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Efficacy of nimodipine in the treatment of subarachnoid hemorrhage: a meta-analysis

Eficácia da nimodipina no tratamento da hemorragia subaracnoidea: uma metanálise

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Abstract

Background Subarachnoid hemorrhage (SAH) is an uncommon and serious subtype of stroke, which leads to the loss of the patient's ability to produce and live for many years.

Objective To investigate the clinical effect of nimodipine in the treatment of SAH.

Methods Electronic databases including China National Knowledge Infrastructure (CNKI), VIP, SinoMed, China Master's Theses Full-text Database (CMFD), China Doctoral Dissertations Full-text Database (CDFD), Cochrane Library, PubMed and Embase were searched from 2010 and 2021. All randomized controlled trials evaluating the efficacy of nimodipine in the treatment of SAH were included in our meta-analysis. The patients were divided into control group and treatment group. Meta-analysis was performed with Stata16.0 software.

Results A total of 10 studies were included. Compared with the control group, the treatment group had higher effective rate (OR = 3.21, 95% CI: 2.25, 4.58; $p < 0.001$), and lower incidence of adverse reactions (OR = 0.35, 95% CI: 0.19, 0.67; $p = 0.001$). Before treatment, no significant differences were identified in middle cerebral artery blood flow velocity and Glasgow coma scale (GCS) score between the two groups. However, after treatment, the middle cerebral artery blood flow velocity (SMD = −1.36, 95% CI: −2.28, −0.49; $p = 0.002$) and GCS score (SMD = 1.24, 95% CI: 0.58, 1.89; $p < 0.001$) in the treatment group were significantly better than those in the control group.

Conclusions Nimodipine is effective in the treatment of SAH, lowering incidence of adverse reactions and therefore improving the prognosis of patients.

Keywords
- Nimodipine
- Subarachnoid Hemorrhage
- Meta-analysis
- Treatment Outcome

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Resumo

Antecedentes Hemorragia subaracnóidea (SAH) é um subtipo raro e grave de acidente vascular cerebral (AVC), o que leva à perda da capacidade do paciente de produzir e viver por muitos anos.

Objetivo Investigar o efeito clínico da nimodipina no tratamento da SAH.

Métodos As bases de dados eletrônicas, incluindo a China National Knowledge Infrastructure (CNKI), VIP, SinoMed, Masters Theses Full-text Database (CMFD), China Doctoral Dissertations Full-text Database (CDFD), Cochrane Library, PubMed e Embase foram pesquisadas no período de 2010 a 2021. Todos os ensaios controlados aleatorizados que avaliam a eficácia da nimodipina no tratamento da SAH foram incluídos na nossa meta-análise. Os pacientes foram divididos em grupo controle e grupo de tratamento. Meta-análise foi realizada com o software Stata 16.0.

Resultados Foram incluídos um total de dez estudos. Em comparação com o grupo controle, o grupo de tratamento tinha uma taxa mais elevada (OR = 3,21, 95% CI: 2,25, 4,58; $p < 0{,}001$), e menor incidência de reações adversas (OR = 0,35, 95% CI: 0,19, 0,67; $p = 0{,}001$). Antes do tratamento, não foram identificadas diferenças significativas na velocidade média do fluxo sanguíneo da artéria cerebral e na pontuação de Glasgow coma scale (GCS) entre os dois grupos. No entanto, após o tratamento, a velocidade média do fluxo sanguíneo da artéria cerebral (SMD = −1,36, 95% CI: −2,28, 0,49; $p = 0{,}002$) e a pontuação do GCS (SMD = 1,24, 95% CI: 0,58, 1,89; $p < 0{,}001$) no grupo de tratamento foram significativamente melhores do que os do grupo controle.

Conclusões A nimodipina é eficaz no tratamento da SAH, diminuindo a incidência de reações adversas e, consequentemente, melhorando o prognóstico dos doentes.

