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Intracranial pressure and outcome in critically ill patients with aneurysmal subarachnoid hemorrhage: a systematic review

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UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de Neurosciences Cliniques
Service de Neurochirurgie

Intracranial pressure and outcome in critically ill patients with aneurysmal subarachnoid hemorrhage: a systematic review

THESE

préparée sous la direction du Professeur Roy T. DANIEL
(avec la co-direction du Professeur Mauro ODDO
et la collaboration du Dr. Mahmoud MESSERER ,
du Professeur Marc LEVIVIER et du Professeur Nino STOCCHETTI)

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Intracranial pressure and outcome in critically ill patients with aneurysmal subarachnoid hemorrhage: a systematic review

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Corrélation entre la mesure de la pression intracrânienne et le pronostic fonctionnel chez les patients victimes d'une hémorragie sous-arachnoïdienne post rupture anévrismale :
Revue systématique de la littérature.

L'objectif de ce travail est d'évaluer si la mesure de la pression intracrânienne (PIC), à l'aide d'un capteur intraparenchymateux ou intraventriculaire, est prédictive d'un pronostic fonctionnel ou d'un risque de mortalité plus important chez les patients victimes d'une hémorragie sous-arachnoïdienne post rupture anévrismale (HSAa).

Dans la prise en charge aigue de ces patients aux unités de soins intensifs, le neuromonitoring avec la mise en place d'un capteur intraparenchymateux ou intraventriculaire pour la mesure de la PIC n'est pas standardisé et la décision de neuro monitorer ces patients dépend du praticien et des centres.

Pour essayer à répondre à cette question de l'utilité de ce neuromonitoring, on a réalisé une revue systématique de la littérature en utilisant les bases de donnés PubMed, Cochrane et ClinicalTrials.gov en accord avec les critères PRISMA. Nos critères d'inclusion sont les études ayant inclus des patients adultes avec HSAa et qui ont bénéficié d'une mesure de PIC par capteur intraparenchymateux ou intraventriculaire. On a évalué le pronostic fonctionnel, les complications ischémiques au niveau cérébral et la mortalité associée à l'HSA selon les valeurs de la PIC. On a exclu toutes les études incluant une population pédiatrique ou sans monitorage de la PIC par les méthodes citées. La qualité des évidences de nos différentes conclusions a été évaluée selon le système GRADE.

Vingt-six articles ont été inclus.
Une corrélation a été démontrée entre les valeurs de PIC élevées et le taux de mortalité après HSAa. Toutefois les valeurs absolues de la PIC ne sont pas des valeurs prédictives indépendantes du pronostic fonctionnel à long terme (qualité d'évidence basse).
Une relation faible a été trouvée entre les valeurs de PIC et les complications ischémiques cérébrales par vasospasme (qualité d'évidence très basse). Les valeurs dérivées de la PIC ont une valeur supérieure que les valeurs absolues de la PIC dans la prédiction de la récupération fonctionnelle (qualité d'évidence modérée).

En raison de l'absence de conclusions de haute qualité d'évidence définissant la relation entre la PIC et le pronostic fonctionnel des patients avec HSAa, des études ultérieures prospectives et randomisées sont nécessaire pour démontrer l'intérêt du monitorage de la pression intracrânienne et ses implications cliniques.
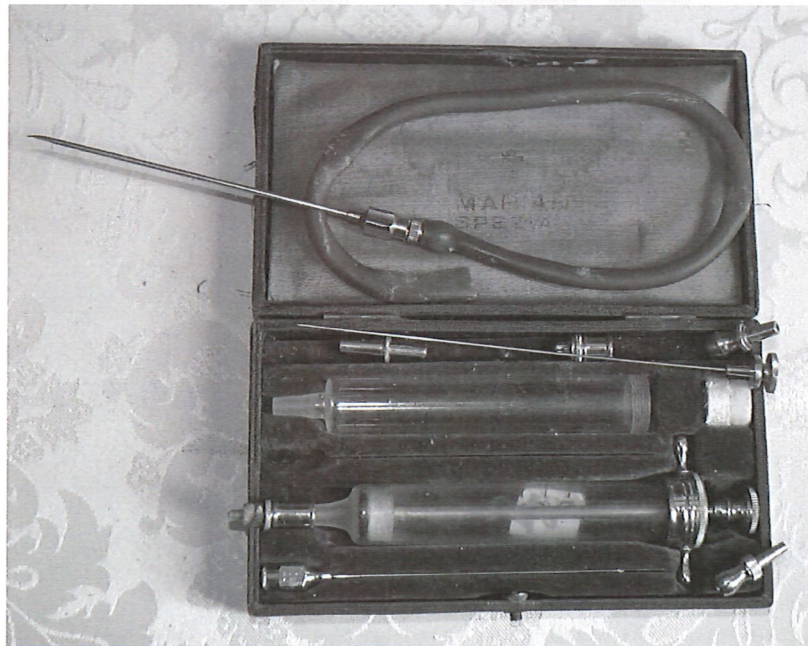
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REVIEW

