Received: 18.09.2013 / **Accepted:** 07.10.2013
DOI: 10.5137/1019-5149.JTN.9270-13.0

Effects of Intensive Blood Pressure Lowering on Intracerebral Hemorrhage Outcomes: A Meta-Analysis of Randomized Controlled Trials

Yoğun Kan Basıncı Azaltmanın İntraserebral Kanama Sonuçlarına Etkileri: Randomize Kontrollü Çalışmaların Bir Meta-Analizi

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ABSTRACT

AIM: Elevation of blood pressure (BP) is common after intracerebral hemorrhage (ICH). Early BP treatment may be beneficial after ICH, but the effect of intensive BP lowering on ICH outcomes is not known and no systematic review or meta-analysis was published regarding this issue.

MATERIAL and METHODS: We conducted a meta-analysis to compare the effect of more versus less intensive BP targets on clinical outcomes in patients with ICH. Mortality, unfavorable outcome and adverse events were analyzed. Meta-analysis was performed in terms of the odds ratio (OR) and 95% confidence interval (CI).

RESULTS: Five eligible studies were included and analyzed, involving 3243 patients to use systolic BP (SBP) <140 mmHg as target BP and 142 patients to use other BP target in intensive BP target group. The pooled OR of mortality and unfavorable outcome after ICH in intensive BP control group comparing with less intensive BP targets group were 0.99 (95% CI 0.81 to 1.23) and 0.90 (95% CI 0.78 to 1.03) respectively. The pooled OR were 0.97 (95% CI 0.80 to 1.18) for neurological deterioration and 0.83 (95% CI 0.61 to 1.11) for hematoma expansion. There is no difference in other adverse events between two groups.

CONCLUSION: Acute lowering of SBP to 140 mmHg is probably beneficial for functional outcome in patients with ICH, but the evidence is still insufficient. Further large multicenter studies are required to enhance the evidence to guide the BP lowering target following ICH.

KEYWORDS: Blood pressure, Intracerebral hemorrhage, Intensive BP control

ÖZ

AMAÇ: İntraserebral kanama (İSK) sonrasında kan basıncında (KB) artışa sık rastlanır. İSK sonrasında erken KB tedavisi faydalıdır ama yoğun KB azaltmanın İSK sonuçları üzerine etkisi bilinmemektedir ve bu konuyla ilgili herhangi bir yayınlanmış sistematik derleme veya meta-analiz yoktur.

YÖNTEM ve GEREÇLER: İSK hastalarında klinik sonuçlar üzerine daha yüksek ve daha düşük KB hedeflerinin etkisini karşılaştırmak üzere bir meta analiz yaptık. Mortalite, olumsuz sonuçlar ve yan etkiler analiz edildi. Meta-analiz risk oranı (OR) ve %95 güven aralığı (GA) açısından yapıldı.

BULGULAR: Beş uygun çalışma dahil edilip analiz edildi ve böylece hedef KB olarak sistolik KB (SKB) <140 mmHg şeklinde 3243 hasta ve yoğun KB tedavisi grubunda başka bir KB hedefi için 142 hasta seçildi. İSK sonrası mortalite ve olumsuz sonuç için yoğun KB kontrol grubunda birleştirilen OR, daha az yoğun KB tedavisi grubuyla karşılaştırıldığında 0,99 (%95 GA 0,81- 1,23) ve 0,90 (%95 GA 0,78 – 1,03) bulundu. Birleştirilmiş OR 0,97(%95 GA 0,80 -1,18) ve hematom genişlemesi için 0,83 (%95 GA 0,61- 1,11) bulundu. İki grup arasında diğer yan etkiler açısından bir fark yoktu.

SONUÇ: SKB'nin 140 mmHg'ya akut olarak düşürülmesi muhtemelen İSK hastalarında işlevsel sonuç açısından faydalıdır ama kanıtlar hala yetersizdir. İSK sonrasında KB azaltılmasını yönlendirmek üzere kanıtları artırmak için daha fazla sayıda büyük ve çok merkezli çalışma gereklidir.