Palavras-chave
- Nimodipina
- Hemorragia Subaracnóidea
- Metanálise
- Resultado do Tratamento

INTRODUCTION

Subarachnoid hemorrhage (SAH) refers to a clinical syndrome caused by sudden rupture and hemorrhage of blood vessels at the base or surface of the brain, due to various causes, and the subsequent direct blood flow to the subarachnoid membrane.[1] It is a cerebrovascular disease with rapid onset and frequent recurrence, accompanied by cerebral vasospasm (CVS) and other high-risk complications.[2] Clinical studies have shown that intracranial aneurysm rupture, cerebrovascular malformations, and vascular abnormalities at skull base can induce this disease, especially intracranial aneurysm rupture.[3]

Clinical studies have shown that nimodipine can effectively prevent and treat CVS after SAH, and therefore reduce mortality without increasing the risk of rebleeding.[4] Nimodipine has high lipid solubility and can smoothly pass through the blood-brain barrier into the nervous system.[5–7] This drug, as a calcium channel blocker, reduces Ca2 + influx in brain cells and free radical formation, and encourages the vascular smooth muscle to become relaxed, thereby reducing vasospasm.[8,9] Additionally, nimodipine also has the effects on anti-free radical injury and antagonistic effect on endothelin neurotoxicity, thus improving the tolerance of nerve cells to ischemia and hypoxia, and improving neurological functions, reducing cerebral ischemia-caused death and global cerebral infarction after SAH, and, consequently, effectively improving prognosis.[10,11] Several meta-analyses have evaluated the efficacy of nimodipine in the treatment of SAH. Vergouwen et al.[12] found no effect of nimodipine on the prognosis of patients with traumatic SAH by including five studies in their analysis. Liu et al.,[13] in 2011, found by meta-analysis results that nimodipine significantly reduced CVS and delayed neurological deficits, as well as cerebral infarction, compared with placebo. However, in recent years there have been fewer studies on the comprehensive evaluation of the clinical efficacy of nimodipine in the treatment of SAH. Therefore, a critical systematic review would be very beneficial for clinicians. In this study, a meta-analysis was used to comprehensively evaluate the efficacy and safety of nimodipine in the treatment of SAH using a large sample size.

METHODS

Literature search strategy

The electronic databases including China National Knowledge Infrastructure (CNKI), VIP, SinoMed, China Master's Theses Full-text Database (CMFD), China Doctoral Dissertations Full-text Database (CDFD), Cochrane Library, PubMed and Embase were used to search for the efficacy of nimodipine in the treatment of SAH from 2010 to 2021. The keywords using the following terms: (*nimodipine*) AND (*subarachnoid hemorrhage* OR *SAH*) AND (*clinical effect*). The Chinese database was also searched using the above search terms in Chinese. Additionally, a manual search of references to relevant journals and retrieved articles was conducted by reviewing titles and abstracts. There were no language restrictions in the literature search process.

Inclusion criteria

1) Types of studies: randomized controlled trials (RCTs). 2) Study subjects: patients diagnosed with SAH by clinical examination. 3) Types of intervention: the patients were divided into control

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group and treatment group according to different treatment methods. The control group mainly received routine treatment including oxygen inhalation, hemostasis, lowering intracranial pressure, maintaining stable blood pressure, symptomatic treatments (such as analgesia, sedation, preventing infection, correcting metabolic disorders), and bed rest. The treatment group was treated with continuous administration of nimodipine adjuvant therapy by intravenous pump on the basis of routine treatment. The treatment lasted for 2 weeks in both groups. 4) Outcome measures: effective rate, incidence of adverse reactions, comparison of the middle cerebral artery (MCA), blood flow velocity (BFV), and the Glasgow coma scale (GCS) score before and after treatment in both groups. Adverse reactions mainly include hemorrhage, CVS, cerebral infarction, hydrocephalus, death, decreased blood pressure, and intracranial infection.

Exclusion criteria

Literature that met any of the following criteria was excluded: studies in which the data required by this meta-analysis were not provided and could not be obtained; the original text could not be obtained; studies with missing data; duplicates; case reports, systematic reviews, opinion articles, or studies with animal experiments.

Literature screening and quality evaluation

Two reviewers independently initially screened studies by reading titles and abstracts. Then, the full text of randomized controlled trials was required to be read to determine whether it met the inclusion criteria, followed by cross-checking. The final included studies were jointly decided by two reviewers. During this process, the disagreement was resolved by discussion between the two or by a third party's decision. For the repeated or extended reports, the recently published ones with complete data were selected.