Intracranial pressure and outcome in critically ill patients with aneurysmal subarachnoid hemorrhage: a systematic review

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ABSTRACT

BACKGROUND: Evidences supporting the use of intracranial pressure (ICP) monitoring after aneurysmal subarachnoid hemorrhage (aSAH) are limited. The aim of our paper was to examine whether elevated intracranial pressure and ICP-derived variables predict mortality and functional outcomes after aSAH.
EVIDENCE ACQUISITION: A systematic review of the literature was performed through PubMed and Cochrane databases up to June 2015. Population was restricted to aSAH patients requiring admission to the intensive care unit. ICP was included in the analysis as absolute value as well as variables derived from ICP monitoring (pressure reactivity index, ICP pulse wave amplitude, ICP-arterial blood pressure wave amplitude correlation and ICP variability). Outcomes included mortality, neurological recovery and delayed cerebral ischemia (DCI). Quality of evidence was rated using the GRADE system.
EVIDENCE SYNTHESIS: Twenty-six studies were examined. Due to heterogeneity in qualifying studies, a meta-analysis could not be generated. We found a correlation between elevated ICP and mortality. However, ICP absolute values were not independent predictors of long-term functional outcomes (low quality of evidence). A variable relationship between elevated ICP and DCI was found (very low quality of evidence). ICP-derived variables had higher accuracy than ICP absolute values in predicting functional outcomes (moderate quality of evidence).
CONCLUSIONS: Elevated ICP was associated with higher mortality however absolute ICP values *per se* were not independent predictors of functional recovery. Variables derived from ICP monitoring are more accurate than ICP absolute values in predicting outcome. Given the absence of good quality data, additional large studies may help to better define the prognostic value of ICP after aSAH.

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Key words: Subarachnoid hemorrhage - Brain ischemia - Intracranial pressure - Neurophysiological monitoring - Mortality.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a critical condition, accounting for 5% of all strokes.[1] Despite recent advances in surgical and endovascular techniques and improved peri-operative management protocols, aSAH remains a life-threatening disease

with a variable case mortality of 7-36%[2-4] and significant disability among survivors.[5-7]

In the past, poor-grade patients were mostly treated conservatively. Further studies showed that early aggressive management might improve final prognosis.[8-10] Outcome after aSAH is determined by early brain injury (EBI),[11-13] secondary insults and delayed brain injury, namely delayed cerebral ischemia (DCI),[14] which may be potentially preventable and treatable with individualized targeted therapies in the intensive care unit (ICU).

Clinical assessment of neurological deterioration may not always be reliable, particularly in comatose and/or sedated patients. An early aggressive management through the use of invasive neuromonitoring techniques might help to understand the physiology of the injured brain, to guide therapy and to potentially improve functional outcome after aSAH.

Guidelines for the use of ICP monitoring have been established principally in patients with severe traumatic brain injury (TBI), with values superior to 20 mmHg predicting a worse outcome.[15] However the value of ICP monitoring has been questioned by recent studies.[16-18]

The ICP cut off found in TBI patients is assumed to be valid also in aSAH patients. Early elevation of ICP, with profound reduction of cerebral perfusion pressure (CPP), is in fact common after SAH and may impair cerebral blood flow (CBF).[19, 20] Further ICP elevations may be due to acute hydrocephalus[21] and to brain edema.[22] However, evidence to support the use of ICP monitoring after aSAH is limited and there is considerable variability in its clinical application. More importantly, whether ICP predicts prognosis in this setting is unclear. Previous studies provided conflicting results and focused on particular aspects of ICP monitoring after aSAH. For this reason, we conducted a systematic review of the literature to examine the association of ICP with several outcome endpoints, including DCI, mortality and functional recovery. We restricted our analysis to critically ill patients with aSAH and specifically examined the association with outcome of: a) absolute ICP value and b) ICP-derived variables, such as the Pressure Reac-

tivity Index (PRx), the ICP waveform amplitude (ICPWA), the ICP-ABP wave amplitude correlation (IAAC), and the ICP variability.

Evidence acquistion

This systematic review was conducted according to the PRISMA criteria.[23]

Search strategy

Literature search was performed in duplicate by GC and MM using PubMed platform through Medline database and including literature from January 1970 up to June 2015. The search was conducted using the MeSH terms "subarachnoid hemorrhage" AND "intracranial pressure". The additional filter of "Human" species was used to eliminate preclinical studies. This same search was also performed through Cochrane database and in ClinicalTrials.gov. A secondary search in PubMed with the terms "pressure reactivity index PRx" (free text) alone or coupled with "subarachnoid hemorrhage" (free text) was then performed.

Additional relevant studies were also searched in reference lists of identified studies manually and by using the "related articles" tool in PubMed. Articles already included in the primary search and duplicate studies were eliminated.

No unpublished data or congress presentations were considered.

Study selection

Three authors (GC, MM and MO) reviewed independently the abstracts, full text articles and citations to select pertinent studies.

