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Cerebral perfusion pressure targets individualised to pressure-reactivity index in moderate to severe traumatic brain injury: A systematic review

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Abstract

Traumatic Brain Injury (TBI) frequently triggers a disruption of cerebral autoregulation. The cerebral perfusion pressure (CPP) at which autoregulation is optimal ("CPPopt") varies between individuals, and can be calculated based on fluctuations between arterial blood pressure and intracranial pressure. This review assesses the effect of individualising cerebral perfusion pressure targets to pressure reactivity index (a measure of autoregulation) in patients with TBI.

Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and Cumulative Index of Nursing and Allied Health Literature were searched in March 2015 for studies assessing the effect of targeting CPPopt in TBI. We included all studies which assessed the impact of targeting CPPopt on outcomes including mortality, neurological outcome and physiological changes. Risk of bias was assessed using the RTI Item Bank and evidence quality considered using the GRADE criteria.

Eight cohort studies (based on six distinct datasets) assessing the association between CPPopt and mortality, Glasgow Outcome Scale and physiological measures in TBI were included. The quality of evidence was deemed very low based on the GRADE criteria. Whilst the data suggests an association between variation from CPPopt and poor clinical outcome at 6 months, the quality of evidence prevents firm conclusions, particularly regarding causality, being drawn.

Available data suggests that targeting CPPopt might represent a technique to improve outcomes following TBI, but currently there is insufficient high-quality data to support a recommendation for use in clinical practice. Further prospective, randomised controlled studies should be undertaken to clarify its role in the acute management of TBI.

Keywords: Traumatic Brain Injury, CBF Autoregulation, Vascular Reactivity, Therapeutic Approaches for the treatment of CNS injury

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults, with a significant personal, social and economic impact. In Europe alone, around 2.5 million people will sustain a TBI per year, of which 1 million will be admitted to hospital. Despite improvements in care, 75,000 of these will die, and a substantial proportion of survivors will suffer ongoing disability.[1]

Following TBI, maintenance of appropriate cerebral blood flow is imperative to mitigate against the relative adverse effects of ischaemia and hyperaemia. In healthy states, the cerebral vasculature compensates for variations in systemic blood pressure and cerebral metabolic requirements with judicious alterations of blood vessel diameter, known as autoregulation.[2] In injured brains, this autoregulation can be impaired, and observational studies have demonstrated a relationship between loss of autoregulation and poor outcome.[3-6]

In patients with poor intracranial compliance, changes in cerebral blood volume, as dictated by vessel diameter, are expressed as variations in intracranial pressure (ICP). By analysing the dynamic relationship between mean arterial pressure (MAP) and ICP over a given time period (the length may be chosen arbitrary, but it should be substantially longer than respiratory and pulse period), an appreciation of cerebrovascular pressure reactivity can be gained, providing information about the integrity of autoregulation.[7] Perhaps the best known calculated index of cerebral autoregulation in the Pressure Reactivity Index (PRx), which is correlation coefficient between ICP and arterial pressure using ten seconds-averaged samples as datapoints and calculating correlation coefficients using a 5 min data window.

Measurement of PRx allows an assessment of the effect of various therapeutic manoeuvres on autoregulation. Changes in cerebral perfusion pressure (CPP),[8] temperature[9] and respiration[10] modulate autoregulation, as does the use of certain anaesthetic agents.[11,12]

Investigation into the effect of CPP on autoregulation has led to the discovery that the CPP at which autoregulation is best preserved ("optimal CPP" or CPPopt) varies both between individuals, and throughout time in an individual patient.[13] Certain neurocritical care units utilise CPPopt techniques

as an adjunct to standard care, in order to tailor CPP targets to each patient. To date, however, there are no systematic reviews assessing its clinical utility.

The objective of this systematic review is to determine the effect of individualising CPP targets to optimal PRx compared with standard CPP targets in patients with moderate to severe TBI on mortality and functional recovery.

Materials and methods

This review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[14] Details of the protocol for this systematic review were registered on PROSPERO (registration number CRD42014013048) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013048#.VWQ7K0Z0eSo.