ANAHTAR SÖZCÜKLER: Kan basıncı, İntraserebral kanama, Yoğun KB kontrolü

ABBREVIATIONS: ICH: intracerebral hemorrhage, **BP:** blood pressure, **SBP:** systolic blood pressure, **MAP:** mean arterial pressure, **DBP:** diastolic blood pressure, **CPP:** cerebral perfusion pressure, **ICP:** intracranial pressure, **RCT:** randomized controlled trials, **GOS:** Glasgow Outcome Scale, **mRS:** Modified Rankin Scale, **NIHSS:** National Institute of Health stroke scale, **OR:** Odds Ratio, **CI:** confidence interval, **ATACH:** Antihypertensive Treatment of Acute Cerebral Hemorrhage trial, **INTERACT:** Intensive blood pressure reduction in acute cerebral haemorrhage trial.

INTRODUCTION

Intracerebral hemorrhage (ICH) is a serious public health problem that causes morbidity and mortality throughout the world (17, 18). Early elevation of blood pressure (BP) is common after ICH (24). In an survey of 45330 patients with acute ICH, about 75% of patients had systolic blood pressure (SBP) >140 mmHg and about 20% patients had SBP >180 mmHg (15). It has been suggested that elevated BP is associated with hematoma expansion and poor outcome after acute ICH in several nonrandomized studies. As the result, early BP treatment may be beneficial after ICH (5, 20). However, optimal blood pressure for treating acute ICH is uncertain, because BP control have always debated whether it is adaptive (to reduce rebleeding and perihematoma edema expansion) or potentially deleterious (to decrease cerebral perfusion and increase ischemic event) (4, 13, 23).

American Heart Association guidelines in the year of 2010 suggested a modest reduction of BP, with target mean arterial pressure (MAP) of 110 mmHg or target BP of 160/90 mm Hg, and considered to maintain a reasonable cerebral perfusion pressure (CPP) (≥60 mm Hg) in patients with suspected elevations of intracranial pressure (ICP). However, the recommendation in the guideline for target BP is arbitrary with incomplete efficacy evidence (Class IIb; Level of Evidence: C) (13).

In the last few years, several multicenter clinical trials evaluating the effects of different intensities of BP lowering on ICH outcomes provides an opportunity to update the evidence for lower BP targets (1, 2, 6, 12, 14). In order to provide the best available evidence of BP lowering targets on ICH, we conducted an up-to-date meta-analysis of all randomized controlled trials in present article.

MATERIAL and METHODS

The present study was performed according to the PRISMA guidelines. The protocol of this meta-analysis has not been previously registered.

Type of Included Studies

We included only published randomized controlled trials (RCTs) comparing more versus less intensive BP targets with pharmacological BP lowering agents in patients with ICH.

Types of Outcome Measures

The following outcomes were evaluated: 1) mortality at the end of scheduled follow-up; 2) unfavorable outcome (either death or dependency) at the end of scheduled follow-up (dependency assessed at least one month after ICH); 3) hematoma expansion; 4) neurologic deterioration; 5) other adverse events, including hypotension and cardiovascular events. We defined dependency as being dependent on others for activities of daily living, for example having a Glasgow Outcome Scale (GOS) score<4, GOSE<4, modified Rankin Scale score graded 3 to 5, Barthel Index 0 to 60 (10, 21).

Search Strategy

We performed a systematical search of Cochrane Central Register of Controlled Trials, PubMed, MEDLINE (Ovid), EMBASE (Ovid) from 1980 to July 2013, with the combination of the English key terms of target BP, intensive BP control, intensive BP treatment, strict BP control, strict BP treatment, tight BP control, tight BP treatment, and the English key terms of intracerebral hemorrhage. The details of full electronic search strategies were presented in Additional File 1. The reference lists of all relevant papers and literature reviews were checked.