The search was focused on whether the assessment of ICP/ICP derived variables could help in the stratification of long-term prognosis in poor grade aSAH patients. A P.I.C.O. question was formulated to guide the literature selection. Population was defined as ICU patients with confirmed aSAH. Intervention was real-time ICP monitoring through any invasive device, including intra-ventricular, intra-parenchymal, subarachnoid, subdural or epidural

probes, isolated or coupled with an external ventricular drain (EVD). Non-invasive assessment of ICP was not considered. Control was no ICP monitoring or any other type of monitoring. Studies not having a control group were also considered. Outcome included delayed cerebral ischemia/infarction, mortality and functional neurological recovery (from 3-6 months to 1 year), assessed through the Glasgow Outcome Scale (GOS), the modified Rankin Scale (mRS), the National Institutes of Health Stroke Scale (NIHSS) and the Short Form 36 Health Survey (SF-36). In many articles the outcome was dichotomized into good or favorable outcome and poor or unfavorable outcome. Table I illustrates the dichotomized outcome based on GOS and mRS scores.

Reviews, case reports, preclinical studies and pediatric trials were excluded. Randomized controlled trials comparing ICP to variables derived from other types of neuromonitoring techniques were preferred but also prospective or retrospective studies were considered and included if pertinent. We did

not evaluate the various therapeutic options to treat elevated ICP nor the clinical implications of each therapeutic strategy. Studies not in English, French, German, Italian or Spanish were not considered.

In case of disagreement about the inclusion of a study, this was discussed and considered eligible only if a consensus from the three examiners was reached.

Assessment of methodological quality

The methodological quality of selected articles was evaluated without masking the source of authorship. Data were extracted independently and summarized. The GRADE system was used to assess the benefit/risk balance of each intervention and thus the quality of evidence of each statement.[24] The quality of evidence was classified as high (grade A), moderate (grade B), low (grade C), or very low (grade D) (Table II).[25] Divergent opinions were discussed until a unanimous opinion was obtained from all authors.

TABLE I.—*Correspondence between the dichotomized outcome and GOS/mRS scores.*

Outcome		GOS		mRS
GOOD	1	Good recovery	0	Asymptomatic
			1	No significant disability, independent
			2	Slight disability
	2	Moderate disability (disabled but independent)	3	Moderate disability (able to walk unassisted)
POOR	3	Severe disability (conscious but disabled and needing assistance with activities of daily living)	4	Moderately severe disability (assistance for daily life activities and unable to walk unassisted)
	4	Vegetative state	5	Severe disability (constant nursing care)
	5	Death	6	Death

GOS: Glasgow Outcome Scale; mRS: modified Rankin Scale.

TABLE II.—*Definition of the quality of evidence according to the GRADE system.*

Quality of evidence	Definition	Type of studies
High (grade A)	Further researches are unlikely to change our confidence in the estimate of effect	RCTs
Moderate (grade B)	Further research is unlikely to have an important impact on our confidence in the estimate of effect and may change the estimate	RCTs with serious limitations or important inconsistencies, uncertainties about directions, imprecise data or bias.
Low (grade C)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	Observational studies
Very low (grade D)	Any estimate of the effect is very uncertain	Other evidence such as expert consensus or observational studies with consistent limitations

Modified from Atkins et al.[25]

Evidence synthesis

Results of the literature search

The flow chart in Figure 1 describes our literature search. A total of 475 articles were identified by our primary search in PubMed. After exclusion of 233 articles (not clinical studies or in foreign languages), 242 articles were screened on the basis of title and abstract. Among them, 221 articles were excluded because not focused on our pre-defined endpoints (P.I.C.O.). Twenty-one articles were further assessed for eligibility. One study was selected through our secondary search in PubMed, one article was eligible from the Cochrane research and three related articles were identified, for a total of 26 studies included in the final analy-sis. No further eligible articles were identified through the ClinicalTrials.gov search.

The majority of the studies were retrospective[26-42] or prospective[43-47] single-center studies. No multicenter studies were identified. Four studies were randomized controlled trials (RCT)[48-51] conducted in ICU patients with aSAH to compare the efficacy of invasive ICP to predict prognosis (mortality, DCI or functional outcome). Due to the marked heterogeneity in qualifying studies, a meta-analysis could not be generated.

