The efficacy of mild hypothermia combined with edaravone in the treatment of craniocerebral injury：A meta-analysis

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DOI: https://doi.org/10.56293/IJASR.2022.5450

IJASR 2022
VOLUME 5
ISSUE 6 NOVEMBER - DECEMBER **ISSN: 2581-7876**

Abstract: Purpose: The purpose of this meta-analysis was to evaluate the efficacy of mild hypothermia combined with edaravone in the treatment of craniocerebral injury. **Methods:** Databases, including Cochrane Library, PubMed, Embase, Medline, WebofScience, CNKI, VIP, and Wanfang Database were searched from the dateof their establishmentto October 2021, toaccessclinical randomized controlled trials(RCTs) of mild hypothermia combined with edaravonefor craniocerebral injury.Ameta-analysis was then conducted byusing RevMan 5.4.1software programs.**Results:**A total of 14 RCTs including 1166 patients were included. The results of the meta-analysis were as followed, combination group compared with the control group, can reduce the degree of brain edema [RR=1.94,95%CI=(1.59, 2.36)] and improve the recovery of patients with craniocerebral injury from coma [MD=-0.74,95%CI=(-0.81,-0.67)].Effectively reduce the degree of postoperative neurologic deficits [MD = 4.41, 95% CI = (3.65, 5.18)], patient quality of life improved after discharge [MD = 0.74, 95% CI = (0.81, 0.67)].**Conclusion:**Mild hypothermia combined with edaravonehas efficacy in the treatment of the craniocerebral injury.It helps to reduce the degree of brain edema and improve the prognosis of patients with craniocerebral injuries.

Keywords: mild hypothermia; edaravone; craniocerebral injury

Introduction

Craniocerebral injuryis a common clinicalneurosurgical condition, mainly caused by traffic accidents, fall injuries, conflict, brawls, and violent abuse [1].Although there have been many advances in clinical treatment and basic research in recent years, the condition of craniocerebral injury patients is complex and still has a high mortality and disability rate, so the clinical treatment of craniocerebral injury is still the focus of neurology.Currently, the treatment of patients with craniocerebral injury still adopts a comprehensive approach, aiming to reduce intracranial pressure and protect brain tissue. The main surgical treatment modalities are simple craniotomy for hematoma removal and decompression of the debridement flap. Medication is used for dehydration, hibernation combination, and hormones. Other adjuvant treatments aremild hypothermia and hyperbaric oxygen [2].Edaravone is the only new free radical scavenger that has passed phase III clinical trials [3]. It is a potent hydroxyl radical scavenger and antioxidant, which can effectively scavenge free radicals, inhibit lipid peroxidation and delay neuronal cell death and is widely used by neurologists in neurological diseases [4]. Mild hypothermia can protect brain tissue, and its clinical application effectively reduces the mortality rate of patients with craniocerebral injury and improves the quality of survival without serious complications. Currently, there are only a few clinical studies on the use of subfreezing combined with edaravone in treating patients with craniocerebral injury, and no relevant meta-analysis has been published. Therefore, this paper aims to compile relevant studies and conduct a meta-analysis to evaluate the clinical efficacy of mild hypothermia combined with edaravone in the treatment of craniocerebral injury, to provide a basis for clinical practice.

Information and methods

1. Literature inclusion and exclusion criteria

1.1 Study type

Randomized controlled trials (RCTs), with or without allocation concealment and blinding.

1.2 Study subjects

Patients with craniocerebral injury, whose age, gender, race, nationality, disease duration, and type of craniocerebral injury were not limited.

1.3 Interventions

The control group was treated with conventional therapeutic therapies, such as surgery and drug conventional treatment. The experimental group was treated with mild hypothermiabased on the control group, including the use of mild hypothermia treatment apparatus or intravenous continuous drip of dormant muscarinic combination set to rectal temperature (RT) 34 ~ 35 ℃ for 4-7 days. At the same time, an edaravone injection of 30 mg was added to 0.9% sodium chloride injection 100 mL intravenously, once in the morning and once in the evening, for two weeks as a course of treatment.