Study Selection and Data Extraction

Three review authors (JM, HL and YL) independently screened the titles, abstracts and keywords of citations obtained from the searches of the electronic databases and excluded studies that were clearly irrelevant. We obtained the full text of the remaining studies and the same three review authors independently assessed which trials met the predefined inclusion criteria. Disagreements were resolved by consensus between investigators. The following data of included studies were extracted independently by the same three authors: first author, year of publication, journal, study center, study population characteristics (inclusion and exclusion criteria, age, gender, similarity of groups at baseline, baseline BP), sample size, BP target in each group, interventions of BP control, duration of follow-up and outcome measures. The methodological quality of each trial was evaluated using Jadad scale and the risk of bias assessment tool in the Cochrane Handbook for Systematic Reviews of Interventions (7, 9). The criteria included randomization, allocation concealment, blinding, and an explanation of withdrawal or loss to follow up. Clinical trials with Jadad scores ≥3 were considered to have lower bias risks. Any discrepancies were resolved by consensus between investigators.

Statistical Analysis and Assessment for Bias

Meta-analysis was performed to calculate the Odds Ratio (OR) and 95% confidence interval (CI) via a fixed-effect model if there is no evidence of statistical heterogeneity. The random-effects model was employed to pool studies when statistical heterogeneity occurred. We intended to perform subgroup analysis according to the range of intensive BP target, as well as number of patients, BP level at baseline, ethnicity if possible. Sensitivity analysis was performed according to the quality of included studies (Jadad scores ≥3 vs.<3). We assessed and quantified statistical heterogeneity for each pooled summary estimate using Cochran's Q statistic and the I^2 statistic, respectively. Substantial heterogeneity will be considered to exist with $I^2 > 50\%$ and Chi^2 test $P < 0.1$. All analyses were performed using Review Manager Software, RevMan 5.2.

RESULTS

Trial Selection and Characteristics

The combined search strategy identified 173 citations.

After title, abstract and full text screen, five completed RCTs satisfied all inclusion criteria for final analysis, including a total of 3385 patients (Figure 1). Two trials, involving 3243 patients, used SBP<140 mmHg as target BP in aggressive BP target group. Two trial, totally involving 100 patients, used SBP <150 mmHg or 145-155 mmHg as target BP in aggressive BP target group. The other group with 42 patients, used MBP <110 mmHg as target BP in aggressive BP target group. The details of included studies were described in Table I.

Assessment of Trial Quality

Five eligible studies were assessed for risks of bias using both Cochrane Handbook for Systematic Reviews of Interventions and the Jadad scale. Details of our assessment of the risk of bias in the included studies were presented in Table II. We intended to access publication bias using funnel ***plot*** and linear regression test, however there were too few included studies to enable meaningful analysis.

Effects of Interventions

Mortality

All studies with 3373 patients were available for analysis of mortality. The pooled OR for mortality at end of scheduled follow-up was 0.99, 95% CI 0.81 to 1.23, p=0.96. Heterogeneity: $Chi^2 = 1.55$, df = 4 (P = 0.82); $I^2 = 0$ % (Figure 2).

Unfavorable outcome

Four studies with 3300 patients were available for analysis of unfavorable outcome (either death or dependency). The pooled OR for unfavorable outcome at end of scheduled follow-up was 0.90, 95% CI 0.78 to 1.03, p=0.12. Heterogeneity: $Chi^2 = 4.02$, df = 3 (P = 0.26); $I^2 = 25$ % (Figure 3).

Neurological deterioration, hematoma expansion and other adverse events

Four studies were available for analysis of neurological deterioration and hematoma expansion. The pooled OR for neurological deterioration was 0.97, 95% CI 0.80 to 1.18, P_{value}=0.75, $P_{heterogeneity}$= 0.88. The pooled OR for hematoma expansion was 0.83, 95% CI 0.61 to 1.11, P_{value}=0.21, $P_{heterogeneity}$=0.19. Other target adverse events in observation were presented in Table III. There is no difference between two groups.

