High Blood Pressure & Cardiovascular Prevention (2021) 28:115–128
https://doi.org/10.1007/s40292-021-00435-z

REVIEW ARTICLE

Therapeutic Variation in Lowering Blood Pressure: Effects on Intracranial Pressure in Acute Intracerebral Haemorrhage

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Received: 27 September 2020 / Accepted: 3 February 2021 / Published online: 18 February 2021

Abstract

Introduction Intracerebral haemorrhage (ICH) is associated with high morbidity and mortality. Blood pressure (BP) control is one of the main management strategies in acute ICH. Limited data currently exist regarding intracranial pressure (ICP) in acute ICH. The relationship between BP lowering and ICP is yet to be fully elucidated.

Methods We conducted a systematic review to investigate the effects of BP lowering on ICP in acute ICH. The study protocol was registered on PROSPERO (CRD42019134470).

Results Following PRISMA guidelines, MEDLINE, EMBASE and CENTRAL were searched for studies on ICH with BP and ICP or surrogate measures. 1096 articles were identified after duplicates were removed; 18 studies meeting the inclusion criteria. Dihydropyridine calcium channel blockers (CCBs) were the most common agent used to lower BP, but had a varying effect on ICP. Other BP-lowering agents used also had a varying effect on ICP.

Discussion and Conclusion Further work, including large observational or randomized interventional studies, is needed to develop a better understanding of the effect of BP lowering on ICP in acute ICH, which will assist the development of more effective management strategies.

Trial Registration The study protocol was registered on PROSPERO (CRD42019134470) on 29/05/2019.

Keywords Intracranial pressure · Stroke · Blood pressure · Intervention · Intracerebral haemorrhage

1 Introduction

Intracerebral haemorrhage (ICH) accounts for approximately 15% of all stroke, and is considered the least treatable form of stroke [1]. Spontaneous ICH is associated with high mortality and morbidity with a case fatality of 40% at 1 month [2, 3]. Due to an ageing population, incidence of ICH is likely to rise in the future, so finding effective management strategies is imperative [4].

Despite the significant burden of ICH, limited effective management options exist. Elevated blood pressure (BP) is a common feature after the onset of ICH [5] and is associated with expansion of the underlying haematoma [6] and poor outcome [7]. Therefore, BP control remains one of the mainstays of acute ICH management. Two large BP lowering trials in acute ICH, the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial and the second Antihypertensive Treatment of Acute Cerebral Haemorrhage trial, showed discordant results [8, 9]. However, pooled analysis from these trials suggest that early and sustained BP control may improve outcomes [10], and intensive BP lowering as part of an "ABC care bundle" in ICH, that additionally consisted of rapid anticoagulant reversal and prompt neurosurgical referral in suitable patients, was associated with lower case fatality[11].

The relationship between systemic BP and cerebral physiology is complex, and may be adversely affected in ICH. First, cerebral autoregulation (CA) maintains a constant

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cerebral blood flow (CBF) despite variations in cerebral perfusion pressure (CPP). There is already evidence of impaired CA and lower CBF velocity in acute ICH [12], which raises concern that intensive BP lowering may result in ischaemia. Secondly, the haematoma and its growth can cause surrounding vasogenic oedema, further contributing to raised intracranial pressure (ICP), mass effect and midline shift [13], which may be associated with serious adverse effects [14]. Intracranial hypertension is common in spontaneous ICH with Kamel and colleagues reporting it in up to 70% of ICH patients undergoing ICP monitoring [15]. However, there is a relative paucity of data on the effect of systemic BP lowering on ICP and CPP. We therefore conducted a systematic review investigating the effects of BP lowering on ICP in acute ICH.

2 Methods

The protocol for this systematic review was registered on PROSPERO (CRD42019134470), and was in accordance with the Preferred Reporting Items for Systematic Reviews Meta-analysis [17]. The checklist results are presented in Supplementary material Figure 1.

2.1 Search Strategy

Studies were identified with a search strategy across three databases (MEDLINE, EMBASE and CENTRAL), between 1974 and April 2019. Appropriate subject headings or subcategories for each database were used (Supplementary material Figure 2). The reference lists of included papers were searched for any other titles that were relevant, as were reference lists of relevant papers.

2.2 Inclusion and Exclusion Criteria

Studies with BP measurements, and ICP or surrogate measures in acute ICH were included. Eligibility was assessed by reading abstracts, and, if necessary, whole articles. The effects of ICP changes on clinical outcome were assessed. Excluded were non-English language articles, non-human studies, healthy population, participants under 18 years old and non-ICP or surrogate measure outcomes. Studies were screened initially by title and abstract by two reviewers (MK and JSM). TGR was asked to adjudicate any disagreements. Included studies were evaluated as full papers by both reviewers against the inclusion and exclusion criteria (MK and JSM).