1.4 Outcome indicators

①GCS score after 7 days of treatment; ②GCS score after 14 days of treatment; ③Degree of cerebral edema after 14 days of treatment; ④NHISS score; ⑤GOS score.

1.5 Exclusion criteria

①Non-RCT studies; ② Studies with inconsistent interventions; ③ Studies with no outcome indicators of interest; ④ Repeatedly published studies.

2. Literature search strategy search

Computer searches of CNKI, WanFang Data, VIP, PubMed, Embase, Cochrane Library, and Web of Science databases were conducted to collect RCT studies on mild hypothermia combined with edaravone in the treatment of craniocerebral injury, all with a search time frame of build to October 2021. The search was conducted using a combination of subject terms and free words. Chinese search terms included: hypothermia, edaravone, craniocerebral injury, traumatic brain injury, randomized controlled trial, etc.; English search terms included: Hypothermia, Induced, Edaravone, Craniocerebral Trauma, Randomized controlled trial, etc. PubMed was used as an example.

3. Literature screening and data extraction

First, duplicates were removed using Endnote literature management software, and then two investigators independently screened the literature according to the inclusion and exclusion criteria, extracted the data, and cross-checked them. Studies that had disagreements and were difficult to determine for inclusion were discussed with the third investigator to decide whether to include them. The information extracted included: (1) basic information about the included studies: including study title, first author, and publication time; (2) basic characteristics of the study subjects: including sample size of each group, age, sex, and disease status of patients; (3) interventions, follow-up time, etc.; (4) information related to the risk of bias assessment; (5) outcome indicators and outcome measures of interest, clinical effectiveness, safety, etc. and made into a table to build a meta-analysis database.

4. Risk of bias evaluation for the included studies

Two evaluators evaluated the quality of the included studies and cross-checked the results according to the risk of bias assessment tool provided by the Cochrane systematic review manual for RCT studies. The content mainly included: randomization method, allocation concealment, patient investigator blinding, outcome evaluation blinding, data completeness, selective reporting, and other biases.

5. Statistical methods

Meta-analysis was performed using Revman 5.4.1. Continuous variables: weighted mean difference (WMD) was used as an effective indicator if the same intervention, unit of measurement, and method of measurement were consistent; if there was inconsistency in a unit of measurement and method of measurement, standardized mean

difference (SMD) was used as an effective indicator. All used 95% confidence interval (CI). Dichotomous variables: relative risk (RR) was used as the effect indicator. If P>0.05 and I2≤50%, the heterogeneity among the studies was considered small, and the fixed-effect model was selected for analysis; if P≤0.05 and I2 ＞50%, the heterogeneity among the groups was considered large, and the sources of heterogeneity could be found and the causes of high heterogeneity could be analyzed by excluding the studies with high heterogeneity one by one, conducting subgroup analysis or Meta-regression according to the different nature of the studies, etc. If the literature with high heterogeneity was excluded, the causes of high heterogeneity could be significantly reduced. If eliminating the literature with high heterogeneity can significantly reduce the heterogeneity and does not affect the evaluation results, then the high heterogeneity studies can be retained and the random effects model can be used for data analysis. If the above methods could not significantly reduce the between-group heterogeneity, qualitative descriptions were used and Meta-analysis was not performed.

Results

1. Literature selection process and results.

Ninety pieces of relevant literature were examined (of which 29 literature were retrieved from English databases), and after stratification screening, 14 pieces of literature involving 14 studies were finally included [5-18], with a total of 1166 patients included in the study. The literature screening process and results are shown in **Figure 1.**

2. Basic characteristics of included studies and results of risk of bias evaluation

The basic characteristics of the included studies are shown in **Table 1,** and all 14 studies were two interventions and two-by-two comparisons. All 14 included studies [5-18], mentioned randomization, but only 9 studies [5-11, 15, 16] described the randomization method. Due to the limitations of the studies themselves, all studies did not describe concealed grouping and blinding of patients and assessors. The specific results of the risk of bias evaluation of the included studies are shown in **Figures 2 and 3.**