The review is being prepared as part of the CENTER-TBI project, a large European research project that aims to improve the care for patients with Traumatic Brain Injury. [1,15,16]

Information sources

Using the NHS Library Healthcare Database search engine, the following databases were searched up to March 2015: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and Cumulative Index of Nursing and Allied Health Literature. There were no language or date restrictions, and we included studies irrespective of publication status. The search strategy was developed in consultation with a search expert using the following combination of subject headings and keywords: (Brain Injuries/ or Craniocerebral Trauma/ or ((head* or brain*) adj2 (injur* or trauma*)).ti,ab)[17] AND (Cerebral perfusion pressure OR Pressure reactivity OR Cerebrovascular reactivity.ti,ab).

Grey literature, ongoing trials and conference abstracts were searched for via The ClinicalTrials.gov registry, Google Scholar and abstracts from neurocritical care and international neurotrauma

conferences. Reference lists from included studies and other pertinent articles were screened, and citation tracking of included studies (via SCOPUS) was conducted. Experts leading research into cerebrovascular reactivity were consulted to identify any unpublished data.

Study selection

We included RCTs, quasi-RCTs, CCTs, and observational studies with a control group (i.e. cohort studies and case-control studies) that investigated the effect of targeting CPPopt in patients with moderate to severe TBI on one or more of our relevant outcomes. These outcomes included: mortality, functional outcomes (e.g. Glasgow Outcome Scale (GOS)) and physiological measures (such as brain tissue oximetry). Whilst we recognise the limitations of including observational studies in a systematic review of intervention effectiveness, an anticipated lack of controlled trials necessitated this decision in order to comprehensively evaluate the available data. We included all age groups and any methods for calculating CPPopt. Studies not measuring any of our pre-specified outcomes were excluded.

The first author (EN) screened all search results on citation, and removed clearly irrelevant articles. Two authors (EN, VN) then independently screened the remaining citations and abstracts identified to determine their eligibility for inclusion. Agreed citations were retrieved in full text and reviewed by the two authors independently; any disagreement was resolved by discussion until consensus was reached.

Data collection and assessment of risk of bias

Two authors (EN, CM) independently assessed the risk of bias of included studies; disagreement was resolved by discussion until consensus was reached. Data extraction was conducted by EN and corroborated by CM. The following data was extracted from the studies: study characteristics (including site and year), study participants (e.g. number, age, severity), method for calculating CPPopt, and clinical outcomes.

Where dichotomous data was available, we presented it as risk ratios (RR) with p-values. Continuous data was presented in the form that it appeared in the original publication.

Risk of bias was assessed using the RTI item bank.[18] The RTI item bank assesses risk of bias based on 12 domains. Each domain is rated as low, high or unclear risk of bias, according to specific criteria.

Data synthesis

To synthesise the data, we grouped studies by outcome, and considered the results of each study contributing to that outcome. Due to the heterogeneity of design and outcome measures, we report the results in a narrative manner, rather than performing meta-analysis. Where studies used shared, or overlapping datasets, this is highlighted. The risk of bias of included studies was used to inform an assessment of the quality of the evidence contributing to each outcome, as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[19] According to the GRADE approach, observational research is considered to be low quality evidence that may be downgraded further (or in rare instances upgraded) according to specific criteria.

Two authors (EN,AS) independently applied the GRADE criteria for each outcome and reached agreement through discussion (Supplementary Table 1).

Results

Study selection

A total of 2022 de-duplicated citations were identified, with 74 titles included on citation and abstract, and 22 retrieved in full text. Of these, 12 studies did not address the relationship between CPPopt and a clinically relevant outcome, and two abstracts[20,21] reported the same data as full text reports[22,23] thus were also excluded (Supplementary Table 2). Of the eight included studies, six were full texts, and two were abstracts from conference proceedings (Figure 1). There were no disagreements between the authors.

Study characteristics

We included eight study reports, assessing the effect of CPPopt in 972 patients with moderate to severe TBI (Table 1). One study group (Cambridge, UK) published three articles using overlapping, but not identical, datasets.[22,24,25] Due to overlap of patients in these three studies, we collated them as the "Cambridge Cohort". Therefore, there were six entirely distinct datasets. All studies took place in academic neuroscience centres in high-income countries. No studies assessed the use of CPPopt in children. All studies used a cohort design, with six studies retrospectively analysing prospectively gathered observational data.[22-26,28] The remaining two were prospective studies; one assessed the feasibility of adhering to a CPPopt-guided protocol,[29] and the other assessed the effects of targeting CPPopt on the partial pressure of brain tissue oxygen ($PbrO_2$).[27] No study directly compared a CPPopt-guided protocol with standard CPP targets.