Subgroup analysis and sensitivity analysis

Due to the inadequate data, we only performed subgroup analysis according to the range of intensive BP target,

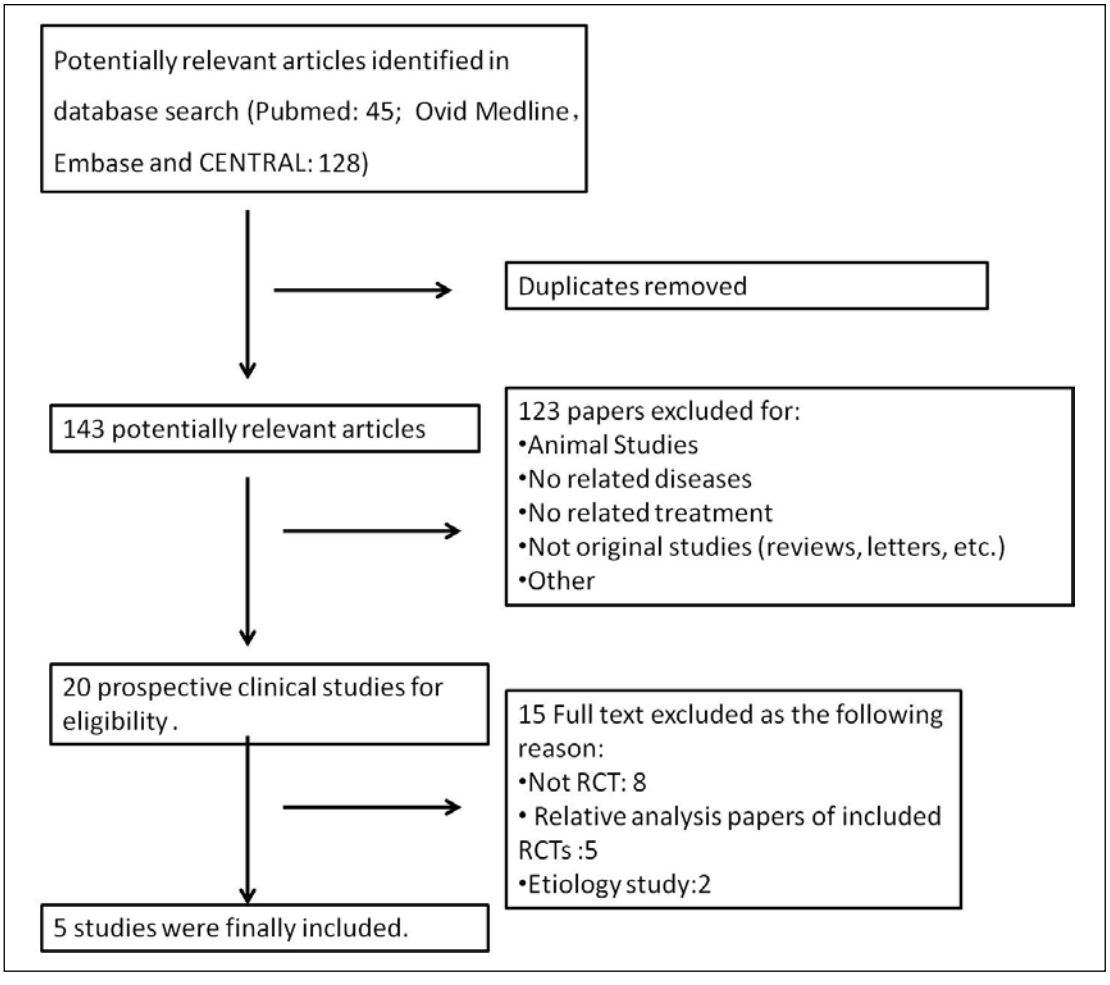

Figure 1: Flow diagram of study selection.

Table I: Characteristics of the RCT Involving the Comparison of More Versus Less Intensive BP Targets in Patients with ICH