The literature quality was evaluated using the Newcastle-Ottawa scale (NOS).[14]

Data extraction

Reference Aid for Medicine v3.0 and Endnote X5 (Clarivate Analytics, London, UK) were used to manage and extract the data including: ①basic information: the first author, publication time, number of included population; ② baseline information of patients: age, diagnosis, etc.; ③ intervention measures: the total number of patients in the control and treatment groups, the number of males and females, and the treatment method; ④ study results: the number of CVS, rebleeding, and deaths; ⑤ study design type: clinical randomized controlled trial.

Statistical analysis

The Stata 16.0 (StataCorp LLC., College Station, TX, US) software was used for statistical analysis of the collected data. The included enumeration data (binary variables), such as effective rate, incidence of CVS, and incidence of adverse reactions were presented and analyzed using an odds ratio (OR) and 95% confidence interval (CI), while measurement data (continuous variables) were analyzed using mean difference (MD) and 95% CI. The heterogeneity analysis of recruited studies was performed by I^2 statistic. The random-effect model (REM) was adopted for meta-analysis if significant heterogeneity was assessed ($p < 0.10$ and $I^2 > 50\%$); Otherwise, the fixed-effect model (FEM) was employed. A statistically significant difference was indicated if $p < 0.05$.

RESULTS

Results of literature screening and quality evaluation

According to the search strategy, a total of 611 studies were retrieved. Of these, 531 irrelevant studies were excluded after evaluating titles and abstracts. Then, 34 duplicate articles were excluded, and 13 were eliminated after reading the full text. Finally, 10 studies[15–24] were included for meta-analysis. The literature screening process is shown in ►**Figure 1**.

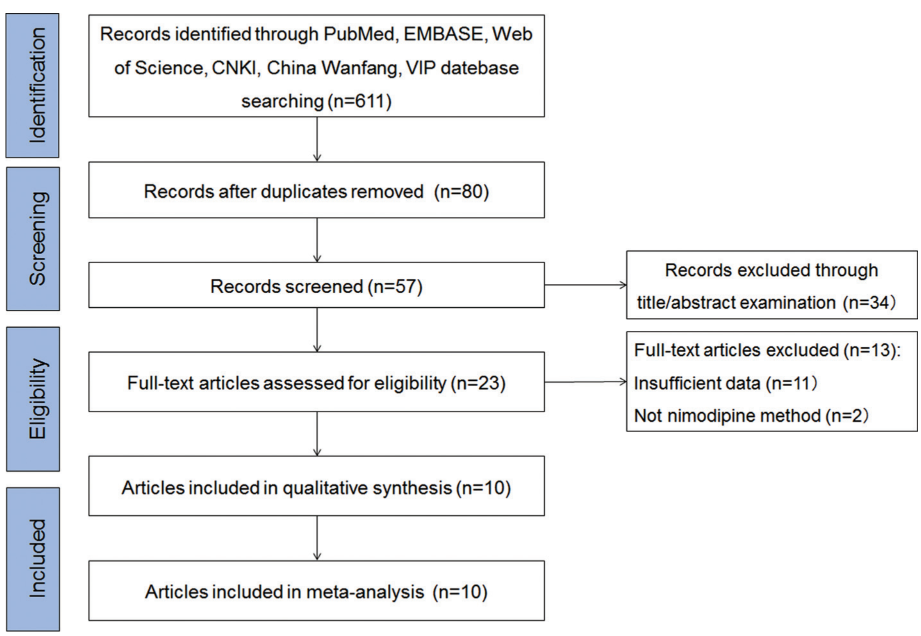

Figure 1 Literature screening process.

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The basic characteristics of the included studies are shown in ►**Table 1**. All studies were RCTs, and the subjects were patients with traumatic SAH in 9 studies, and non-traumatic SAH in 1 study.[22] A total of 882 patients were included in the study, including 439 in the control group and 443 in the treatment group. There were no significant differences between the treatment group and the control group in terms of patient age, and male to female ratio. All literature had NOS scores greater than 6, which were of high quality and could be included in the meta-analysis. Finally, the risk of bias graph and risk of bias summary are observed in ►**Figure 2A-B**.