3. Meta-analysis results

3.1 Level of coma

The Glasgow coma scale (GCS), the most widely used coma scoring system, is used to assess the level of consciousness and degree of impairment after craniocerebral injury. A total of 7 studies [6, 9, 11-14, 16] reported the outcome indicators of GCS scores after 7 days of treatment, and a total of 579 patients were included with moderate heterogeneity between groups (P=0.01, I2 =64%), so a random-effects model was used for Meta-analysis, see Figure 4. 1.88, 95% CI=(-2.32, -1.45), P<0.01]. The analysis revealed that the heterogeneity was mainly derived from the study of Xie Xiaoyong [13], and after excluding this literature, the heterogeneity between groups was reduced (P=0.06, I2 =52%) and the difference between groups was not statistically significant. The conclusions were unchanged after re-running the Meta-analysis, and the heterogeneity may be related to differences in the duration of the patient's

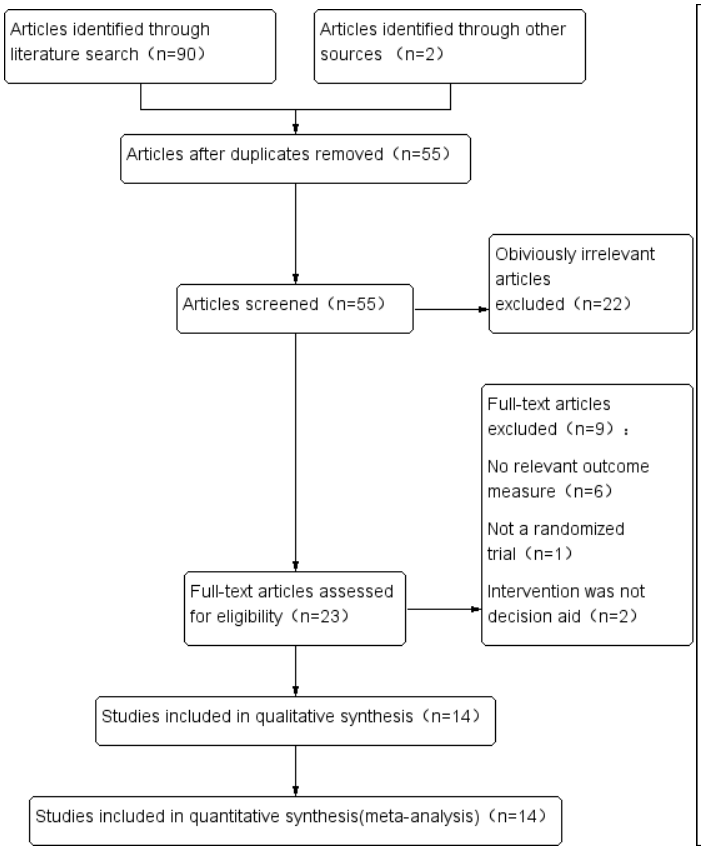

Figure 1. Flow chart for study inclusion and exclusion process

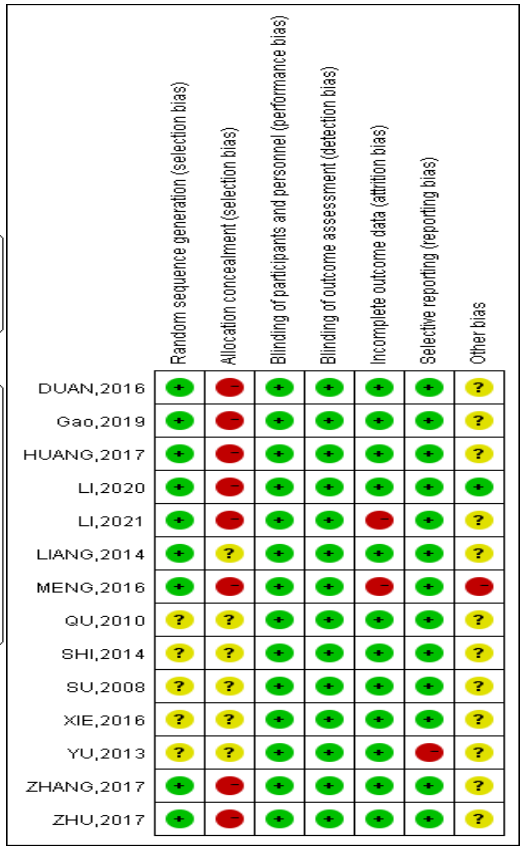

Figure 2. Risk ofbias of included RCTs

Disease and their level of medical care. The outcome indicators of GCS scores in patients after 14 days of treatmentwere reported in 11 studies [6, 7, 9-16, 18], which included a total of 865 patients with a high degree of heterogeneity between groups (P < 0.01, I2 = 80%), so a random-effects model was used for Meta-analysis, see **Figure 5**. 2.03, 95% CI = (-2.58, -1.48), P < 0.01]. Due to the high heterogeneity, we excluded studies one by one and found that they originated from two studies by Meng Qingjun [11] and Xie Xiaoyong [13]. After exclusion, heterogeneity was significantly lower (P = 0.13, I2 = 36%) and the difference between groups was not statistically significant. The conclusions were unchanged after re-running the Meta-analysis, and the analysis of the causes is still considered to be related to the treatment modality and the age of the patients.