Patient population

Five studies enrolled exclusively poor-grade patients (Hunt and Hess grade 4-5 or WFNS Scale 4-5)[38, 40, 45, 47, 51] while the oth-
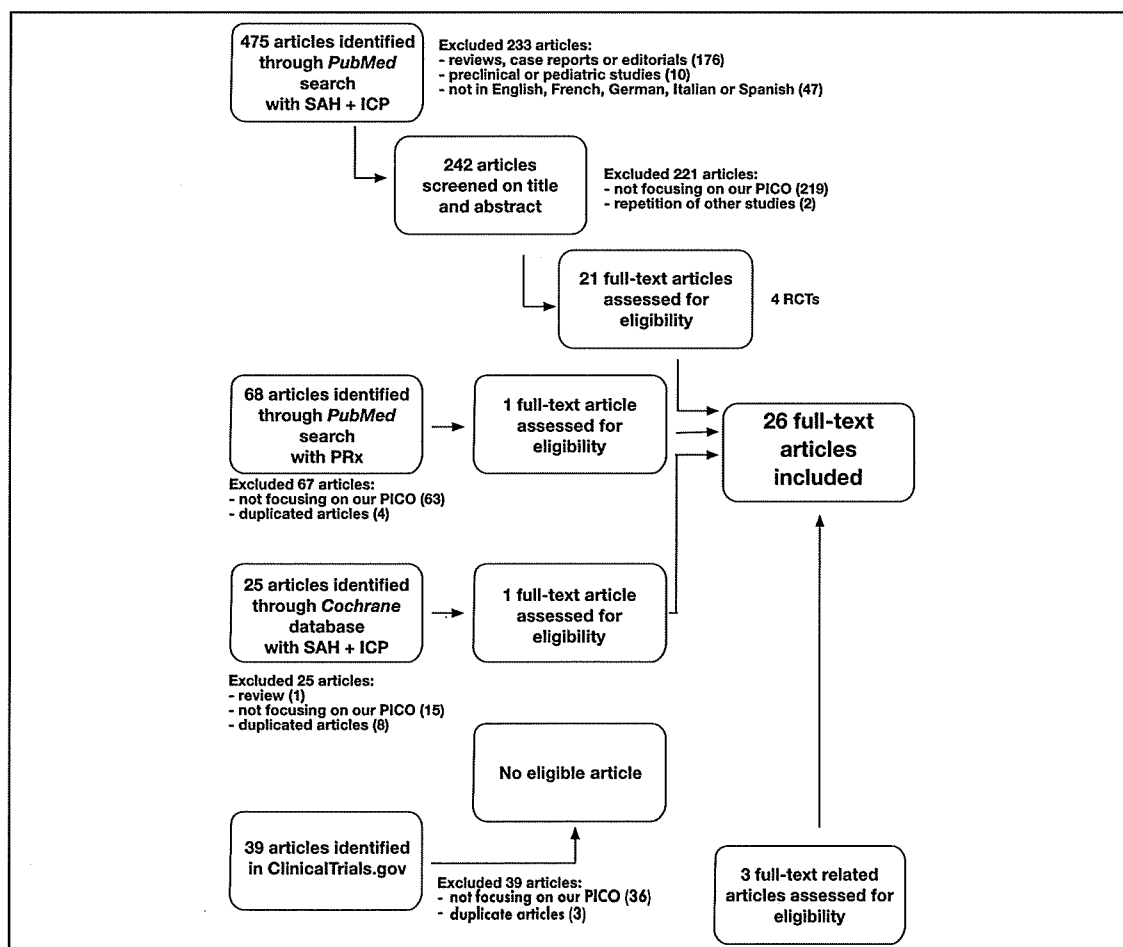

Figure 1.—Flow chart showing the literature search and the process of articles' selection.

ers considered a miscellaneous population in terms of clinical and radiological presentation.[26-37, 39, 41-44, 46, 48-50]

Type and duration of monitoring

The type of ICP probe used was heterogeneous across the studies. Nine studies reported the use of intra-ventricular probes, [29-31, 35, 42-44, 48, 51] 8 studies used intra-parenchymal probes,[36, 39-41, 46, 47, 49, 50] 4 studies used both.[27, 37, 38, 45] One study used intra-ventricular or subdural probes,[26] 2 studies only subdural [32, 33] and 2 studies only epidural probes.[28, 34]

The duration of monitoring also varied widely, but it was generally on average of four days.[26, 27, 31, 37, 39, 45] More severe patients had a longer monitoring [44] and generally ICP probes were removed after 24 hours of ICP less than or equal to 20mmHg without any ICP treatment.[26, 27]

Monitoring technique

Studies eligible for the analysis were classified into four groups:
— ICP as absolute value;
— comparison between ICP-targeted therapy and continuous cerebro-spinal fluid (CSF) drainage through an EVD;
— variables derived from the analysis of the ICP monitoring curve (PRx, ICPWA, IAAC, ICP variability);
— comparison between ICP monitoring alone and ICP monitoring coupled with multimodal monitoring (MMM), including brain tissue oxygen and/or cerebral microdialysis.

ICP AS ABSOLUTE VALUE

Twelve studies examined the predictive value of ICP in aSAH patients.[26-32,34,35,42,43,52] All studies except one [43] were retrospective. Five studies had no control group,[26-29, 42] while the other seven used the CPP monitoring and/or the trans-cranial doppler monitoring as terms of comparison.[30, 32, 34, 35, 43, 52] The outcome evaluation was different among the studies: the Glasgow Coma Scale (GCS),[27] the GOS,[26-28, 30, 31, 43] the mRS,[35] the NI-HSS,[33] the SF-36,[43] DCI incidence,[27, 29, 32-35] were alternatively used. Different thresholds for the definition of elevated ICP were used, varying from >20 mmHg,[26, 27, 32, 33, 35] >25 mmHg,[29-31] >30 mmHg,[28, 33, 42] up to >40mmHg (Table III).[33]