Seven of the studies produced CPPopt data using ICM+ software, which analyses high-frequency ICP/CPP data to calculate an optimal individualised CPP target, based on the PRx values seen over a range of CPP levels. (http://www.neurosurg.cam.ac.uk/pages/ICM/).[22-25, 27-29] Two of these also used alternative methods: dynamic adaptive target of active cerebral autoregulation (DATCAR), a technique using the weighted averages of a number of low-resolution autoregulation index (LAx – a similar method to ICM+, but using low frequency data) curves generated at multiple time intervals and over multiple time windows,[23] and Long-PRx (L-PRx), a PRx variant based on lower frequency changes in ICP/MAP.[25] The remaining study used a bespoke technique which is not fully described.[26] These alternative methods are detailed further in Appendix 1.

Six studies reported outcome data for mortality at six months,[22-26,28] five GOS at six months,[22,24,25,28,29] one functional outcome (assessment tool not detailed) at six months [26] and one $PbrO_2$.[27]

All studies were funded by non-government sources. Five studies were co-authored by the creators of ICM+ software, who have a financial interest in a part of the licensing fee.[22,24,25,28,29]

Risk of bias

Given the inherent paucity of data presented in abstract-only publications, these were considered to be at unclear risk of bias.[24,26] Broadly, the remaining studies were judged as being at high risk of bias (Table 2). The main source of bias arose because of a failure to account for confounding factors in the analysis, such as intercurrent sepsis and severity of injury.[22,25,28,29] One study performed multivariate analysis, thus addressing this to some degree,[23] and one described physiological data only, therefore these were deemed at low risk.[27] All data gathered were observational, and thus was only able to describe associations rather than apportion causality.

Mortality

All six studies assessing mortality reported an increased risk with variance from CPPopt, particularly when managed below CPPopt.[22-26,28] This was displayed in differing ways across the studies: Aries (Cambridge cohort)[22] and Colton[26] described reduced mortality rates in those managed within 5mmHg of CPPopt (RR 0.28, p = 0.015[22] and RR 0.42 , p = not recorded (NR)[26]); Lang and Smielewski (Cambridge Cohort) and Steiner reported a decrease in mortality in those managed above CPPopt (no effect size stated, p <0.01;[24,25]RR 0.17, p = NR[28]); and Depreiterre showed that survivors spent longer within 5mmHg of CPPopt than non-survivors (25.6% vs 19.6% p = 0.01).[23] The difference between actual CPP and CPPopt was an independent predictor of survival when using the CRASH outcome prediction model variables of age, Glasgow Coma Scale, pupil reactivity, and presence of extracranial injury as covariates for a multivariate logistic regression (p = 0.017).[23] Lang also reported that 72% of non-survivors were managed with CPP lower than CPPopt (p = NR).[25]

According to the GRADE criteria however, the quality of this evidence was judged as very low (downgraded for a failure to address potential confounding factors across most studies, and a lack of comparison to standard management), thus our confidence in effect estimate is limited, and firm conclusions of the effect of CPPopt on mortality cannot be drawn.

Neurological outcome

All six studies assessing neurological outcome identified worsening in neurological outcome with variance from CPPopt, particularly when managed above CPPopt.[22,24-26, 28,29] It should be noted that the commonly used definition of "poor outcome" (GOS 1 to3) incorporates death, and thus some of the following results composite disability and death.

In Aries (Cambridge cohort), a good outcome (GOS 4 to5) at 6 months was more frequent in those with median CPP within 5mmHg of CPPopt; (RR 1.65, $p \leq 0.001$). Severe disability (GOS 3) was particularly likely in patients with median CPP greater than 5mmHg above CPPopt (RR 1.88, $p \leq 0.001$).[22] This pattern was reflected in Colton where risk of poor neurological outcome was higher in those with median CPP greater than 10mmHg away from CPPopt (RR 2.14, p = NR).[26] As the neurological outcome scale used is not specified, the findings cannot be directly compared to Aries.[22]

Lang and Smielewski (Cambridge cohort) found that CPP above CPPopt was associated with increased disability in their dataset, but did not publish the effect size ($p = 0.005$,[25] $p \leq 0.025$[28]).