Results of meta-analysis

Effective Rate and Incidence of Adverse Reactions

A total of 9 articles[15–20,22–24] reported the effective rate of treatment. No heterogeneity was identified among these studies ($I^2 = 0.0\%$, $p = 0.949$), so FEM was utilized to pool the effect size. The results showed that the effective rate in the treatment group ($n = 397$) was significantly higher than that in the control group ($n = 393$) (OR = 3.21, 95% CI: 2.25, 4.58; $p < 0.001$) (►**Figure 3A**).

Additionally, 8 articles[15–19,22–24] reported the incidence of adverse reactions. Marked heterogeneity was identified in these studies ($I^2 = 65.7\%$, $p = 0.005$), so REM was utilized to pool the effect size. The results showed that the incidence of adverse reactions after treatment in the treatment group ($n = 359$) was significantly lower than that in the control group ($n = 355$) (OR = 0.35, 95% CI: 0.19, 0.67; $p = 0.001$) (►**Figure 3B**).

MCA blood flow velocity before and after treatment

There were 7 articles[15–17,20–22,24] which reported MCA blood flow velocity before treatment. No heterogeneity was identified among these studies ($I^2 = 0.0\%$, $p = 0.961$), so FEM was adopted for pooling the effect size. The results revealed no significant difference in MCA blood flow velocity before treatment between the two groups (SMD = −0.01, 95% CI: −0.17, 0.14; $p = 0.85$) (►**Figure 4A**), indicating the comparability of the experiments.

Furthermore, the heterogeneity ($I^2 = 96.8\%$, $p < 0.001$) was identified in the 10 articles[15–24] reporting MCA after treatment, so REM was used to pool the effect sizes. The result showed that MCA blood flow velocity after treatment in the treatment group ($n = 443$) was significantly lower than that of the control group ($n = 439$) (SMD = −1.36, 95% CI: −2.28, −0.49; $p = 0.002$) (►**Figure 4B**).

GCS score before and after treatment

Only half, 5, of the selected articles[16,17,20,21,24] reported GCS score before treatment. No heterogeneity was identified among these studies ($I^2 = 0.0\%$, $p = 0.462$), so FEM was adopted for pooling the effect size. The results revealed no significant difference in GCS score before treatment between the two groups (SMD = −0.06, 95% CI: −0.25, 0.12; $p = 0.504$) (►**Figure 4C**).

Further, marked heterogeneity ($I^2 = 90.3\%$, $p < 0.001$) was identified in the 10 articles[15–24] reporting GCS score after

Table 1 The basic characteristics of inclusion in the literature

Study	Year	Sample time	Cases Treat/Con	Age (years)		Sex ratio (M/FM)		Study design	Treatment time (day)	NOS score	Outcome measures
				Treat	Con	Treat	Con				
Liu Y. et al.[15]	2014	2009.10~2012.09	31/31	38 ± 12	37 ± 14	18/13	15/16	RCT	28	7	①②③④
Zheng SB et al.[16]	2017	2015.06~2017.01	60/60	48.3 ± 6.5	49.3 ± 6.7	40/20	38/22	RCT	14	6	①②③④⑤⑥
Ma LJ. et al.[17]	2019	2017.01~2018.12	40/40	54.3 ± 8.3	53.1 ± 8.6	23/17	25/15	RCT	14	6	①②③④⑤⑥
Tian Y. et al.[18]	2014	2009.01~2012.01	31/31	43.8 ± 3.2	33.2 ± 2.8	20/11	18/13	RCT	14	6	①②④
Cao YB. et al.[19]	2014	2013.01~2013.12	32/28	34.1 ± 8.4	33.8 ± 7.9	19/13	16/12	RCT	21	6	①②④
Zuo MX.[24]	2017	2015.06~2017.01	45/45	36.5 ± 2.3	36.2 ± 2.1	20/25	22/23	RCT	21	7	①②③④⑤⑥
Zhu ZY.[20]	2019	2016.01~2018.12	38/38	45.6 ± 7.6	44.2 ± 1.8	15/23	16/22	RCT	28	7	①③④⑤⑥
Wang Y., Zhan JN.[21]	2011	2008.03~2010.02	46/46	47.1 ± 8.9	46.5 ± 9.2	26/20	25/21	RCT	21	7	③④⑤⑥
Dong XF. et al.[22]	2019	2014.04~2017.04	80/80	46.4 ± 4.6	47.2 ± 4.3	45/35	42/38	RCT	56	7	①②③④
Cao YS. et al.[23]	2011	2008.08~2009.12	40/40	49.7 ± 2.4	50.2 ± 2.5	31/19	32/18	RCT	14	6	①②④