Included study /Year	Inclusion Criteria (Age, Blood pressure, Tine)	No. of Participants (Active / Control)	Hematoma volume (ml) (Active / Control)	Baseline BP(mmHg) (Active / Control)	BP Target in Active Group (mmHg)	BP Target in Control Croup (mmHg)	Mean Age (y) (Active / Control)	Male (%) (Active / Control)	Duration of Follow-up	Outcome
INTERACT2 (1), 2013	>18 years old, SBP: 150 ~ 220 mmHg, within 6h of ICH onset	2839(1403/1436)	11/11	SBP: 179/179	SBP <140 mm Hg	SBP <180 mm Hg	63.0/64.1	64.2/61.7	3 months	death or dependency, mRS, mortality, AE, quality of life
INTERACT (2), 2008	>18 years old, SBP: 150 ~ 220 mmHg within 6h of ICH onset	404 (203/201)	15.2/15.4	SBP: 180/182	SBP<140 mm Hg	SBP <180 mm Hg	63/62	61/69	3 months	death or dependency, mRS, NIHSS, Barthel index, AE.
CHHIPS (14), 2009	>18 years old, SBP > 200 mm Hg and/ or DBP> 120 mm Hg, within 36h of ICH onset	25(18/7)	---	SBP:182/181	SBP:145–155 mm Hg	SBP> 155mm Hg	74/74	---	3 months	dead or dependent, mRS, AE.
ADAPT (6), 2013	>18 years old, SBP≥150 mm Hg	75(39/36)	25.9/26.9	SBP: 182/184	SBP:<150 mm Hg	SBP:150~180	70.7/68.7	67/78	3 months	mortality , mRS, Barthel Index
Koch S (11), 2008	>18 years old, MAP > 110 mmHg	42(21/21)	12.5/8.5	MAP: 144/151	MAP < 110 mmHg	MAP 110–130 mmHg	61.2/60	42.9/66.7	3 months	favorable outcome (mRS ≤ 2), mortality

AE: *adverse event;* ***mRS:*** *Modified Rankin Scale;* ***NIHSS:*** *National Institute of Health stroke scale;* ***BP:*** *blood pressure;* ***SBP:*** *systolic blood pressure;* ***DBP:*** *diastolic blood pressure;* ***MAP:*** *mean arterial pressure.*

number of patients, BP level at baseline. Sensitivity analysis was performed according to the quality of included studies (Jadad scores ≥3 vs.<3). The results are presented in Table IV.

DISCUSSION

The present meta-analysis, including five RCTs with 3385 patients, explored the influence of BP lowering on ICH outcomes. We found that early intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of mortality (0.99, 95% CI 0.81 to 1.23, p=0.96). Intensive lowering of blood pressure seems to have a trend to slightly reduce the poor functional outcomes in ICH patients, although there is not statistic significant (OR 0.90, 95% CI 0.78 to 1.03, p=0.12). In addition, there was no excess of neurological deterioration or other adverse events related to intensive BP lowering. There was also no clear evidence of substantial heterogeneity in the effect of treatment in any prespecified subgroup and sensitive analysis (BP Target, study sample size and BP level at baseline).

The results of this meta-analysis suggest acute lowering of SBP to 140 mmHg in ICH patients is probably safe and beneficial for functional outcomes. Acute intensive blood-

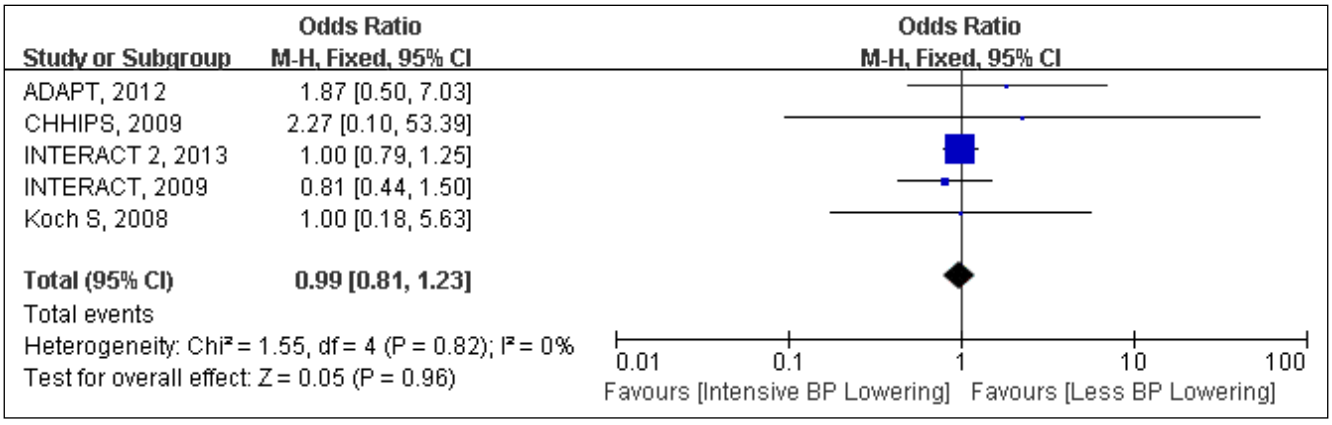

Figure 2: Odds ratio for mortality at the end of follow-up: the comparison between more and less intensive BP targets in patients with ICH.