2.3 Data Extraction

The following data were extracted: (1) number of patients and controls (where applicable), (2) sex, (3) age, (4) previous hypertension, (5) previous history of stroke, (6) systolic and diastolic BP, (7) heart rate, (8) ICP, (9) CPP, (10) central venous pressure, (11) clinical outcome, (12) neurosurgical procedures, and (13) main conclusions. The methodological quality of the selected studies was assessed by the Newcastle-Ottawa scale (NOS) for observational studies. This scoring system evaluates the quality of an article based on 3 broad perspectives: the cohort selection (0–4 points), comparability (0–2 points), and assessment of outcomes (0–3 points). A score of $\geq$7 points was suggestive of a high-quality study. Both reviewers (MK and JSM) undertook the methodological quality screening and any discrepancies were settled by consensus.

3 Results

3.1 Summary of Included Studies

A detailed flow diagram of study selection is shown in Fig. 1. 1226 publications met the search criteria and were evaluated. After removing duplicates, 1089 articles were screened. 978 articles were removed after title and abstract screening. 7 further articles were found through other sources. 117 articles were screened at full text, with 99 articles excluded at this stage; the main reasons being that abstracts had not been available and full text review of the articles showed them to be irrelevant on full text review, and no ICP or surrogate measures were recorded. Overall, eligibility criteria were met by 18 articles (Table 1).

3.2 Risk of Bias in Included Studies

According to the results of the NOS, two out of the eighteen studies scored $\geq$ 7, indicating high quality studies, eleven studies scored $\geq$ 4 indicating moderate quality and five studies scored $<$ 4 indicating low quality. Supplementary material Figure 3 provides the risk of bias indicators of the included studies.

3.3 Demographics of Included Studies

Patient numbers ranged from 1 to 385. Nine studies included patients with ICH only [18–20, 22–27]; the remaining nine studies included other brain injury patients as well as ICH patients. These studies included patients with subarachnoid haemorrhage (SAH), traumatic brain injury, acute ischaemic