Abbreviations: Treat, treatment group; Con, control group; M, male; FM, female; RCT, randomized controlled trial; NOS, Newcastle-Ottawa scale. **Notes:** ①: effective rate of treatment; ②: adverse effects rate; ③: blood flow velocity of middle cerebral artery before treatment; ④: blood flow velocity of middle cerebral artery after treatment; ⑤: Glasgow coma scale (GCS) score before treatment; ⑥: GCS score after treatment.

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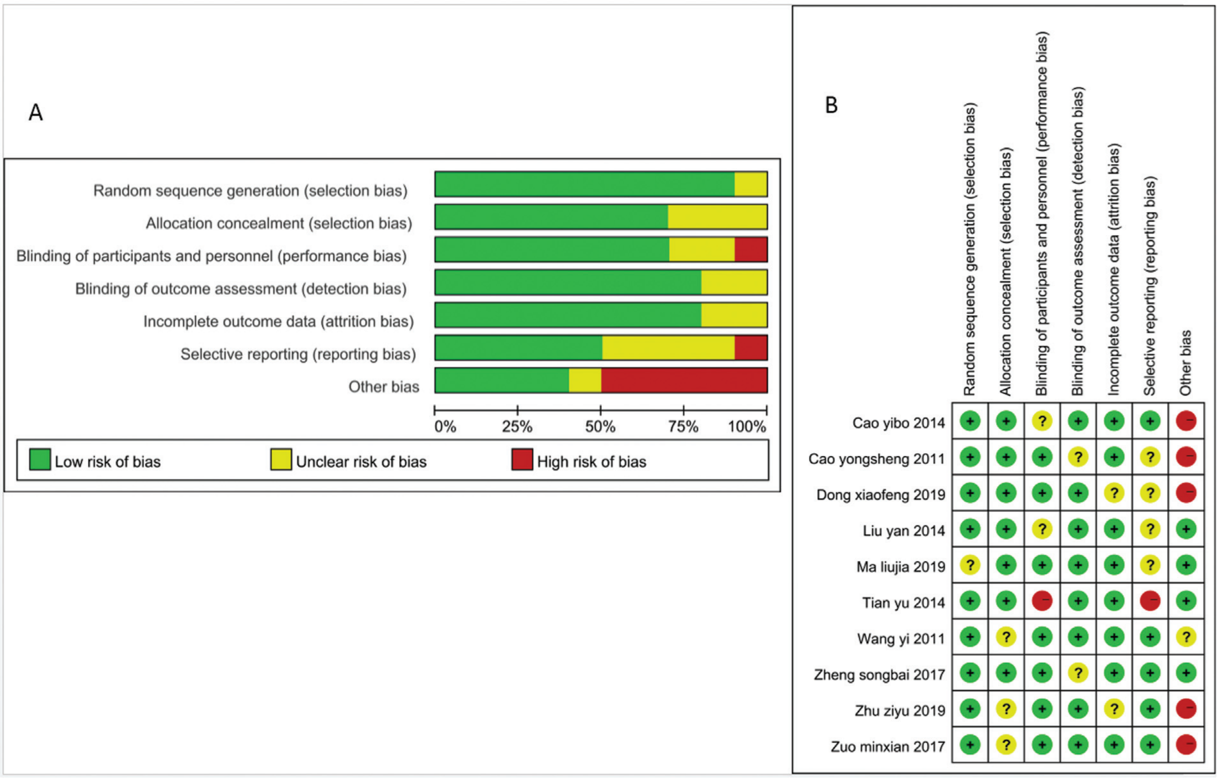

Figure 2 The risk of bias graph (A) and bias summary (B).