The main findings of these studies are as follows:
— poor-grade patients are more likely to have elevated ICP values on admission. Elevated ICP is associated with EBI development [27, 29, 36] and mortality.[27, 36, 43] (Low quality of evidence – grade C);
— a variable correlation between elevated ICP and vasospasm / DCI incidence was showed.[27, 32, 34, 42, 52] (Very low quality of evidence – grade D);
— increased ICP was associated with worse prognosis in univariate analysis (including post-operative GCS and long-term GOS),[27, 29-31, 43] but ICP values were not independent predictors of long-term functional outcome in the multivariate analysis in all studies analyzed,[26, 27, 31] except in one.[35] (Low quality of evidence – grade C);
— elevated ICP refractory to therapeutic measures (defined as ICP persistently > 20mmHg and not responsive to standardized treatment protocols) was associated with worse functional outcomes.[27] (Low quality of evidence – grade C).

ICP COUPLED TO AN EXTERNAL VENTRICULAR DRAINAGE

Two studies [44, 48] investigated the benefit of an intermittent CSF drainage on the basis of the ICP values *versus* a strategy of continuously open EVD in terms of reduction of DCI incidence. Kim *et al.* [44] conducted a prospective pilot study, while the study of Olson *et al.* [48] was a RCT prematurely interrupted because of the higher rate of complications in the open EVD group. No differences in outcome (DCI) were recorded between the two groups but the statistical power was weak. (Very low quality of evidence – grade D) (Table IV).

ICP-DERIVED VARIABLES

Six studies fitted the inclusion criteria and they examined the value of the PRx,[37, 38] the ICPWA,[36, 49] the IAAC [50] or the variability of ICP values in different timescales.[39] They consisted of two RCTs [49, 50] and four retrospective studies.[36-39] Early GCS,[36, 49, 50] long-term functional recovery including GOS [36, 37, 39] or mRS,[38, 49, 50] mortality [38, 39] and DCI [38, 39, 50] were the outcome endpoints evaluated (Table V).

PRx.—PRx is an index of the state of cerebral autoregulation and is calculated using the on-line Pearson's linear correlation coefficient between the ICP and the mean arterial pressure.[53, 54] A negative PRx or a PRx close to 0 defines normal autoregulation, while a positive PRx (threshold of PRx >0.2) is a marker of impaired cerebro-vascular pressure reactivity.[53, 54] Two studies found that negative values of PRx (indicating preserved cerebro-vascular reactivity) were associated with a higher likelihood of survival and better functional outcome (GOS and mRS).[37, 38] (Low quality of evidence – grade C).

ICPWA.—Intracranial compliance can be estimated by analyzing the ICP wave shape and amplitude (ICPWA). This method showed to be superior to the simple follow-up of ICP absolute values. A low ICPWA was associated with a better functional outcome, including mRS or GOS.[35,48] (Moderate quality of evidence– grade B).

IAAC.—The IAAC is an indirect measure of cerebrovascular pressure reactivity, estimated by the Pearson correlation coefficient between corresponding amplitudes of ICP and ABP waves, as illustrated by Eide *et al.*[50] The IAAC was significantly associated with 12-month GOS and allowed the distinction between the various functional classes, better than PRx.[59] (Moderate quality of evidence – grade B).

Variability of ICP values.—The follow-up of ICP variability may be superior to mean

ICP for predicting 6-month survival and GOS. A higher faster variability (5-seconds and 5-minutes ICP variability) was associated to a favorable prognosis, while greater 24-hour variability was related to a poorer outcome.[38] (Low quality of evidence – grade C).

Of note, none of the ICP-derived variables tested were predictive of DCI.[38, 39, 50] (Moderate quality of evidence – grade B)

ICP COUPLED WITH MMM DERIVED VARIABLES

ICP and CPP monitoring can be coupled with MMM techniques, mainly brain tissue oxygen partial pressure ($PbtO_2$) probes and cerebral microdialysis. Six studies considering a MMM were included in this group: one RCT,[51] three prospective [45-47] and two retrospective studies.[40, 41]

Overall, the results of these studies were concordant in showing that increased ICP/CPP values are not correlated with early hypoxic events and/or with metabolic compromise. Cerebral hypoxia and ischemia may still occur despite normal ICP or CPP values and remain undetected with isolated ICP monitoring.[46, 47] Metabolic changes are related to mortality,[45, 46] DCI [40] and functional outcomes [47, 51] and may occur before an increase in ICP occurs.[40, 46, 47]

Discussion

Data on the prognostic value of ICP in critically ill SAH patients are limited, even if intracranial hypertension after aSAH has been described more than 40 years ago.[55] The utility of ICP for the management of comatose aSAH patients has not been proven yet and there are no precise recommendations in the literature concerning the type and the duration of monitoring and the threshold for therapeutic interventions. In many centers, ICP monitoring is used in aSAH patients according to the experience accumulated in TBI.