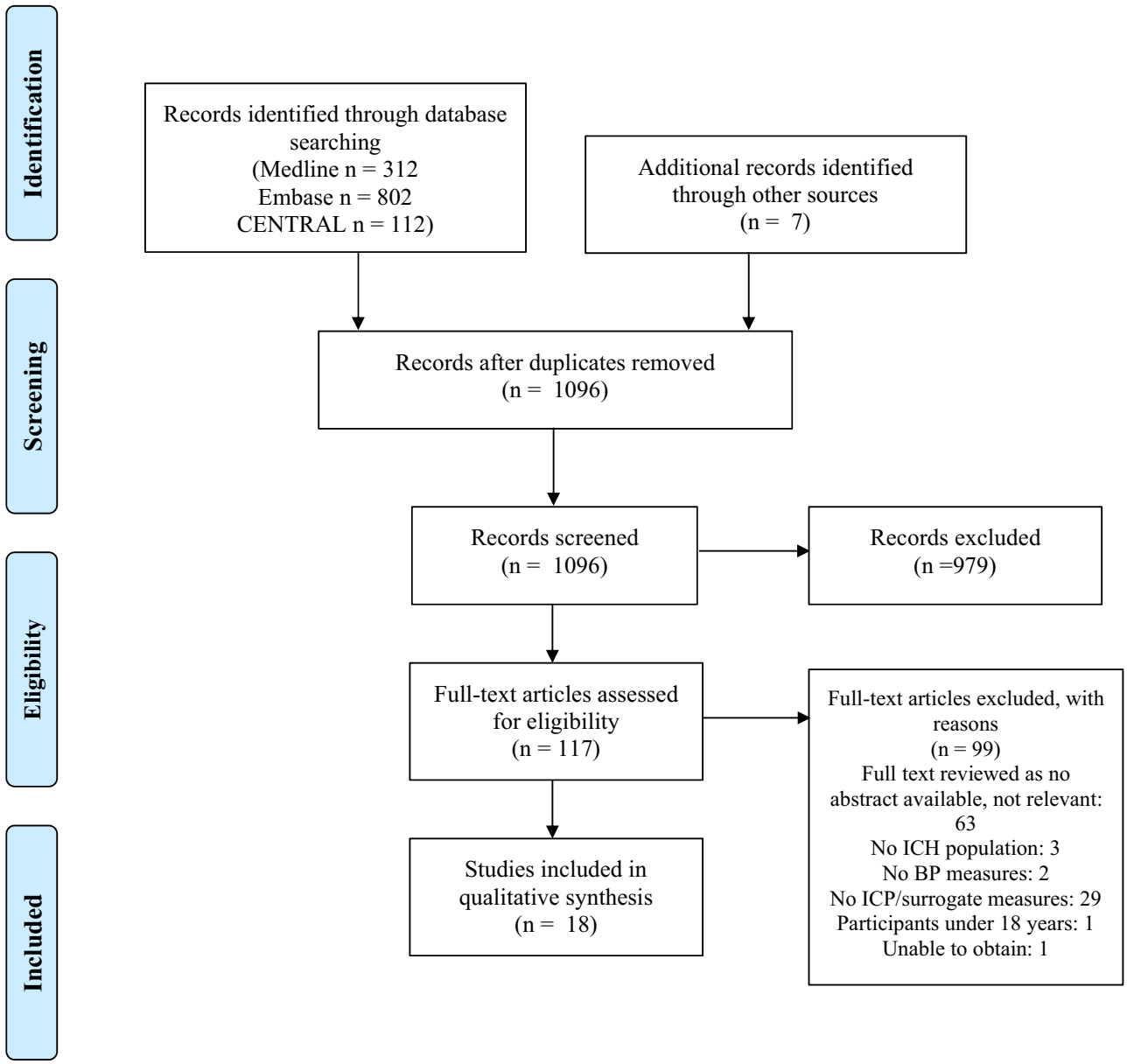

Fig. 1 PRISMA flow diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

stroke, hypoxic brain injury, anoxia, encephalitis and arteriovenous malformation [16, 21, 28–34]. The mean age of patients varied from 43 years to 70 years. Two studies randomized patients to a control or placebo group [16, 24], whilst one study randomized patients to different blood pressure targets [20].

3.4 BP and ICP Changes in Included Studies

The main findings of the included studies are presented in Table 1. Overall, sixteen studies included ICP measures [18, 19, 21–34], eleven studies included ICP and CPP measures [19, 22–24, 26–28, 30–33], and two studies included CPP

Table 1 Characteristics of included studies

Study	Year	BP lowering intervention	Sample size	Age (years) mean ± SD	Males (%)	Systolic BP pre lowering (mmHg) ± SD	Systolic BP post lowering (mmHg) ± SD	ICP pre lowering (mmHg) ± SD	ICP post lowering (mmHg) ± SD	CPP pre lowering (mmHg)	CPP post lowering (mmHg)	Main findings
Li et al	2015	IV NC or IV NM administered. Nitroprusside administered if systolic BP remained >140 mmHg	87 (46 in NC group & 41 in NM group)	62±9 (NC) 60±8(NM)	39 (NC) 46 (NM)	176±17 (NC) 172±19 (NM)	136±4 (NC) 138±8(NM) (t60)	18±8 (NC) 14±6(NM)	16±8 (NC) 16±5(NM) (t60)			BP and ICP decreased during administration of NC BP decreased and ICP increased, although not significantly during administration of NM
Elwood et al	2018	Clevidipine infusion	14 (Intracranial haemorrhage in 69.2%)	(Median) 48 (range18-77)	78.6	149.88	136.41	11.31	11.69	77.53	69.88	Conference abstract. BP and CPP decreased with administration of clevidipine, no significant change in ICP
Gavito-Higuera et al	2017	IV labetalol boluses and nitroprusside infusion	1	52	0	Case report. When BP decreased, ICP decreased. CPP appeared to be marginally decreasing.						

Table 1 (continued)

Study	Year	BP lowering intervention	Sample size	Age (years) mean ± SD	Males (%)	Systolic BP pre lowering (mmHg) ± SD	Systolic BP post lowering (mmHg) ± SD	ICP pre lowering (mmHg) ± SD	ICP post lowering (mmHg) ± SD	CPP pre lowering (mmHg)	CPP post lowering (mmHg)	Main findings
Tamm et al	2016	Labetalol, hydralazine and IV enalapril	73 (37 in <150 mmHg group & 36 in <180 mmHg group)	70 (IQR 60-80)	74	182 ± 20 (<150) 184 ± 25 (<180)	<150 <180				Absolute ipsilateral hemispheric CPP 14.0 ± 5.3 (<150 mmHg) 15.2 ± 3.9 (<180 mmHg) Absolute contralateral hemispheric CPP 14.3±5.8 (<150 mmHg) 15.2±3.8 (<180 mmHg)	No significant difference in CPP between <150 mmHg and<180 mmHg groups
Strong et al	2017	Study assessed effectiveness of emergency provider's BP management in ICH – BP management protocol not stated	187 intracranial haemorrhage (101 in the tSBP ≥161 mmHg group and 86 in the tSBP ≤160 mmHg group)	NA	NA	≤160 ≥161		24 (IQR 15–30, ≤160 mmHg) 20 (IQR 15–25, ≥161 mmHg)				Conference abstract. Lower BP associated with higher ICP