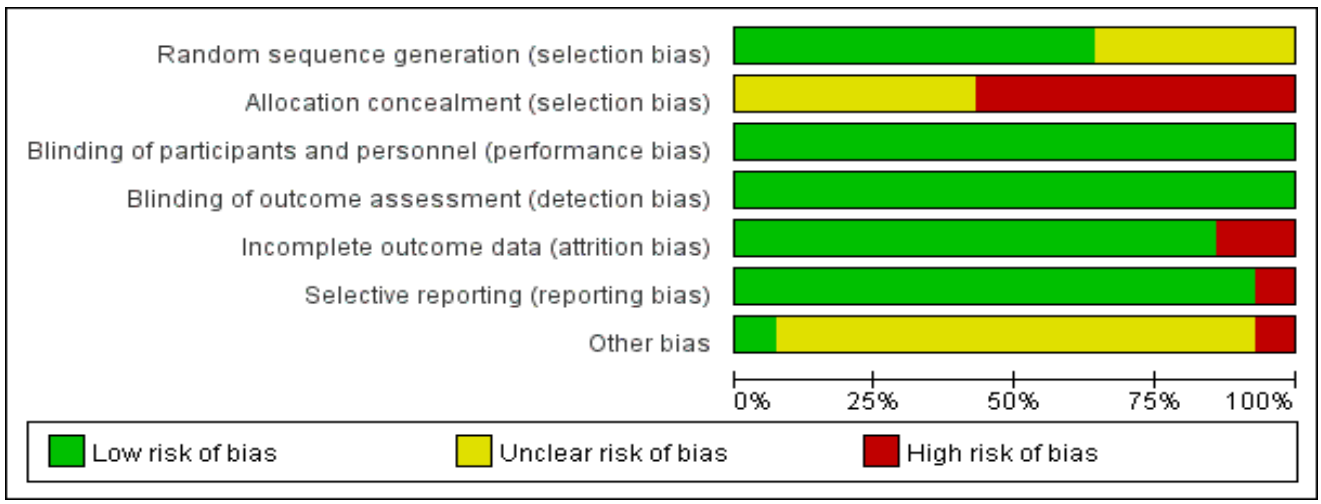

Figure 3.Cochrane Risk of Bias Chart of included RCTs

Table1.Characteristics of included studies

Citation	Location	Cases/n	Male/Female	Age(Y)	Outcome
XIE,2016[13]	China	68	42/26	19-70（48.33±5.92）	①②③
LI,2021[9]	China	50	27/23	30-60（42.32±3.86）	①②③⑤
MENG,2016[11]	China	200	112/88	15-60（43.7±11.2）	①②③⑤
ZHU,2017[15]	China	76	42/34	40-69（52.8±4.0）	②④
YU,2013[14]	China	80	56/24	18-69（33.8）	①②③⑤
SHI,2014[12]	China	80	55/25	19-70（33.5±1.3）	①②③⑤
LIANG,2014[10]	China	50	31/19	19-71（31.8±1.9）	②③⑤
ZHANG,2017[16]	China	42	24/18	21-69（37.8±9.3）	①②③⑤
LI,2020[8]	China	100	43/57	30-65	④
HUANG,2017[7]	China	80	43/37	27-69	②④
DUAN,2016[6]	China	78	53/25	17-65（34.3±4.5）	①②
Gao,2019[5]	China	120	69/51	24-56	③④⑤
QU,2010[17]	China	62	40/22	23-56（38.5）	⑤
SU,2008[18]	China	80	43/37	NA	②⑤

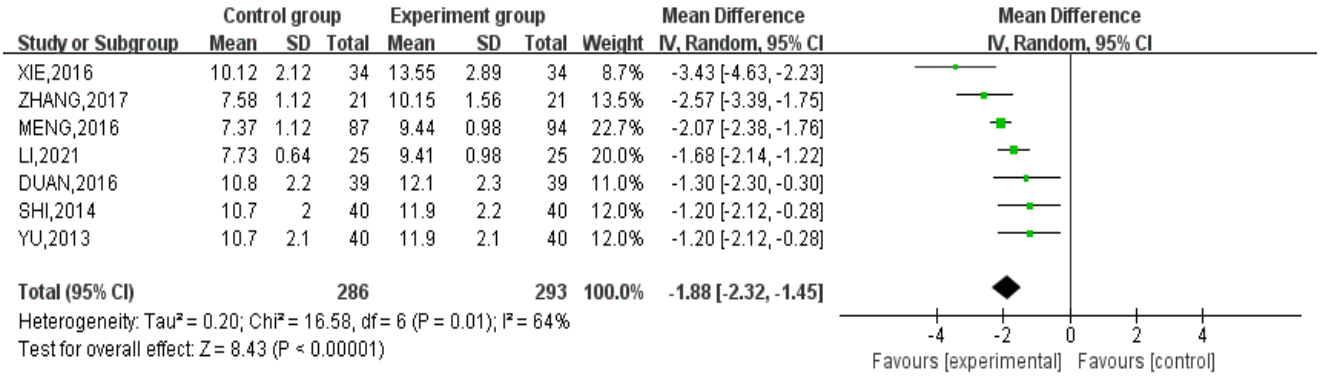

Figure 4. Meta-analysis forest plot of GCS scores after 7 days of treatment

3.2 Degree of cerebral edema

Brain edema is the increase of water in the brain tissue and the increase of brain volume. It is the response of brain tissue to various pathogenic factors, resulting in increased intracranial pressure and subsequent functional and structural damage to brain tissue. The degree of cerebral edema can reflect some extent the severity and prognosis of the patient's disease. A total of nine studies [5, 9-14, 16, 18] reported the degree of brain edema in patients 14 days after treatment, but three of these studies [5, 9, 11] took actual values of intracranial pressure to assess the degree of cerebral edema and had a small sample size; the remaining six studies [10, 12-14, 16, 18] used mild, moderate, and severe degrees to assess a total of 426 patients and included a relatively large sample size. Therefore, for this outcome index, it is proposed to use data from the latter studies with moderate and severe degrees of cerebral edema as the event occurrence outcome. The results showed good homogeneity between the groups (P=0.96, I2=0), so a fixed-effects model was used for Meta-analysis, as shown in **Figure 6**. The results showed that patients in the experimental group had less cerebral edema than the control group [RR=1.94, 95% CI=(1.59, 2.36), P<0.01].