Conversely, Dias found that patients with poor outcome (GOS 3 or less) were managed with CPP lower than CPPopt (-6.6mmHg vs. -1.0mmHg, $p = 0.004$).[29] Note here the inclusion of GOS 1 (Dead); the authors did not specify the proportion in the poor outcome group who died.

Lastly, Steiner reports that the correlation between the difference of mean CPP and CPPopt (meanCPP-CPPopt) with GOS was highly significant ($r= -0.51$, $p < 0.001$), showing that the further from CPPopt a patient was managed, the worse the outcome. This correlation existed for those patients managed below CPPopt ($r = 0.53$, $p < 0.001$) and for those above CPPopt ($r = -0.40$, $p \leq 0.05$).[28]Again it should be noted that GOS of one was included here, and that the overall picture was of increased mortality below CPPopt, and increased disability above it.

The pattern described in these studies suggests that the CPPopt is the point at which CPP is high enough to maximise likelihood of survival, whilst minimising the detrimental effects of cerebral hyperaemia.

We judged the quality of this evidence to be very low (downgraded again for a failure to address potential confounding factors across most studies, and a lack of comparison to standard management), and therefore firm conclusions cannot be drawn.

Physiological outcomes:

One study assessed the relationship between CPPopt and a physiological outcome. Jaeger found a significant correlation between CPPopt and the $PbrO_2$ change point (CPP_{PbrO2}), the level at which $PbrO_2$ no longer rises in a pressure-passive manner alongside CPP ($r = 0.79$, $p < 0.001$). Up to and including CPPopt, the CPP and $PbrO_2$ correlated ($r = 0.51$, $p < 0.001$), whereas no such correlation existed above CPPopt ($r = 0.03$, $p = 0.67$), displaying that brain oxygenation improved up to the point of CPPopt, but no further.[27]

Once more the quality of this evidence was rated as very low (downgraded as the physiological changes represent only a surrogate for clinical outcome, and sample size was very small), and so firm conclusions cannot be drawn.

Discussion

We found eight studies, based on six distinct datasets, assessing the effect of optimising CPP targets to PRx. Six of these addressed mortality risk,[22-26,28] six disability[22,24-26, 28,29] and one $PbrO_2$.[27] Six studies were retrospective observational trials,[22-26,28] whilst the remaining two were undertaken prospectively.[27,29]

All studies which assessed neurological outcome suggested an association between proximity of actual CPP to CPPopt and improved outcome.[22-6, 28-29] One centre reported a pattern of increased mortality when actual CPP was lower than CPPopt, and increased disability when above it.[22,24,25,28]

One study displayed an association between CPPopt and the point at which increases in CPP cease to improve brain tissue oxygenation.[27]

However, owing to the very low quality of the evidence (predominantly through a failure to address the impact of confounding factors which might associate variance from CPPopt and the measured outcomes e.g. shock, and a lack of comparison to standard practice), the results must be interpreted with caution. The nature of very low quality evidence is such that future, robust experimental studies may strengthen but, equally, may contradict these findings. As such, we are unable to draw any firm conclusions about the effect of optimising CPP targets to PRx on any outcomes.

Additionally, targeting $PbrO_2$ thresholds have not been unequivocally shown to improve clinical outcomes, and therefore extrapolating the association between CPPopt and CPP_{PbrO2} to infer a clinically significant effect is as yet unjustified. The other outcomes measures investigated however, are well validated and clinically relevant.

Overall, there is an absence of prospective, controlled trials addressing the utility of targeting CPPopt. In this review, all studies were observational, and described associations based on variance from CPPopt, rather than comparing a CPPopt-based strategy to usual practice. They could therefore only hope to demonstrate association rather than causality; confounding factors, such as shock, could well create such an association between poor outcome and variance from CPPopt, and were not sufficiently accounted for. However, the risk that this confound was a major cause of the observed association with outcome is mitigated by the finding of poorer outcomes when CPP was greater than CPPopt.

