrospinal fluid outflow. J Neurosurg. 1998;89:275–8.

31. Hannerz J, Ericson K. Is there a relationship between obesity and intracranial hypertension? Int J Obes. 1995;19:240–4.

32. Lakke JP, Schut D. Electromanometric examination of CSF pressure response to jugular compression. I. Determination of normal values. Psychiatr Neurol Neurochir. 1968;71:57–64.

33. Puhringer F, Hormann C, Langmayr J, Schalow S, Benzer A. The effect of alfentanil on cerebrospinal fluid pressure in human volunteers. Eur J Anaesthesiol. 1997;14:211–4.

34. Shapiro K, Marmarou A, Shulman K. Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. Ann Neurol. 1980;7:508–14.

35. Skau M, Yri H, Sander B, Gerds TA, Milea D, Jensen R. Diagnostic value of optical coherence tomography for intracranial pressure in idiopathic intracranial hypertension. Graefe's Arch Clin Exp Ophthalmol. 2012;251:567–74.

36. Skipper NT, Igra MS, Littlewood R, Armitage P, Laud PJ, Mollan SP, et al. Do Optic Canal Dimensions Measured on CT Influence the Degree of Papilloedema and Visual Dysfunction in Idiopathic Intracranial Hypertension? Neuro-Ophthalmology. 2019;43:3–9.

37. Pedersen SH, Norager NH, Lilja-Cyron A, Juhler M. Telemetric intracranial pressure monitoring in children. Child's Nerv Syst. 2020;36:49–58.

38. Eide PK, Bakken A. The baseline pressure of intracranial pressure (ICP) sensors can be altered by electrostatic discharges. Biomed Eng Online. 2011;10:76.

39. Pedersen SH, Lilja-Cyron A, Andresen M, Juhler M. The Relationship Between Intracranial Pressure and Age—Chasing Age-Related Reference Values. World Neurosurg [Internet]. Elsevier Inc; 2018;110:119–23. Available from: https://doi.org/10.1016/j.wneu.2017.10.086

40. Williams A, Coyne SM. Effects of neck position on intracranial pressure. Am J Crit Care. 1993;2:68–71.

41. Fleischman D, Berdahl JP, Zaydlarova J, Stinnett S, Fautsch MP, Allingham RR. Cerebrospinal Fluid Pressure Decreases with Older Age. PLoS One. 2012;7:1–9.

42. Riedel CS, Martinez-tejada I, Norager NH, Juhler M. B-waves are present in patients without intracranial pressure disturbances. 2020;517. Available from: file:///C:/Oel/Artikler/PhD - Mxa - 2.