Table 1 (continued)

Study	Year	BP lowering intervention	Sample size	Age (years) mean ± SD	Males (%)	Systolic BP pre lowering (mmHg) ± SD	Systolic BP post lowering (mmHg) ± SD	ICP pre lowering (mmHg) ± SD	ICP post lowering (mmHg) ± SD	CPP pre lowering (mmHg)	CPP post lowering (mmHg)	Main findings
Tuteja et al	2019	Study assessed whether 5 or more post mechanical ventilation interventions would affect BP variability – BP management protocol not stated	147 (63 IPH)	58±14	45	Triage: 184±41		Intracranial opening pressure (cm H_20) 25 (15–30)				Increased BP variability was associated with higher odds ratio of in-hospital mortality
Picetti et al	2014	Paracetamol used as antipyretic, also reduced BP	32 (2 ICH)	54.2 ± 13.9	43.7	156.8 ± 20.2	139.1 ± 21.5 (t60)	14.4 ± 5.1	14.2 ± 3.9 (t60)	81.9 ± 12.2	73.0 ± 10.9 (t60)	As BP decreased, no significant change in ICP, CPP decreased.
Narotam et al	2008	IV NC Other hypertensive agents added as clinically indicated	30 (3 ICH, 1 IVH)	55.1±19.4	1:1.2 M:F	176.26±18.58	140.67±16.3 (t4hrs)	15.56±10.98	12.16±9.78 (t8hrs)	100.90±16.49	79.8±12.48	BP, CPP and ICP decreased with IV NC administration
Willmot et al	2006	Transdermal GTN	18 (2 ICH) (6 in control group & 12 in GTN group)	69.0±5.6 (GTN group) 70.3±10.8 (Control group)	17 (GTN group) 50 (control group)	162±16 (GTN group) 166± 18 (Control group)	GTN lowered peripheral systolic BP by 23 mmHg			43.4±18.0 (GTN group) 59.7± 12.0 (Control group)	50.9±15.8 (GTN group) 59.1± 32.4 (Control group)	BP decreased in GTN group, CPP increased (no significant change in CPP).
Nishiyama et al	2000	IV NC	22	64±15	63.6		BP decreased during and 24hr after end of NC infusion		ICP decreased 24 hr after end of NC infusion		CPP decreased at 24hrs and 72 hrs of infusion	BP, CPP and ICP decreased with NC infusion

Table 1 (continued)

Study	Year	BP lowering intervention	Sample size	Age (years) mean ± SD	Males (%)	Systolic BP pre lowering (mmHg) ± SD	Systolic BP post lowering (mmHg) ± SD	ICP pre lowering (mmHg) ± SD	ICP post lowering (mmHg) ± SD	CPP pre lowering (mmHg)	CPP post lowering (mmHg)	Main findings
Hayashi et al	1988	Sublingual Nifedipine, IM Chlorpromazine, IM Reserpine, IV Furosemide, IV thiopental	38 (22 ICH)	59 (range 43-72)	47.4	Nifedipine: ABP decreased, ICP increased and CPP decreased with administration, Chlorpromazine: ABP decreased, ICP increased and CPP decreased with chlorpromazine administration Reserpine: ABP decreased, ICP increased and CPP decreased with administration Furosemide: ABP not significantly changed, ICP decreased, CPP not significantly changed with administration Thiopental: ABP and ICP decreased with administration, CPP did not change from control as mean ABP and mean ICP showed parallel decreases						
Ko et al	2011	Study assessed feasibility of brain multimodality monitoring for optimizing CPP – BP management protocol not stated	18 (12 in survivors group and 6 in non-survivors group)	59 (IQR42 – 67)	50	MAP 100±18 (survivors) 100±19 (non survivors)		7.8±8.3 (survivors) 16.4±7.4 (non survivors)		93±20 (survivors) 85±196 (non-survivors)		ICP was higher and CPP was lower in non survivors, MAP was similar.
Suarez et al	1998	IV bolus of 23.4% saline (used for treatment of refractory intracranial hypertension)	8 (1 basal ganglia haemorrhage)	55.6±13.2	50	MAP 108.3 ±15	MAP 99.8±16 (t3 hrs)	41.5	14.0 (t3hrs)	66.0±19	83.4±18	MAP and ICP decreased, and CPP increased with administration of 23.4% saline

Table 1 (continued)