To the best of our knowledge, this is the first systematic review published on this topic. Most evidence up to this point has addressed the effect of targeting universal CPP thresholds for all patients. The most frequently utilised practice guidelines amalgamating this evidence are those published by the Brain Trauma Foundation;[30] which recognises the limited evidence available, and suggests a CPP range between 50-70mmHg, to balance between the risks of cerebral ischaemia and the cardiorespiratory complications of induced hypertension. The idea that CPP thresholds may vary between individuals is mentioned, but there is no suggestion as to how this might be applied to clinical practice.

The strengths of this review are that we followed best-practice in systematic review methods,[14] including a rigorous search of published and unpublished material, and two authors extracted and appraised the data. One notable source of potential bias in the review process is that the majority of the studies were published by the Cambridge group who devised, and have a financial interest in, the ICM+ software. Those studies performed entirely independently of any members of the Cambridge cohort,[23,26,27] and those using alternative techniques[23,26] reported similar results to the Cambridge group, which is encouraging against bias, but this potential conflict of interest should be borne in mind by the readership. Additionally, the inclusion of the authors of the Cambridge cohort studies in our review team might introduce bias, however they were not involved in the risk of bias, data synthesis or GRADE ratings of this review.

The published data suggest a positive association between proximity of CPP to CPPopt and clinical outcome, although the poor quality of the evidence prevents firm conclusions from being drawn. Evolving methods are allowing for CPPopt recommendations to be made by applying relatively simple software to data which are routinely gathered, providing the potential for a very cost-effective intervention to be used by even small centres (one could foresee online-access for occasional users). An increasing number of neurocritical care units are adopting the technology, and current data lends some support towards its use.

There is not currently enough high quality evidence to make recommendations for implementing a CPPopt-based strategy over the usual CPP targets suggested by the Brain Trauma Foundation. To truly identify the impact of a CPPopt-based strategy, well designed prospective randomised-controlled trials comparing the standard CPP recommendations to CPPopt targeting must be undertaken. These should address clinically meaningful outcomes such as mortality, Glasgow Outcome Scale and neuropsychological measures, and should include rigorous reporting of confounding factors such as baseline severity, additional injuries and complications during admission. Recommendations for improving the quality of TBI trials have been published as part of the IMPACT Project.[31]

Authors Disclosure Statement:

The software for brain monitoring ICM+ (www.neurosurg.cam.ac.uk/imcplus) is licensed by the University of Cambridge (Cambridge Enterprise). Marek Czosnyka has a financial interest in a part of the licensing fee. All other authors declare that they have no competing financial interests.

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Table 1: Summary of Study Characteristics

Study	Years Studied (Setting)	Design	N =	Age (Years)	TBI Severity	CPPopt Method	Outcomes (Time, months)
Cambridge Cohort	2003-2011 (UK)	Retro. Ax of prosp,data			Severe		GOS (6)
Aries (2012)[22]	*2003-2009*		*327*	*38*		*ICM+ PRx*	
Lang (2014)[25]	*2003-2009*		*307*	*36*		*ICM+ PRx; L-PRx*	
Smielewski (2012)[24]	*2003-2011*		*400*	*NR*		*ICM+ PRx*	
Colton (2014)[26]	2008-2010 (US)	Retro. Ax of prosp,data	138	40	NR	Low frequency PRx	Functional Outcome NOS (6)
Depreitere (2014)[23]	2003-2005 (Belgium)	Retro. Ax of prosp,data	264	33	NR	ICM+ PRx DATCAR (LAx)	Survival (6)
Dias (2015)[29]	2011-2013 (Portugal)	Prospective cohort study	18	42	Severe	ICM+ PRx	GOS (6)
Jaeger (2010)[27]	2005-2007 (Germany)	Prospective cohort study	38	40	Mild-Severe	ICM+ PRx	$PbrO_2$
Steiner (2002)[28]	1997-2000 (UK)	Retro. Ax of prosp,data	114	34	Mild-Severe	ICM+ PRx	GOS (6)

CPP_{opt} = Optimal cerebral perfusion pressure, DATCAR (LAx) = dynamic adaptive target of active cerebral autoregulation (low-resolution autoregulation index), GOS = Glasgow Outcome Scale, ICM+ PRx = cerebrovascular pressure reactivity index calculated by ICM+ software, NOS = Not otherwise specified, NR = Not recorded, Retro. Ax of prosp,data = Retrospective analysis of prospectively collected data