package (clinmon)/Riedel et al. B-waves manuscript_sleep_research_vers3.1.pdf

43. Raboel PH, Bartek J, Andresen M, Bellander BM, Romner B. Intracranial pressure monitoring: Invasive versus non-invasive methods-A review. Crit Care Res Pract. 2012;2012:3–7.
44. Kawoos U, McCarron RM, Auker CR, Chavko M. Advances in intracranial pressure monitoring and its significance in managing traumatic brain injury. Int J Mol Sci. 2015;16:28979–97.
45. Andresen M, Juhler M. Intracranial pressure following complete removal of a small demarcated brain tumor: a model for normal intracranial pressure in humans. J Neurosurg [Internet]. 2014;121:797–801. Available from: http://thejns.org/doi/10.3171/2014.2.JNS132209
46. Petersen LG, Lawley JS, Lilja-Cyron A, Petersen JCGG, Howden EJ, Sarma S, et al. Lower body negative pressure to safely reduce intracranial pressure. J Physiol. England: Wiley Subscription Services, Inc; 2019;597:237–48.
47. Magnéli S, Howells T, Saiepour D, Nowinski D, Enblad P, Nilsson P. Telemetric intracranial pressure monitoring: a noninvasive method to follow up children with complex craniosynostoses. A case report. Child’s Nerv Syst [Internet]. Child’s Nervous System; 2016;32:1311–5. Available from: http://dx.doi.org/10.1007/s00381-016-3023-4
48. Norager NH, Lilja-cyron A, Bjarkam CR, Duus S, Juhler M. Telemetry in intracranial pressure monitoring : sensor survival and drift. Acta Neurochir (Wien). Acta Neurochirurgica; 2018;160:2137–44.
49. Norager NH, Lilja-Cyron A, Hansen TS, Juhler M. Deciding on Appropriate Telemetric Intracranial Pressure Monitoring System. World Neurosurg [Internet]. Elsevier Inc; 2019;126:564–9. Available from: https://doi.org/10.1016/j.wneu.2019.03.077
50. Antes S, Tschan CA, Heckelmann M, Breuskin D, Oertel J. Telemetric Intracranial Pressure Monitoring with the Raumedic Neurovent P-tel. World Neurosurg [Internet]. Elsevier Inc; 2016;91:133–48. Available from: http://dx.doi.org/10.1016/j.wneu.2016.03.096
51. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea syndrome. Arch Ophthalmol. 2000;118:1626–30.
52. Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Scand Suppl [Internet]. 1960;36:1–193. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13764297
53. Magnéli S, Howells T, Saiepour D, Nowinski D, Enblad P, Nilsson P. Telemetric intracranial pressure monitoring: a noninvasive method to follow up children with complex craniosynostoses. A case report. Child’s Nerv Syst. 2016;32:1311–5.
54. Petersen LG, Petersen JCG, Andresen M, Secher NH, Juhler M. Postural influence on intracranial and cerebral perfusion pressure in ambulatory neurosurgical patients. Am J Physiol - Regul Integr Comp Physiol [Internet]. 2016;310:R100–4. Available from: http://ajpregu.physiology.org/lookup/doi/10.1152/ajpregu.00302.2015
55. Lawley JS, Petersen LG, Howden EJ, Sarma S, Cornwell WK, Zhang R, et al. Effect of gravity and microgravity on intracranial pressure. J Physiol. 2017;595:2115–27.