Study	Year	BP lowering intervention	Sample size	Age (years) mean ± SD	Males (%)	Systolic BP pre lowering (mmHg) ± SD	Systolic BP post lowering (mmHg) ± SD	ICP pre lowering (mmHg) ± SD	ICP post lowering (mmHg) ± SD	CPP pre lowering (mmHg)	CPP post lowering (mmHg)	Main findings
Woodcock et al	1982	IV pentobarbital	15 (3 ICH)	43	73.3	Unclear - minimum BP included		ICP lowered in 5 patients				Raised ICP associated with poorer outcome. Barbiturates initially lowered ICP in 11/15 patients
Ziai et al	2012	Study assessed intracranial hypertension in IVH and ICH – ICP and CPP management based on Brain Trauma Foundation Guidelines	100 (78 in rt-treated group & 22 in placebo treated group)	55±10	60	194±40 (rt-treated) 189±34 (placebo treated)		Opening ICP 11 (IQR9) (rt-treated) 13 (IQR11) (placebo treated)		84 (IQR18) (rt-treated) 87 (IQR24) (placebo treated)		ICP elevation > 30 mmHg is a predictor of short term mortality
Hamani et al	2003	Study assessed intraventricular pressure monitoring in thalamic and ganglionic haemorrhages – BP management protocol not stated	10 (3 patients in ICP above 20 mmHg group, 3 patients in ICP below 20 mmHg without hydrocephalus & 4 patients in ICP below 20 mmHg with hydrocephalus)	56.4±15.2	70	166.7 (ICP above 20 mmHg) 166.7 (ICP below 20 mmHg w/o hydrocephalus) 185 (ICP below 20 mmHg with hydrocephalus)		22.7 (ICP above 20 mmHg) 9.7 (ICP below 20 mmHg w/o hydrocephalus) 11 (ICP below 20 mmHg with hydrocephalus)				Patients with initial pressures above 20 mmHg presented very poor outcomes, and patients with initial pressure levels below 20 mmHg w/o hydrocephalus also evolved poorly

Table 1 (continued)

Study	Year	BP lowering intervention	Sample size	Age (years) mean ± SD	Males (%)	Systolic BP pre lowering (mmHg) ± SD	Systolic BP post lowering (mmHg) ± SD	ICP pre lowering (mmHg) ± SD	ICP post lowering (mmHg) ± SD	CPP pre lowering (mmHg)	CPP post lowering (mmHg)	Main findings
Tian et al	2013	Study assessed the relationship between ICP variability and outcome – BP management protocol not stated	56 (35 in improvement group & 21 in deterioration group)	50.46±12.77 (Improvement group) 50.90±18.74 (Deterioration group)	71.43 (Improvement) 71.43 (Deterioration)	MAP lower in deterioration group		ICP higher in deterioration group		CPP lower in deterioration group		Increased ICP, decreased MAP and CPP, and increased ICP variability associated with poorer outcome
Hirayama et al	1994	IV Nitroglycerin or IV NC or IV Diltiazem	385 (35 episodes of BP lowering)	64±7 (Nitroglycerin group) 62±11 (NCgroup) 63±8 (Diltiazem group)	NA	114.2±7.6 (Nitroglycerin) 113.1±7.0 (NC) 110.8±7.1 (Diltiazem)	96.3±6.2 (Nitroglycerin) 86.8±4.8 (NC) 90.4±7.3 (Diltiazem)	16.1±3.5 (Nitroglycerin) 16.6±2.1 (NC) 14.1±7.1 (Diltiazem)	30.3±3.7 (Nitroglycerin) 33.6±4.9 (NC) 20.8±3.7 (Diltiazem)		CPP index 1.80±0.11 (Nitroglycerin) 1.63±0.13 (NC) 1.33±0.07 (Diltiazem)	BP reduced, CPP decreased, ICP increased with administration of Nitroglycerin, NC and Diltiazem

measures only [16, 20]. Dihydropyridine calcium channel blockers (CCBs) were the main agent used to lower BP, with six studies using these agents and including ICP measures [18, 22, 27, 28, 31, 32]. Dihydropyridine CCBs used included nicardipine [18, 22, 27, 31], nimodipine [18], clevidipine [28] and nifedipine [32]; with one study using two CCBs [18]. In two of these studies [22, 32], it was not possible to determine exact numbers, thus a trend in behaviour of BP and ICP was determined from the data available and the studies were not included in Fig. 2. Dihydropyridine CCB administration was associated with BP reduction in all studies. However, ICP response was variable, with three studies showing a reduction with nicardipine administration [18, 22, 31], and one study an increase [27]. ICP also increased with the administration of nifedipine [32] and nimodipine [18], but did not significantly change with clevidipine [28].