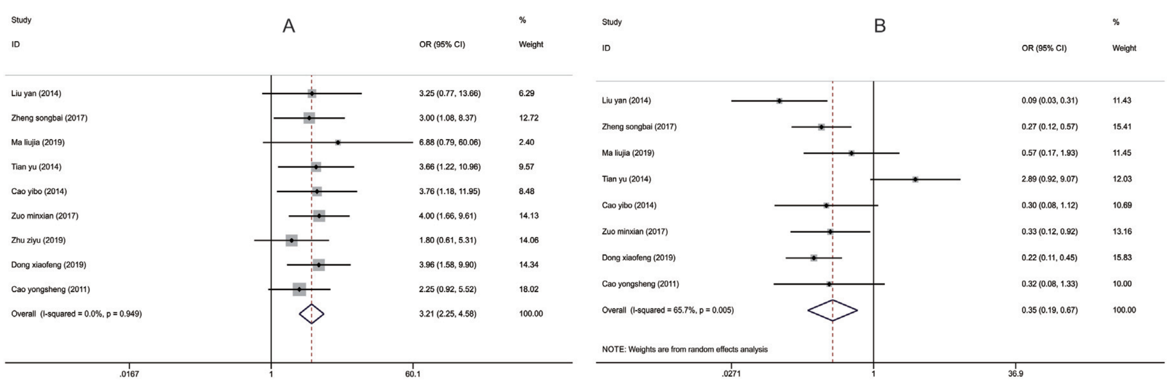

Figure 3 Forest plots of effective rate (A) and incidence of adverse reactions (B).

treatment, so REM was used to pool the effect sizes. The result showed that GCS score after treatment in the treatment group ($n = 229$) was significantly higher than that of the control group ($n = 229$) (SMD = 1.24, 95% CI: 0.58, 1.89; $p < 0.001$) (►**Figure 4D**).

Sensitivity analysis

Due to the heterogeneity of included studies regarding effective rate, incidence of adverse reactions, as well as MCA blood flow velocity and GCS after treatment, sensitivity analysis was required. After eliminating each literature one by one, it was found that the overall heterogeneity did not change significantly (►**Figure 5A-F**), indicating stable and reliable results of this study.

DISCUSSION

As a clinical syndrome, SAH occurs in a critical condition, and is prone to rebleeding and CVS, threatening the life of patients. Studies have shown that there is a correlation between adverse reactions caused by SAH and structural and functional changes in the vascular wall.[25] Nimodipine has a definite neuroprotective effect, such as antioxidant effect, which improves cerebral metabolic rate of oxygen and reduces brain injuries due to calcium overload during cerebral blood flow reperfusion.[26] Its neuroprotective effect can also relieve brain edema and glial cell swelling after SAH, while effectively reducing the risk of death secondary to CVS.[27,28] In this study, we

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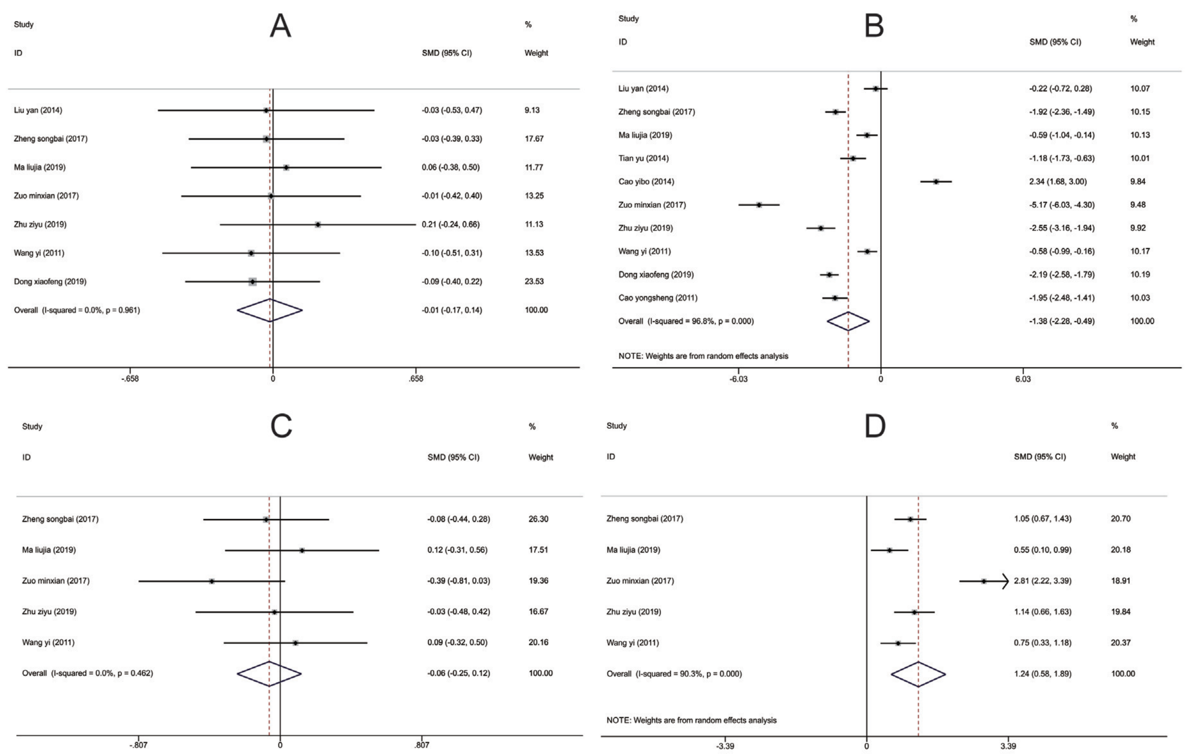