56. Lundberg N. The mean ventricular fluid pressure. Acta Psychiatr Scand Suppl. 1960;36:1–193.
57. Chari A, Dasgupta D, Smedley A, Craven C, Dyson E, Matloob S, et al. Intraparenchymal intracranial pressure monitoring for hydrocephalus and cerebrospinal fluid disorders. Acta Neurochir (Wien) [Internet]. Acta Neurochirurgica; 2017;159:1967–78. Available from: http://link.springer.com/10.1007/s00701-017-3281-2
58. Langvatn EA, Frič R, Due-Tønnessen BJ, Eide PK. Intracranial volume versus static and pulsatile intracranial pressure values in children with craniosynostosis. J Neurosurg Pediatr. 2019;24:66–74.
59. Schwartz KM, Luetmer PH, Hunt CH, Kotsenas AL, Diehn FE, Eckel LJ, et al. Position-related variability of CSF opening pressure measurements. Am J Neuroradiol. 2013;34:904–7.
60. Lee MW, Vedanarayanan V V. Cerebrospinal fluid opening pressure in children: Experience in a controlled setting. Pediatr Neurol. 2011;45:238–40.
61. Kaiser AM, Whitelaw AGL. Normal cerebrospinal fluid pressure in the newborn. Neuropediatrics. 1986;17:100–2.
62. Kawasaki A, Purvin V. Unilateral optic disc edema following trabeculectomy. J Neuro-Ophthalmology. 1998;18:121–3.
63. González-Camarena PI, San-Juan D, González-Olhovich I, Rodríguez-Arévalo D, Lozano-Elizondo D, Trenado C, et al. Dynamic changes of the intraocular pressure and the pressure of cerebrospinal fluid in nonglaucomatous neurological patients. Acta Ophthalmol. 2017;95:e138–43.
64. Avery RA, Shah SS, Licht DJ, Seiden JA, Huh JW, Boswinkel J, et al. Reference range for cerebrospinal fluid opening pressure in children. N. Engl. J. Med. 2010. p. 891–3.
65. Sugita Y, Iijima S, Teshima Y, Shimizu T, Nishimura N, Tsutsumi T, et al. Marked episodic elevation of cerebrospinal fluid pressure during nocturnal sleep in patients with sleep apnea hypersomnia syndrome. Electroencephalogr Clin Neurophysiol. 1985;60:214–9.
66. Wibroe EA, Yri HM, Jensen RH, Wibroe MA, Hamann S. Osmolality of cerebrospinal fluid from patients with idiopathic intracranial hypertension (IIH). PLoS One. 2016;11:e0146793.
67. Beck J, Fung C, Ulrich CT, Fiechter M, Fichtner J, Mattle HP, et al. Cerebrospinal fluid outflow resistance as a diagnostic marker of spontaneous cerebrospinal fluid leakage. J Neurosurg Spine. 2017;27:227–34.
68. Bono F, Lupo MR, Lavano A, Mangone L, Fera F, Pardatscher K, et al. Cerebral MR venography of transverse sinuses in subjects with normal CSF pressure. Neurology. 2003;61:1267–70.
69. Gulbrandsen P, Dietrichs E. Cerebrospinal fluid opening pressure measurements in acute headache patients and in patients with either chronic or no pain. 2010;122:6–11.
70. Avery RA. Interpretation of lumbar puncture opening pressure measurements in children. J Neuro-Ophthalmology. 2014;284–7.
71. Friden HG, Ekstedt J. Volume/pressure relationship of the cerebrospinal space in humans. Neurosurgery. 1983;13:351–66.