Five studies used other agents to lower BP and included ICP measures [19, 27, 30, 32, 33], including glyceryl trinitrate (GTN) [27] and diltiazem (a non-dihydropyridine CCB) [27]. One study was a case report using labetalol and nitroprusside from which it was not possible to ascertain exact values, instead a trend was determine [19]. Hayashi et al assessed the effects of chlorpromazine, reserpine, furosemide and thiopental on arterial BP, ICP and CPP, from which trends were determined [32]. Suarez et al used 23.4% saline for intracranial hypertension, with only mean arterial pressure (MAP) values reported, so this study was not included in Fig. 3 [33]. One study used paracetamol to lower temperature, but because this was associated with BP reduction it was included [30]. Hirayama et al used nitroglycerin and diltiazem to lower blood pressure [27]. BP reduction was seen in all studies, with the exception of furosemide administration [32]. ICP decreased with administration of labetalol and nitroprusside [19], furosemide [32], thiopental [32] and 23.4% saline [33], but increased with administration of nitroglycerin [27], diltiazem [27], chlorpromazine [32] and reserpine [32]. There was no significant change in ICP with paracetamol administration [30].

3.5 BP and CPP Changes in Included Studies

Ten studies included BP lowering and CPP measures [16, 19, 20, 22, 27, 28, 30–33]. However, only three studies have been included in Fig. 4 [28, 30, 31] because either it was not possible to determine the exact degree of BP lowering [16, 20], MAP only was reported [33], the exact degree of CPP lowering was not possible to determine [27] or it was not possible to determine exact degree of both BP and CCP lowering [19, 22, 32]. CPP was reduced with administration of labetalol and nitroprusside [19], nicardipine [22, 27, 31], nitroglycerin [27], diltiazem [27], clevidipine [28], paracetamol [30], nifedipine [32], chlorpromazine [32] and reserpine [32]. However, CPP increased significantly with administration of 23.4% saline [33], and increased with GTN, though this was not statistically significant [16]. There was no change in CPP with administration of furosemide [32] or thiopental [32]. There was no significant difference in CPP between the group randomized to a BP target <150 mmHg compared to <180 mmHg when using labetalol, hydralazine and enalapril to lower BP [20].

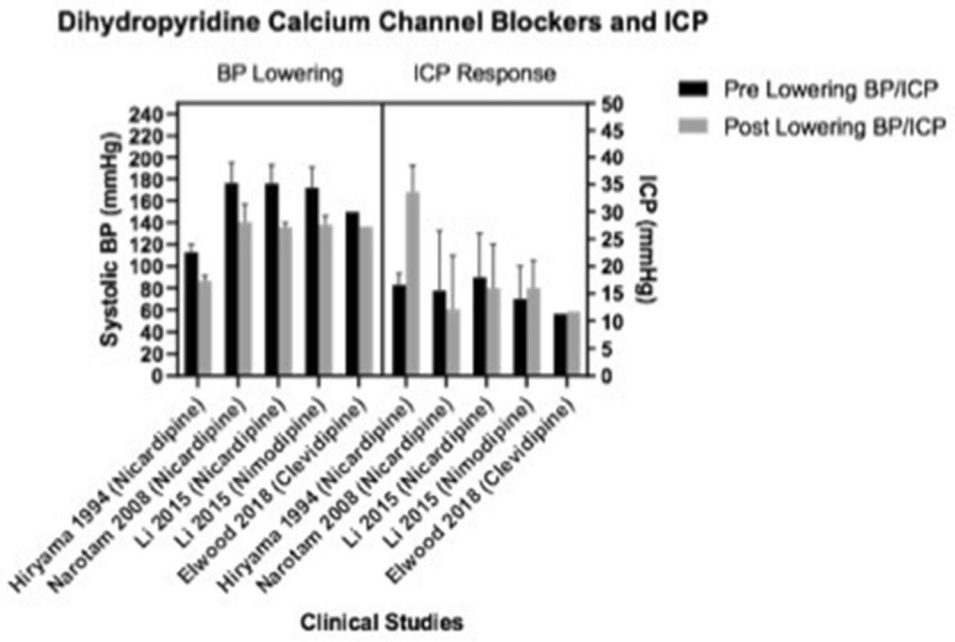

Fig. 2 Effect of dihydropyridine calcium channel blockers on BP and ICP. *BP* Blood pressure, *ICP* intracranial pressure