Figure 4 Forest plots of middle cerebral artery (MCA) blood flow velocity of two groups before (**A**) and after (**B**) treatment; forest plots of the Glasgow coma scale (GCS) score of the two groups before (**C**) and after (**D**) treatment.

systematically provide data on the clinical efficacy of nimodipine in the treatment of SAH. After a comprehensive literature search and evaluation, a total of 10 studies (882 patients with SAH) were included for meta-analysis. The results showed that patients in the nimodipine group had significantly higher treatment efficiency and a significantly lower incidence of adverse effects (including hemorrhage, CVS, cerebral infarction, hydrocephalus, death, decreased blood pressure, and intracranial infection) compared with the control group. This result is consistent with the findings of others. Hockel et al.[29] showed that continuous intra-arterial treatment with nimodipine prevented secondary cerebral ischemia in patients with prolonged severe macrovascular spasm.

Additionally, our study compared the MCA blood flow velocity and found that BFV in MCA was significantly lower in the nimodipine group after treatment. Sun et al.[30] showed that the use of electroacupuncture for CVS in patients with SAH improved CVS by significantly reducing BFV in MCA. These studies suggest that nimodipine may improve CVS by reducing BFV in MCA. The GCS is the most widely used scoring system for level of consciousness.[31] Likewise, the score is also widely used by neurosurgeons for the initial assessment of patients with SAH, with higher scores indicating a lower level of consciousness impairment.[32] Studies by Zheng et al.[16] and Ma et al.[17] then found that the GCS score was significantly higher in the nimodipine combination therapy group of SAH patients after treatment. In the present study, we found that the GCS score of patients in the nimodipine-treated group were significantly higher than those in the control group.

In summary, nimodipine is effective in the treatment of SAH, lowering the incidence of adverse reactions, reducing the incidence of CVS and improving the prognosis of patients.

This study is a secondary research, and therefore its quality mainly depends on the quality of the original researches and may have the following limitations. First, relevant studies are collected by searching the electronic database and manual screening literature and references. Therefore, the omission of related articles may be caused by the possible shortcomings in electronic database collection and search strategy. Second, only domestic studies based on clinical randomized controlled trials are collected, and the comprehensive evaluation of literature quality is not high. Therefore, the statistical results may be biased. Third, the low methodological quality of the included literature and small sample size of many studies will lead to low power of the test, and affect the strength of evidence of this study. Collectively, it is still necessary to carry out a well-designed, scientific, large-sample, multicenter, prospective clinical study to verify the above conclusions, and to provide more reliable clinical evidence of medication.