Immediately after the bleeding, experimental models showed how ICP rise may be extremely sudden and coupled with a decline in CPP, local CBF and $PbtO_2$.[56] Similarly, in-

TABLE III.—*Association of intracranial pressure (ICP) as absolute value with aSAH prognosis.*

Reference	N pts	Study design	H&H or WFNS and Fisher grade	Monitoring tecnique and duration	Comparison
Zoerle T, Crit Care 2015 [26]	116	R	57% WFNS 4-5 73% Fisher 3, 25% Fisher 4	ICP, IV or SD probe median 5d	None
Heuer GG, J. Neurosurg 2004 [27]	433	R	36% H&H 4-5	ICP, IV or IP probe >3d monitoring	None
Soehle M, Acta Neurochir 2007 [43]	18	P	41% WFNS and H&H 4-5	ICP, IV probe	TCD-derived PI and RI
Takeuchi S, Neurosurgery 1989 [28]	55	R	18% H&H 4 38% Fisher 3 18% Fisher 4	ICP, EPI probe Average 8d	None
Voldby B, J Neurosurg 1982 Part 1 [29]	52	R	38% H&H 3-5	ICP, IV probe Average 8d	None
Enblad P, JNNP 1997 [30]	61	R	75% H&H 4-5 88% Fisher 4	ICP, IV probe 1w monitoring	CPP
Ryttlefors M, Neurosurgery 2007 [31]	99	R	69% H&H 4-5 76% Fisher 4	ICP, IV probe >5d monitoring	CPP
Fukuhara T, Neurol Med Chir 1998 [32]	11	R	18% H&H 4-5	ICP, SD probe >7d monitoring	CPP
Karnchanapandh K, Acta Neurochir suppl. 2012 [33]	30	R	30% H&H 4	ICP, SD probe Average 8d monitoring	CPP
Klingelhöfer J, J. Neurol Sci 1996 [34]	32	R	44% H&H 4	ICP, EPI probe Duration ns	CBF RI
Jabbarli R, Eur J Neurol 2014 [35]	423	R	One third H&H 4-5 80% Fisher 3-4	ICP, IV probe Duration ns	None
Hase U, Acta Neurochir 1978 [42]	21	R	52% H&H 4-5	ICP, IV probe	None

CBF: cerebral blood flow; d: days; DCI: delayed cerebral ischemia; EBI: early brain injury; EPI: epidural; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Score; H&H: Hunt-Hess SAH classification; IP: intra-parenchymal; IV: intra-ventricular; MA: multivariate analysis; Min: minimum; Mo: months; MFV: mean flow velocity; NA: not available; NIHSS: National Institute of Health Stroke Score; P: prospective; PI: Pulsatility Index; postop: postoperative; pts: patients; R: retrospective; RI: Resistance Index; SA: subarachnoid; SD: subdural; TCD: Transcranial Doppler; TT: treatment; UA: Univariate analysis.

creased ICP is common during the first hours after aSAH, especially in patients with higher Hunt and Hess grades.[29, 33, 57] After the acute phase, various secondary mechanisms may contribute to ICP elevation: CSF dynamics disturbances, vasospasm/DCI, intra-ventricular and intra-parenchymal hemorrhage, expansion of hematoma, together with brain edema and epileptic seizures, may all impact ICP.[29, 32, 58, 59]

The relationship between ICP and aSAH prognosis remains unclear. Intuitively intracranial hypertension is related to poorer clini-

Statistical analysis	Outcome	Length of follow-up	Findings
UA MA	EBI/mortality GOS	6mo	ICP (>20 mmHg) was associated with 6-mo outcome in UA but not in MA. Elevated ICP associated with EBI and mortality
UA MA	GCS/GOS vasospasm	Postop/6mo	ICP (>20 mmHg) was associated with 6-mo GOS on UA but not in MA. No association between ICP and vasospasm Refractory ICP (>20 mmHg and not responsive to TT) had a stronger association with mortality and poor outcome. Not considered by MA
UA	GOS SF-36	1y	ICP was linearly correlated with 1-y outcome ICP not included as variable in UA
None	GOS	3mo	Average daily ICP >30 mmHg was associated with poor outcome in half of the patients
None	Clinical deterioration DCI	15d	ICP (>25 mmHg) was associated with poor 15-days outcome Higher ICP observed with severe vasospasm before angiographic evidence
UA MA	GOS	14mo	ICP (>25 mmHg) was an independent predictor of outcome
UA MA	CCO/GOS	Discharge/ 6mo	On MA, ICP (>25 mmHg) was associated with outcome at hospital discharge but not with 6-mo GOS
UA	DCI	9d	ICP >20 mmHg was associated with more severe, prolonged and diffuse vasospasm
UA	DCI NIHSS	3mo	Elevated ICP (>20, 30 or 40 mmHg) was not associated with DCI or outcome
UA	DCI	NA	Elevated ICP (cut-off not specified) was correlated with irreversible DCI
UA MA	EBI mortality mRS	6mo	ICP (>20 mmHg) was a strong predictor of EBI. ICP elevation associated with unfavourable mRS and in-hospital mortality
UA	H&H mortality DCI	NA	Average daily ICP >30 mmHg was associated with clinical deterioration and mortality No association between ICP and vasospasm

cal outcomes and ICP may be helpful in the acute period to detect and manage early complications. However, Zoerle et al. [26] recently showed how despite elevated ICP was associated with increased 6-months mortality, it was not an independent predictor of long-term functional outcome on multivariate analysis.