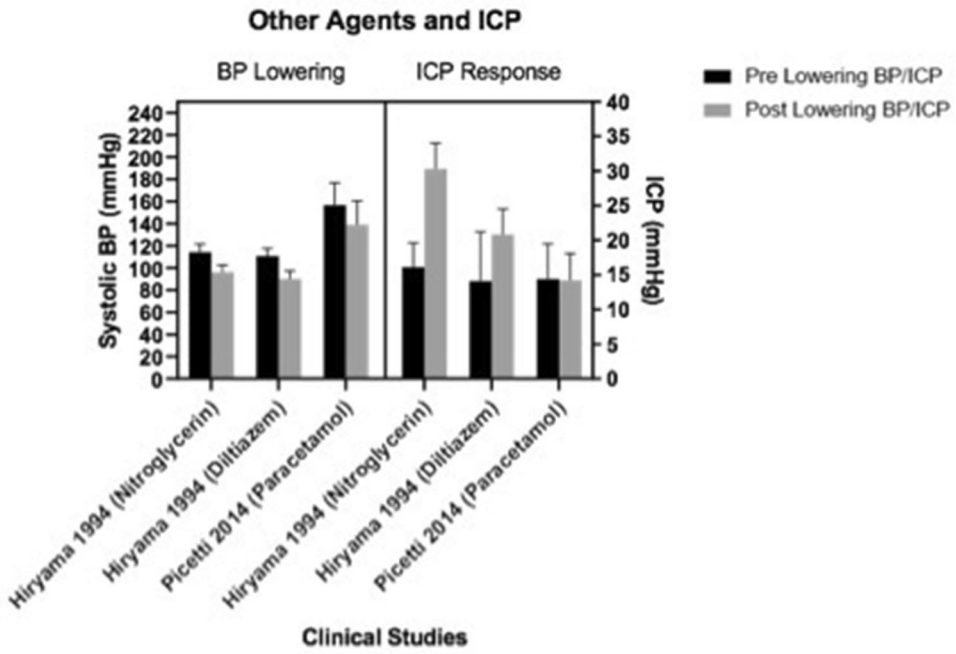

Fig. 3 Effect of other BP lowering agents on BP and ICP. *BP* Blood pressure, *ICP* intracranial pressure

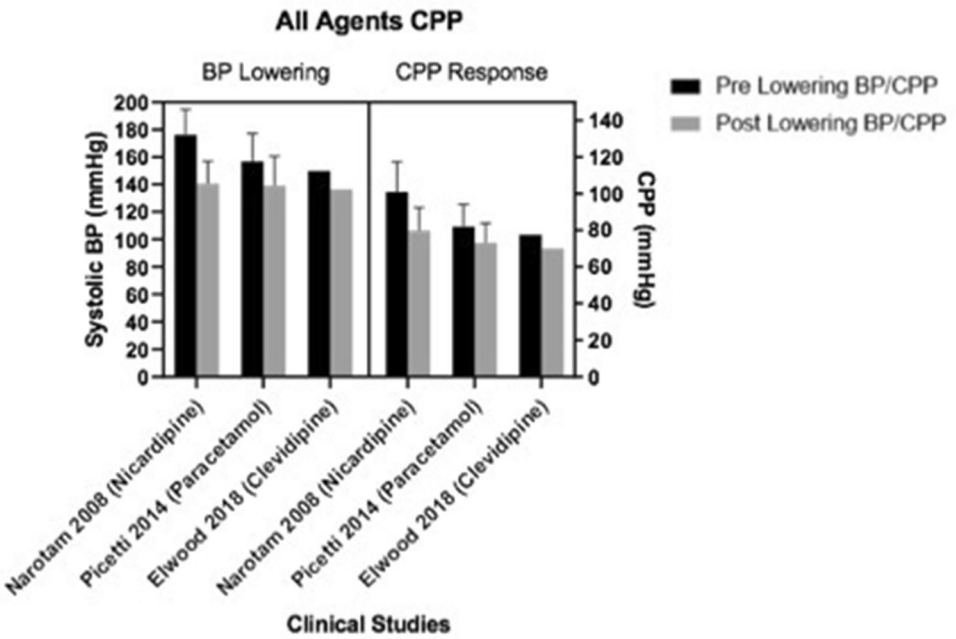

Fig. 4 Effect of all BP lowering agents on BP and CPP. *BP* Blood pressure, *ICP* intracranial pressure

3.6 Quantitative Analysis

Meta-analysis of data was not deemed to be possible due to the lack of outcome measures. Where data were available, figures were created to demonstrate the effect of BP lowering on BP and ICP or CPP.

4 Discussion

This systematic review highlights the therapeutic variation employed in blood pressure lowering, and demonstrates the complex relationship between BP and ICP in acute ICH.

4.1 Dihydropyridine Calcium Channel Blockers and ICP

Dihydropyridine CCBs were the most common agent used to lower BP. Administration reduced BP significantly in all studies, but produced varying results on ICP.

Hirayama et al included patients with low initial BP, which further decreased with administration of nicardipine, whilst ICP significantly increased [27]. These patients may represent a subset of patients who are more unwell and have a poor outcome. Hayashi et al found that administration of nifedipine decreased arterial BP, but increased ICP [32]. Interestingly, the increase in ICP was more significant in patients who already had a higher initial ICP, and again may represent a more unwell patient subgroup.