Table II: Summary of Quality Indicators and Assessment of Risk of Bias in included RCTs

Quality indicators/studies	INTERACT2[1], 2013	INTERACT[2], 2008	ADAPT[6], 2013	CHHIPS[14], 2009	Koch S et al. [14], 2008
Center	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter
Randomized controlled study	Yes	Yes	Yes	Yes	Yes
Appropriate random sequence generation	Yes	Yes	unclear	Yes	unclear
Allocation concealment	unclear	unclear	unclear	Yes	unclear
Blinding of participants and personnel	NO	NO	NO	Yes	NO
Blinding of outcome assessment	Yes	Yes	Yes	Yes	Yes
Explanation for withdrawals and dropouts	Yes	Yes	Yes	Yes	Yes
Jadad scores	3	3	1	5	1

Table III: Odds Ratio for Adverse Events: The Comparison Between More and Less Intensive BP Targets in Patients with ICH

Adverse Event	Events Rate* (More/Less Intensive)	OR (95% CI)	p-Value
Hematoma Expansion	88(5.4%)/105(6.3%)	0.83 (0.64, 1.11)	0.21
Neurological Deterioration	234(14.4%)/244(14.8%)	0.97 (0.80, 1.18)	0.75
Hypotension	10(0.6%)/12(0.7%)	0.84 (0.36, 1.96)	0.69
Cardiovascular event	30(1.9%)/34 (2.1%)	0.90 (0.55, 1.47)	0.67

Table IV: Stratified and Sensitivity Analyses of Intensive BP Control on ICH Outcome

Variables	Study	No. of patients	Mortality			Unfavorable Outcome		
			Events Rate* (More/Less Intensive)	OR (95% CI)	p-Value	Events Rate* (More/Less Intensive)	OR (95% CI)	p-Value
Total	5	3373	199 (11.9%)/202 (11.9%)	0.99 (0.81, 1.23)	0.96	841 (51.2%)/894 (53.9%)	0.90 (0.78, 1.03)	0.12
BP Target								
Intensive SBP target<140mmHg	3	3258	189 (11.7%) /195 (11.9%)	0.98 (0.79, 1.21)	0.72	828 (51.1%)/883 (53.9%)	0.89 (0.78, 1.02)	0.10
Intensive SBP target<150mmHg	1	73	7 (18.9%)/4 (11.1%)	1.87 (0.50, 7.03)	0.36	---	---	---
intensive MBP target<110mmHg	1	42	3 (14.3%)/3 (14.3%)	1.00 (0.18, 5.63)	1.00	13 (61.9%)/11 (52.4%)	1.48 (0.43, 5.05)	0.53
Study sample size								
>300	2	3233	187 (11.7%)/195 (12.0%)	0.97 (0.79, 1.21)	0.80	814 (50.8%)/880 (54.0%)	0.88 (0.77, 1.01)	0.08
<300	3	140	12 (15.8%)/7 (10.9%)	1.56 (0.58, 4.18)	0.38	27 (69.2%)/14 (50.0%)	2.07 (0.75, 5.71)	0.16
Baseline BP								
SBP:175~185	4	3331	196 (11.8%)/199 (11.89%)	1.01 (0.81, 1.23)	0.96	828 (51.1%)/883 (53.9%)	0.89 (0.78, 1.02)	0.18
MAP: 140~150	1	42	3 (14.3%)/3 (14.3%)	1.00 (0.18, 5.63)	1.00	13 (61.9%)/11 (52.4%)	1.48 (0.43, 5.05)	0.53
Jadad Scale								
Jadad scores ≥3	3	3258	189 (11.7%) /195 (11.9%)	0.98 (0.79, 1.21)	0.72	828 (51.1%)/883 (53.9%)	0.89 (0.78, 1.02)	0.12
Jadad scores <3	2	115	10 (17.2%)/7 (12.3%)	1.49 (0.52, 4.22)	0.46	13 (61.9%)/11 (52.4%)	1.48 (0.43, 5.05)	0.53