The same findings were previously reported by Heuer et al.,[27] which showed that an increased ICP was not an independent predictor of GOS at 6 months. Finally, Ryttlefors et al. [31] found an association of ICP with clinical de-

TABLE IV.—*Comparison between ICP-targeted and open external ventricular drain (EVD)-targeted therapy to predict aSAH prognosis.*

Reference	N pts	Study design	H&H or WFNS and Fisher grade	Monitoring technique and duration	Comparison	Outcome	Length of follow-up	Findings
Olson DM, J Neurosurg 2013[48]	60	Unblinded RCT	Median HH 3 and Fisher 3	ICP, IV probe duration ns	Open-EVD	DCI/ mortality/ mRS	Hospital discharge (14d)	No difference in terms of DCI between the two groups. Open EVD group had a greater rate of complications. No intergroup differences for mortality/mRS
Kim GS, Neurocrit Care 2011[44]	37	P	Median HH and Fisher 3	ICP, IV probe duration ns	Open-EVD	DCI/mRS	Hospital discharge	No difference in vasospasm. No difference in mRS at discharge

EVD: external ventricular drain; H&H: Hunt-Hess SAH classification; IV: intra-ventricular; mRS: modified Rankin Scale; ns: not specified; P: prospective; Pts: patients; RCT: Randomized control trial.

terioration at hospital discharge but not with long-term functional outcome. The only study which found an independent association between high ICP and worse 6-month functional outcome using multivariate analysis was the study conducted by Jabbarli et al.[35]

In fact, many pathological mechanisms other than elevated ICP may have an impact on the long-term prognosis. It is therefore not totally unexpected that ICP represents only one component of the complex clinical course after aSAH. This hypothesis is supported by studies considering ICP in association with MMM derived variables: while elevated ICP may reflect altered cerebral metabolism and regional ischemia,[60] low $PbtO_2$ and abnormal brain metabolism (namely elevated cerebral microdialysis lactate/pyruvate ratio) might occur in an early phase and despite normal ICP values.[40, 46, 51, 61]

When considering DCI incidence, its relationship with elevated ICP is complex. Ischemic brain damage may be associated with a secondary ICP rise, due to cellular edema and increased intracranial volume. However water accumulation requires time, and its effect on ICP may depend on several factors, including intracranial compliance and the extent of brain ischemic volume. This may explain why ICP was not found overall to be accurate to detect DCI.

Finally, looking at variables derived from ICP monitoring, Bijlenga et al.[38] found that preserved PRx was predictive for survival and mRS at 3 months. This was in line with data from Rasulo et al.[37] showing a correlation between PRx and GOS at 6 months. Eide et al.[49, 50] used the ICPWA and the IAAC and these variables were more accurate to predict long-term functional outcome than ICP absolute values or the PRx. Altogether these studies suggest that data derived from ICP monitoring and ICP curve analysis may be more informative than absolute ICP values alone. This information may also be useful to better target cerebral perfusion individually given the poor value of CPP alone in predicting long-term outcome in many of the studies analyzed.[32, 33, 36] Larger and multicenter studies are necessary to examine the additive value of these derived variables.

Limitations of the study

Some biases in the literature research and article selection should be considered: studies in languages other than English, French, German, Italian or Spanish were not further analyzed.

The included studies were heterogeneous in terms of population examined (Hunt and Hess and Fisher grade), type and duration of elevated ICP and ICP-derived variables considered, control group (often absent), outcomes