There were several differences between the studies themselves, which may have resulted in the differential effect of BP lowering on ICP. Many of the articles did not provide information on when BP lowering medication was given in the time course of acute ICH which may be relevant in any effect on ICP. Furthermore, studies may also have included several other interventions with potential impact on BP and ICP, for instance Nishayama et al reported that glycerin fructose solution was also given to lower ICP, and thus elucidating the relationship between BP lowering and ICP was difficult [22].

4.2 GTN and ICP/CPP

Recently, there has been significant interest in using GTN to lower BP in acute ICH, though trials have shown conflicting results. The RIGHT trial [35] and subgroup analysis of the ENOS trial [36] found that GTN improved functional outcome in stroke. However, the RIGHT-2 trial [37] showed that GTN did not affect functional outcome, moreover, GTN administration resulted in worse functional outcome in ICH patients [38].

In a study investigating the effects of GTN on patients with recent stroke, BP decreased with administration of transdermal GTN, but CPP increased, although this was not significant [16]. Cerebral vasodilators are usually thought to reduce CPP through dilatation of cerebral vasculature. Willmot et al also measured zero-flow pressure, (ZFP), as a measure of cerebral downstream pressure [16]. GTN did not significantly alter ZFP; the authors postulating that venodilatation increased blood flow out of the cranium, maintaining CPP.

In contrast, Hirayama et al found that nitroglycerin reduced BP, increased ICP, and decreased CPP [27]. These two studies included different patient populations: Willmot et al [16] mild-moderate ischaemic and haemorrhagic stroke patients, and Hirayama et al [27] patients undergoing surgical evacuation of the haematoma. In addition, Willmot et al [16] measured CPP non-invasively using measures of middle cerebral artery blood flow, whereas Hirayama et al [27] measured CPP by subtracting mean ICP from mean systolic blood pressure. Therefore, differences in patient population and study methodology may account for any differences in the effect of BP lowering using GTN on ICP.

4.3 BP, ICP, CPP and Clinical Outcomes

Studies included limited information of clinical outcomes following acute ICH. Two studies investigated the difference in characteristics between survivors and non-survivors, and between those improving and deteriorating [23, 26]. Both studies found that increased ICP and decreased CPP were associated with poorer outcome [23, 26]. Several studies noted that raised ICP was associated with poor outcome [23–26, 34]. Increased BP and ICP variability were also associated with poorer outcome [26, 29]. These studies suggest that not only is it important to control ICP, but also to reduce ICP variability.

4.4 Strengths and Limitations

To our knowledge, this is the first systematic review investigating the effect of BP lowering on ICP in acute ICH, which has included a variety of BP lowering agents. Overall, the review highlights the need for further research.

There are several limitations with the studies included in this systematic review, in particular related to methodological heterogeneity, lack of a control population and small study size. The review was limited to data reported in the selected articles and did not examine individual patient data. Although the majority of the studies included in the review were of moderate quality, some studies were of low methodological quality. Only English language articles were included. Due to the lack of outcome measures, meta-analysis was not possible.

It is also important to note that this review included a specific population of patients with acute ICH. Patients who undergo ICP monitoring are likely to have moderate ICH and less co-morbidities, and this may not reflect the whole ICH population. Furthermore, it is possible that agents administered in the studies did not alter ICP, and the natural history of ICP in ICH was seen instead. However, there were temporal associations between administration of BP-lowering agents and ICP.

4.5 Future Work

Considering the methodological variation and the small patient numbers, further work is needed to develop a better understanding of the effect of BP lowering on ICP in acute ICH. A large prospective observational or randomized

intervention study is needed to further elucidate the relationship between BP lowering on ICP in acute ICH. The agent used to lower BP and the timing of administration should be considered carefully. Understanding the relationship between BP lowering and ICP in acute ICH may help to develop more effective management strategies, which is much needed, considering the significant burden of acute ICH.

5 Conclusions

Administration of a CCB reduced BP, but had a varying effect on ICP in patients with ICH, other agents were also used to lower BP, and similarly had a varying effect on ICP. This review found considerable variation in methodology of included studies and small patients numbers, suggesting further work is needed to understand the effect of BP lowering on ICP in acute ICH such as large prospective observational or randomized intervention study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40292-021-00435-z.

Declarations

Funding MK is an NIHR Academic Clinical Fellow. JSM is an NIHR Clinical Lecturer in Older People and Complex Health Needs. APJ is an NIHR Clinician Scientist. TGR is an NIHR Senior Investigator. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health, or the authors' respective institutions.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Availability of data and material Material and data included in manuscript.

Author contributions MK, TGR, APJ and JSM conceived and designed the review. MK, PD and JSM searched and selected the studies. MK and JSM prepared the figures. All authors read and approved the final manuscript.

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