Study	Sample Definition and Selection	Inclusion and exclusion criteria	Interventions and Exposure	Outcome	Creation of Treatment Groups	Blinding	Soundness of Intervention	Follow Up	Analysis Comparability	Analysis Outcome	Interpretation	Presentation and Reporting
Cambridge Cohort	Low	Low	Low	Low	High	Low	Low	Low	High	Low	Low	Low
Aries (2012)[22]	*Low*	*Low*	*Low*	*Low*	*High*	*Low*	*Low*	*Low*	*High*	*Low*	*Low*	*Low*
Lang (2014)[25]	*Low*	*Low*	*Low*	*Low*	*High*	*Low*	*Low*	*Low*	*High*	*Low*	*Low*	*Low*
Smielewski (2012)[24]	*U*	*U*	*U*	*U*	*U*	*U*	*U*	*U*	*U*	*U*	*U*	*U*
Colton (2014)[26]	U	U	U	U	U	U	U	U	U	U	U	U
Depreitere (2014)[23]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dias (2015)[29]	Low	Low	Low	Low	High	High	Low	Low	High	Low	Low	Low
Jaeger (2010)[27]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Steiner (2002)[28]	Low	Low	Low	Low	High	Low	Low	Low	High	Low	Low	Low

Table 2: Summary of Risk of Bias

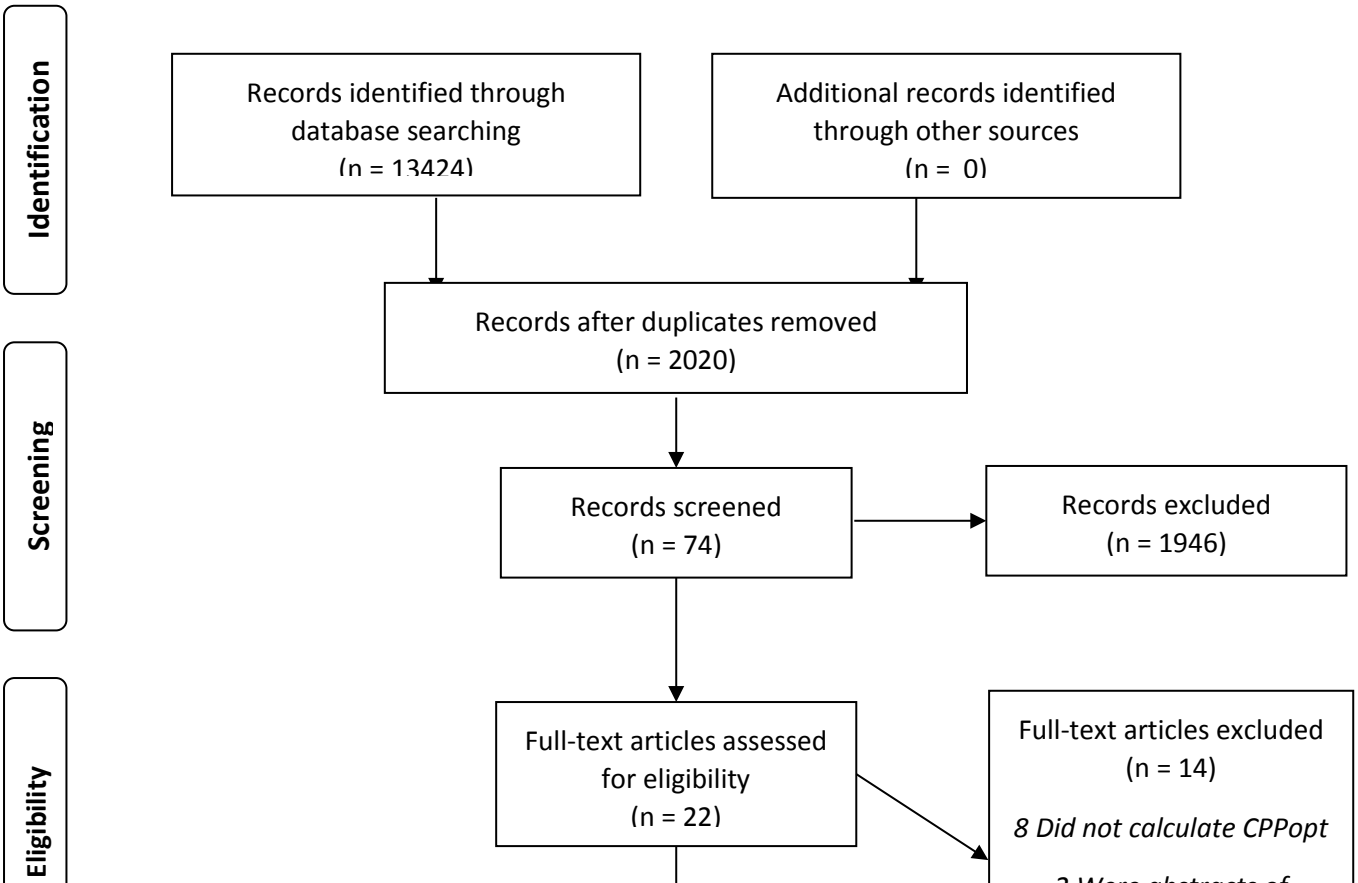
U = Unclear

Study	Mortality	Neurological Outcome	Physiological Outcome
Cambridge Cohort[22,24,25]	RR 0.28 (p = 0.015) if (ΔCPP-CPPopt) <5mmHg More likely if CPP<CPPopt (No effect size reported; p<0.001)	GOS 4-5 more likely if (ΔCPP-CPPopt) <5mmHg (RR 1.65; p <0.001) Severe disability (GOS 3) more likely if CPP >5mmHg above CPPopt (RR 1.88 p<0.001). Severe disability (GOS 3) more likely if CPP>CPPopt (p=0.005; No effect size reported) CPP > CPPopt correlated with greater rate of severe disability (p<0.025; No effect size reported).	