TABLE V.—*Association of different ICP-derived variables with aSAH prognosis.*

Reference	N pts	Study design	H&H or WFNS and Fisher grade	Monitoring technique and duration	Comparison	Statistical analysis	Outcome	Length of follow-up	Findings
Eide PK, Acta neurochir 2006 [36]	27	R	18 H&H 4-5 15 Fisher 4	ICP, IP probe Duration 1-6d	ICPWA/ CPP	UA	GCS/GOS	1-6 d/6mo	ICPWA was associated to GCS and GOS. Mean ICP higher in non-survivors but not a good discriminant among functional classes. CPP was not predictive of outcome.
Eide PK, Neurosurgery 2011 [49]	97	RCT	46 H&H 4-5 90 Fisher 4	ICP, IP probe Duration 1-3w	ICPWA	UA	GCS/mRS	1-3w/ 12mo	Better GCS in the ICPWA group. RSS was better in ICPWA group. The 12mo RSS correlated with mean ICP and MWA at week 1.
Eide PK, J Neurosurg 2012 [50]	25	RCT	Same as Eide PK, 2011	PRx, IP probe Duration 1w	IAAC	UA	GCS/mortality mRS/DCI	1w/ 12mo	IAAC but not PRx, was associated with early GCS. PRx and IAAC higher in pts who died. IAAC distinguished RSS categories at 12mo. Mortality was 3x in patients with IAAC >0.2. No difference for vasospasm.
Rasulo FA, J neurosurg anesthesiol 2012 [37]	29	R	Various WFNS, Median Fisher 3	PRx, IV or IP probe Mean duration 4-5d	CPP	UA MA	GOS	6mo	PRx associated with 6mo GOS on MA. PRx was useful to target "optimal" CPP
Bijlenga P, Neurocrit Care 2010 [38]	42	R	WFNS 4-5	PRx, IV or IP probe 2-24d monitoring	CPP	UA	DCI/mortality/mRS	3mo	Negative values of PRx in the first 48h were correlated with survival. PRx correlated with mRS. PRx not affected by vasospasm.
Kirkness CJ, AJCC 2009 [39]	90	R	25% H&H 4-5	Variability of ICP on 24-h, 1-h, 5-min, 5-sec. IP probe Mean monitoring 4d	ICP	UA	Vasospasm/ survival/ GOS extended	6mo	ICP variability predictive of 6-mo survival and GOS: high 5-sec or 5-min variability protective and high 24-h variability deleterious. Mean ICP not associated with survival or GOS. ICP values and ICP variability not correlated to vasospasm.

d: days; h: hours; H&H: Hunt-Hess SAH classification; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Score; IAAC: ICP–ABP wave amplitude correlation; ICPWA: ICP wave amplitude; IP: intra-parenchymal; IV: intra-ventricular; m: monitoring; MA: multivariate analysis; min: minutes; mo: months; mRS: modified Rankin Score; ns: not significant; PPV: positive predictive value; PRx: Pressure reactivity index; Pts: patients; R: retrospective; sec: seconds; UA: univariate analysis; wk: weeks.

TABLE VI.—*Summary of study findings and GRADE quality of evidence.*

		Main findings	GRADE Quality of Evidence	Main references
ICP as absolute value		ICP is a useful tool in the detection and management of early brain injury	Low (grade C)	Zoerle [26], Takeuchi [28], Jabbarli [35]
		ICP is not an independent predictor of long-term functional outcome	Low (grade C)	Zoerle [26], Heuer [27], Ryttlefors [31]
		Weak and variable correlation between ICP and delayed cerebral ischemia	Very low (grade D)	Heuer [27], Fukuhara [32], Kamchanapandh [33], Klingelhoefer [34]
Variables derived from ICP	PRx	Predicts survival, Glasgow Outcome Score and modified Rankin Scale	Low (grade C)	Rasulo [37], Bijlenga [38]
	ICPWA	Superior to ICP in predicting Glasgow Outcome Score and modified Rankin Scale	Moderate (grade B)	Eide [36, 49]
	IAAC	Superior to PRx in predicting Glasgow Outcome Score	Moderate (grade B)	Eide [50]
	ICPvar	Superior to ICPm in predicting survival and Glasgow Outcome Score	Low (grade C)	Kirkness [39]

IAAC: ICP – ABP wave amplitude correlation; ICPvar: Intracranial pressure variability; ICPWA: intracranial pressure wave amplitude; PRx: Pressure Reactivity Index.

evaluated and length of follow-up. For these reasons, therefore a meta-analysis was not attempted. The issue of duration is of particular importance: based on the present study, it was not possible to examine outcome effects of prolonged *versus* isolated ICP elevation.

The impact of ICP on outcome may differ according to the clinical condition (*e.g.* ICP secondary to SAH-related hematoma vs. global cerebral edema) or the approach used to treat ruptured aneury-sm (surgical clipping vs. endovascular treatment). Our study does not allow precise answers to these important issues.

Only 5 of the 26 studies enrolled exclusively poor-grade patients:[38, 40, 45, 47, 51] this may have influenced the lack of correlation between ICP values and long-term functional outcomes.

Furthermore elevated ICP was actively treated in most of the studies included, which may then have an impact on its predictive value.

Finally, it may simply be that ICP may not be sensitive enough to detect functional evolution.

Conclusions

The main results of our systematic review are summarized in Table VI. Elevated ICP is associated with higher mortality in critically ill patients with aSAH. The threshold to define elevated ICP varies consistently between studies and there is no independent association between elevated ICP and long-term aSAH functional recovery. There is a weak relationship between elevated ICP and DCI. ICP-derived variables to assess cerebrovascular reactivity and brain compliance appear superior to ICP absolute value alone in predicting aSAH prognosis. Quality of the data was generally low-to-moderate due to limited sample-size and single-center studies. Further multicenter studies would be required to further determine the prognostic value of ICP after aSAH.

Key messages

— Elevated ICP is associated with increased mortality after aneurysmal SAH.

— Elevated ICP is not an independent predictor of long-term functional outcome after aneurysmal SAH

— A variable correlation between elevated ICP and DCI was found

— ICP-derived variables assessing cerebral compliance (*e.g.* PRx) seem to have a higher accuracy than ICP absolute values in predicting prognosis after aneurysmal SAH.

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