Authors' Contributions

JL, CS, YW, QL, ML: substantial contributions to the design and development of the study; GN, QD, JY: substantial

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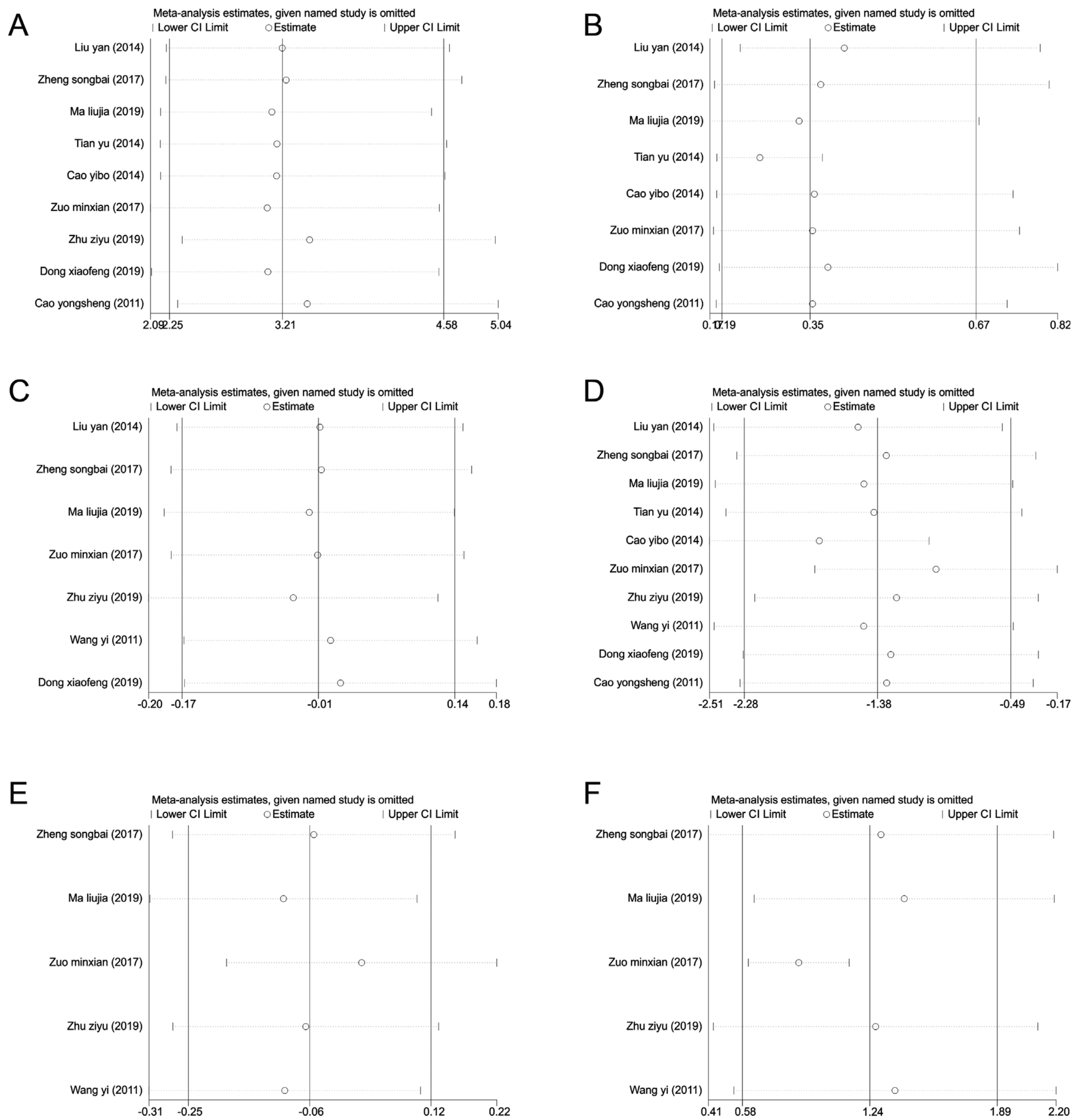

Figure 5 Sensitivity analysis of effective rate (**A**) and incidence of adverse reactions (**B**); sensitivity analysis of middle cerebral artery (MCA) blood flow velocity of two groups before (**C**) and after (**D**) treatment; sensitivity analysis of Glasgow coma scale (GCS) score of the two groups before (**E**) and after (**F**) treatment.

contributions in the collection, analysis, and interpretation of data; QL, ML: substantial contributions in the writing of the article, and in its critical revision; All authors: substantial contributions in the approval of the final version. Jianqiang Liu, Cuimei Sun and Ying Wang contributed equally in this article.

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Conflict of Interest

The authors have no conflict of interests to declare.

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