72. Blomquist HK, Sundin S, Ekstedt J. Cerebrospinal fluid hydrodynamic studies in children. J Neurol Neurosurg Psychiatry. 1986;49:536–48.
73. Hulme A, Cooper R. The Effects of Head Position and Jugular Vein Compression (JVC) on Intracranial Pressure (ICP). A Clinical Study. Intracranial Press III. 1976. p. 259–63.
74. Lipe HP, Mitchell PH. Positioning the patient with intracranial hypertension: how turning and head rotation affect the internal jugular vein. Heart Lung. 1980;9:1031–7.
75. Holmlund P, Eklund A, Koskinen LOD, Johansson E, Sundström N, Malm J, et al. Venous collapse regulates intracranial pressure in upright body positions. Am J Physiol - Regul Integr Comp Physiol. 2018;

Figures

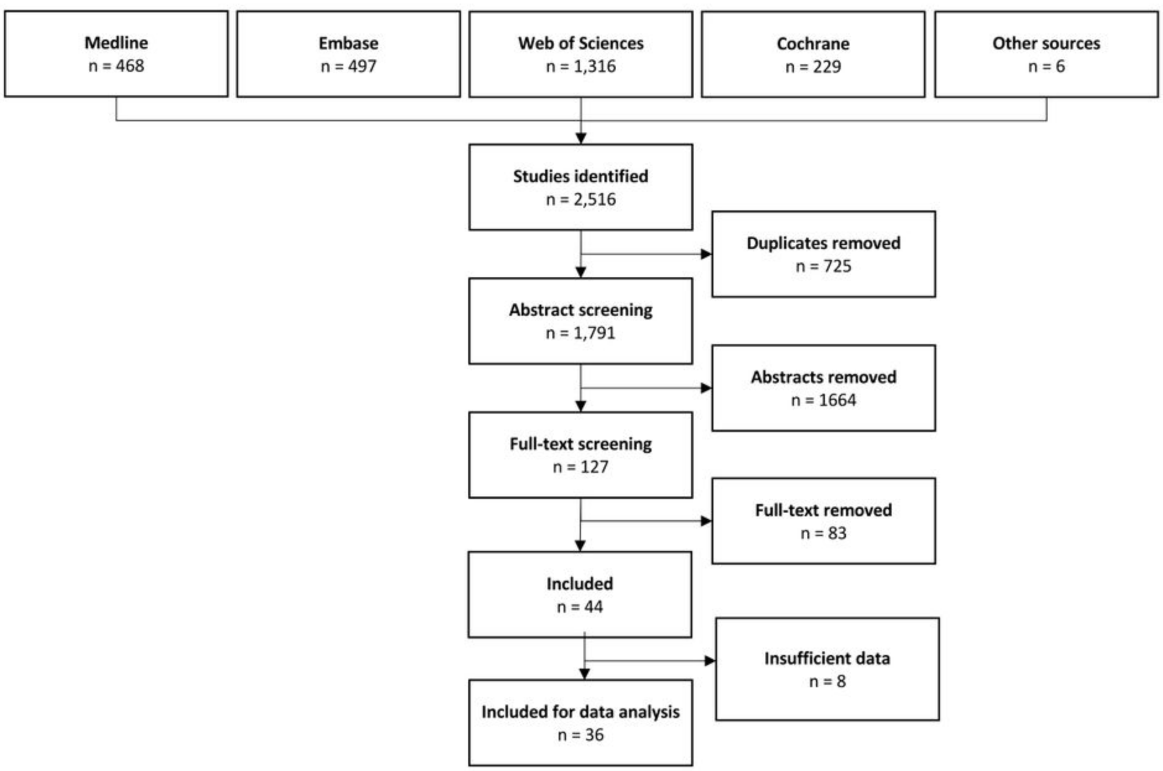

Figure 1

Flowchart of study selection process The section “insufficient data” covers that these studies did not report sufficient statistical data to be included in statistical analysis. Thus, no standard deviations,

confidence intervals or reference intervals were reported in these studies. The included articles “Other sources” were found by manual searching the reference list of included studies.

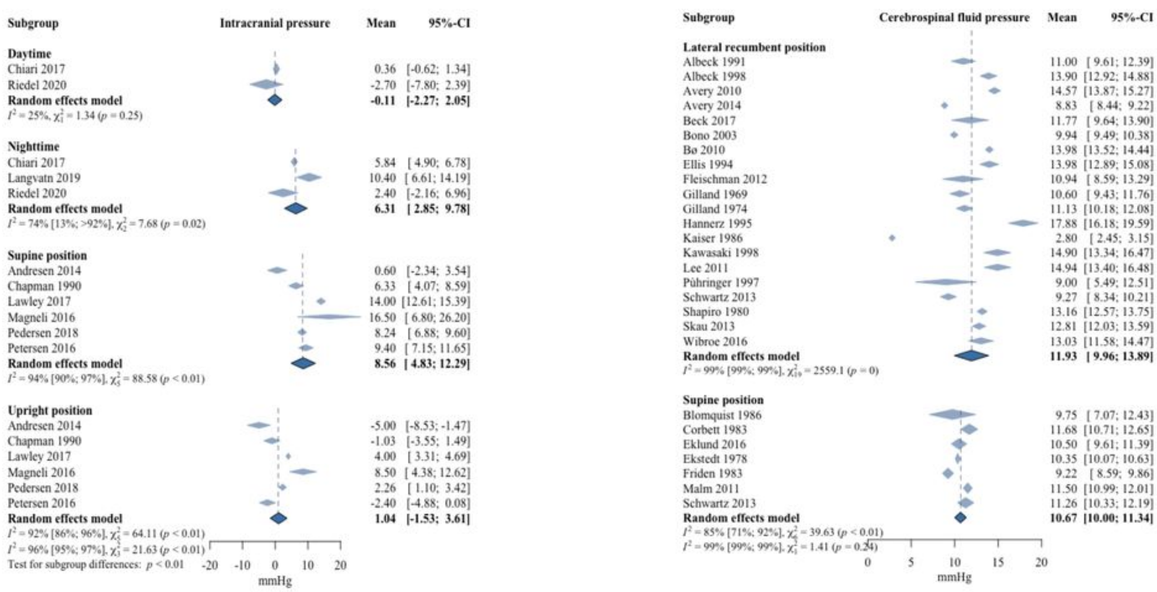

Figure 2

Forest plot of lumbar cerebrospinal fluid pressure and intracranial pressure Two forest plots describing the weighed average of lumbar cerebrospinal fluid pressure (LCSFop) and intracranial pressure (ICP) reported in each included study. The LCSFop is presented to the left, and grouped into different body positions: lateral recumbent position and supine position. ICP is presented to the right, and also subgrouped into different body positions: daytime, nighttime, supine and upright position.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1PRISMAchecklist.doc
- Appendix2Searchstrategy.docx
- Appendix3QualityAssessment.docx