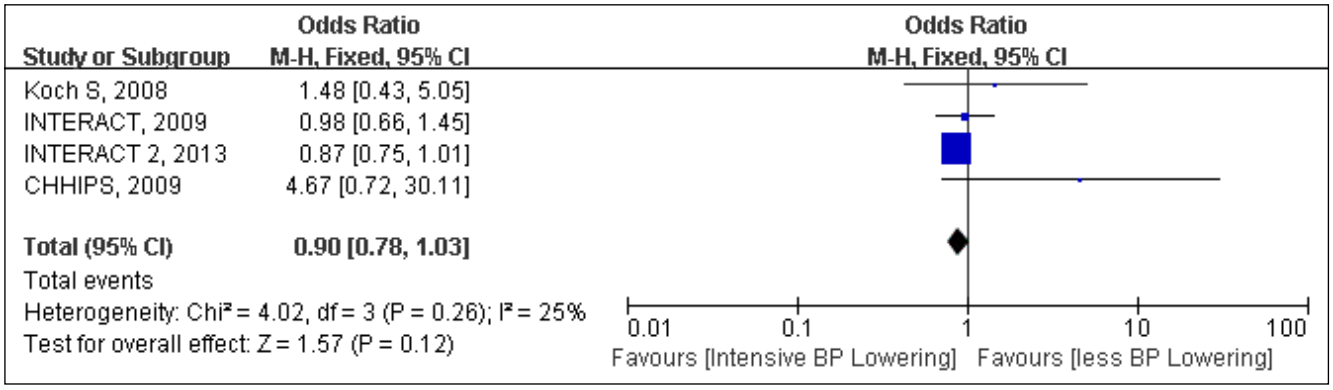

Figure 3: Odds ratio for unfavorable outcome at the end of follow-up: the comparison between more and less intensive BP targets in patients with ICH.

pressure reduction to a target SBP<140 mmHg appears to be a reasonable option for most ICH patients (3, 8). However, the available data are far from sufficiency to recommend a definitive policy and further large multicenter studies are still required.

In any meta-analysis, the possibility of publication bias should be considered as a potential threat to validity. But in this paper, we believe that the risk of publication bias affecting the results is minimal due to our extensive and sensitive searching. The high qualities of most included RCTs and subgroup analysis also reduce potential source of risk of bias. There is not any evidence of statistical heterogeneities in pooled analysis of each outcome. However, in this meta-analysis, several limitations should be noted:

First, it is not clear that ethnicity has a major effect on BP control and clinical outcomes in patients with ICH (22). About two thirds of the participants were recruited from China (14, 15). We intended to perform subgroup analysis according to ethnicity, but the inadequate data is not available to construct meaningful subgroup analysis (1). Second, ICP in most included patients may not increase significantly, because the hematoma volume in most included studies was relatively small (Table I). There is no data on ICP or CPP observed. As patients with elevated ICP may require a higher MAP to maintain adequate CPP, the small hematoma volume may reduce the rate of ischemia followed by intensive SBP treatment and limit the generalizability of the results (19). As the result, further clinical trial should be considered to stratify different hematoma volume for analysis. In addition, regular ICP monitoring may guide individualized BP control with appropriate CPP in such a population (11).

At present, Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial is ongoing complement to INTERACT2, which also randomized assigns patients to a target SBP<140 mmHg or <180 mmHg with similar primary and secondary end points and outcome measures (1, 16). It is hoped that this trial could enhance the evidence to guide the intensive BP lowering target in patients with ICH.

CONCLUSIONS

Acute lowering of SBP to 140 mmHg is probably beneficial for functional outcome in patients with ICH. But the available data of acute lowering BP on ICH outcome are far from sufficiency to recommend a definitive policy and further large multicenter studies are still required to enhance the evidence to guide the BP lowering target following ICH.

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