Colton (2014)[26]	RR 0.42 if (ΔCPP-CPPopt) <5mmHg vs (ΔCPP-CPPopt) >10mmHg (no P-value reported)	Poor outcome (NOS) more likely if (ΔCPP-CPPopt) >10mmHg vs <5mmHg (RR 2.14; no P-value reported)	
Depreitere (2014)[23]	Proportion of time spent within 5mmHg of CPPopt higher for survivors than non-survivors (25.6% vs 19.6% p=0.01).		

Table 3: Summary of Main Outcomes

	(ΔCPP-CPPopt) = independent negative predictor of survival (p=0.017; No effect size reported)		
Dias (2015)[29]		CPP<CPPopt lower in those with GOS <3 (-6.6mmHG vs -1.0mmHg; p=0.04)	
Jaeger (2010)[27]			CPP and $PbrO_2$ correlate up to, but not higher than, CPPopt (r=0.51; p<0.001)
Steiner (2002)[28]	RR 0.17 if CPP > CPPopt (no P-value reported)	(ΔCPP-CPPopt) correlates with GOS (r= -0.51; p<0.001), both when CPP<CPPopt (r=0.53; p<0.001) and when CPP>CPPopt (r=-0.40; p=<0.05)	

CPP = cerebral perfusion pressure, CPPopt = optimal cerebral perfusion pressure, ΔCPP-CPPopt = difference between actual CPP and CPP_{opt}, GOS = Glasgow Outcome Sale, NOS = Not otherwise specified, $PbrO_2$ = partial pressure of brain tissue oxygen, RR = relative risk



GRADE criteria	Rating	Footnotes (reasons for downgrading)	Quality of the evidence
Neurological Outcome			
Risk of Bias	*Serious (-1)*		

Figure 1: Flow Diagram of Study Selection Process. CPP_{opt} = Optimal cerebral perfusion pressure

GRADE criteria	Rating	Footnotes (reasons for downgrading)	Quality of the evidence
		Confounders poorly controlled for across most studies	*Very Low*
PbO_2			
Risk of Bias	*No*	Single study at low risk of bias	
Inconsistency	*No*	Effect direction and sizes similar	*Very Low*
Indirectness	*Serious (-1)*	Only one study	
Indirectness	*Serious (-1)*	No comparison with usual management	
Imprecision	*Not assessable*	Surrogate outcome for clinical relevance	
Imprecision	*Serious (-1)*	Number of events and confidence intervals not presented	
Publication Bias	*Undetected*	Highly significant result but very small number of participants	
Publication Bias	*Undetected*		
Other	*No upgrading factors*		
Mortality			
Risk of Bias	*Serious (-1)*	Confounders poorly controlled for across most studies	*Very Low*
Other	*No upgrading factors*		
Inconsistency	*No*	Effect direction and sizes similar	
Indirectness	*Serious (-1)*	No comparison with usual management	
Imprecision	*Not assessable*	Number of events and confidence intervals not presented.	
Publication Bias	*Undetected*		
Other	*No*	RR <0.5 in at least 2 studies, but plausible confounders present	

Supplementary Table 1. Quality of Evidence (GRADE)

PbO_2: Brain tissue oxygen partial pressure

Supplementary Table 2: Summary of Excluded Studies

CPPopt = Optimal cerebral perfusion pressure

Appendix 1: Summary of CPPopt Techniques

The cerebrovascular pressure reactivity index (PRx) is a marker of cerebrovascular autoregulation derived from the response of intracranial pressure (ICP) to slow fluctuations in arterial blood pressure (ABP). All the described CPPopt calculations below are based on this index.

Study	**Reason for Exclusion**
Aries 2014[20]	Data presented as full-text in other included article
Guiza 2013[21]	Data presented as full-text in other included article
Nordstrom 2005[32]	No data presented
Ang 2007[33]	CPPopt not calculated
Zweifel 2008[34]	No new data; quotes data from Steiner et al. 2002
Brady 2009[35]	CPPopt not calculated
Consonni 2009[36]	CPPopt not calculated
Radolovich 2011[37]	CPPopt not calculated
Aries 2012[38]	CPPopt not correlated with outcome measure
Budhohoski 2012[39]	CPPopt not calculated
Smielewski 2012[40]	CPPopt not correlated with outcome measure
Sorrentino 2012[41]	CPPopt not calculated
Johnson 2014[42]	CPPopt not calculated
Lazaridis 2014[43]	CPPopt not calculated

ICM+ PRx:

Digitized signals from ICP and ABP monitors are sampled at a frequency of 100 Hz, and recorded using ICM+ software. Time-averaged values of ICP, ABP, and CPP are calculated using waveform time integration over 60-sec intervals. A moving Pearson correlation coefficient is calculated between 30 consecutive, 10-sec averaged values of ABP and corresponding ICP signals (with 80% overlap of data) to provide a measure of cerebrovascular PRx. The influence of the pulse- and respiratory-frequency wave components is supressed by the averaging over 10 seconds. A U-shaped curve is fitted to the PRx values over the range of CPP seen in the preceding 4 hours, with the lowest PRx value indexing current value of CPPopt. If certainty of U-shape curve fit is low, CPPopt value is

automatically discarded. This routine is repeated every minute and CPPopt may be presented as a monitored variable, compared to real CPP trend.

Long-PRx:

The Long-PRx relies on the same method as ICM+ PRx, but is calculated as a moving Pearson correlation coefficient between 20 data points of ICP and ABP averaged over a 60 second period, as opposed to 30 data points averaged over a 10 second period in PRx. There are no particular advantages suggested over the standard PRx method, simply an alternative measure.

Dynamic adaptive target of active cerebral autoregulation (DATCAR; LAx):

The low-resolution autoregulation index (LAx) is calculated as the correlation coefficient between minute-by-minute measurements of ICP and ABP for 8 separate time intervals 3, 5, 10, 20, 30, 60, 90, and 120 minutes.

CPPopt is calculated as in ICM+ PRx, fitting a U-shaped curve with the most negative values of the autoregulation index indicating optimal CPP. Instead of limiting this to the previous 4 hours of data however, the method is applied on time windows of 1, 2, 4, 6, 8, 12, and 24 hours, for each LAx time interval defined above. Therefore, 45 plots are generated for each point in time. These plots are then weighted based on 2 criteria: the better the fit of the U-shaped curve, and the lower the LAx-value corresponding to the plot-specific CPPopt. The final CPPopt is thus computed as the weighted average of the CPPopts. This method of calculating CPPopt aims to optimize the ability to detect periods of active autoregulation in the preceding period, thereby being more likely to generate a mathematically reliable CPPopt.