3.3 Degree of neurological deficits

The NHISS score can be used to assess the degree of neurological deficits in stroke patients, at baseline to assess stroke severity and periodically after treatment to assess treatment outcome. A total of 4 studies reported patient NHISS scores [5, 7, 8, 15], including a total of 376 patients. There was a high degree of heterogeneity between

groups (P=0.004, I2 =78%), so a random-effects model was used for Meta-analysis, see **Figure 7**. The degree of neurological deficit was lower in the experimental group than in the control group [MD=4.71, 95% CI=(3.01, 6.42), P<0.01]. The heterogeneity was derived from the study of Huang Xiang [7] and was significantly reduced after exclusion (P=0.18, I2=41%), and the difference between groups was not statistically significant. The conclusions were unchanged after re-running the Meta-analysis and analyzing the reasons considered to be related to individual patient variability.

3.4 Degree of prognosis

The Glasgow Outcome Scale (GOS) can be used to assess patients during and after recovery from traumatic brain injury, stroke, or similar neurological injury, and can reflect the prognosis of patients to some extent. A total of 9 studies reported patient GOS scores [5, 9-12, 14, 16-18], but 2 of them [12, 14] took a GOS grading to assess patient prognosis, while the remaining 5 [5, 9-11, 16-18], which included a total of 297 patients, used continuous values. Due to the small sample size and few relevant research results, there was still a high degree of heterogeneity between groups (P < 0.01, I2 = 89%), so a random-effects model was used for Meta-analysis, as shown in **Figure 8.** Patients in the experimental group had a better prognosis than the control group [MD = -0.74, 95% CI = (-0.81, -0.67), P < 0.01]. Heterogeneity was mainly derived from the studies of Qu Jiahu [17] and Su Gang [18] and was significantly reduced after exclusion (P=0.13, I2=44%), with no statistically significant difference between groups. The conclusions were unchanged after re-running the Meta-analysis, and the reasons for this were considered to be related to the timing of measurement of outcome indicators by different researchers, and the existence of individual differences in the measurement criteria of outcome indicators by different measures.

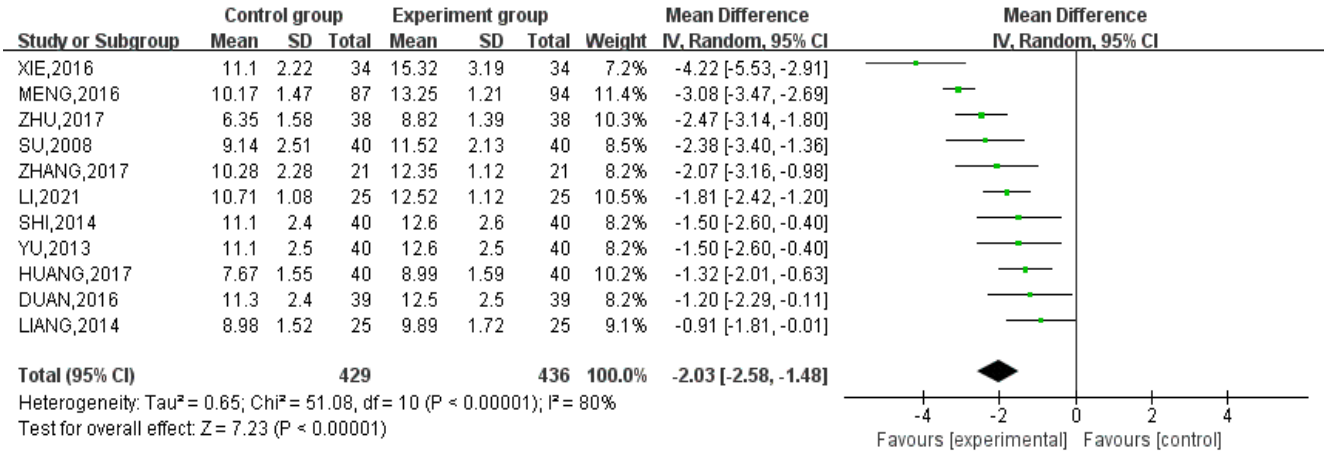

Figure 5. Meta-analysis forest plot of GCS scores after 14 days of treatment

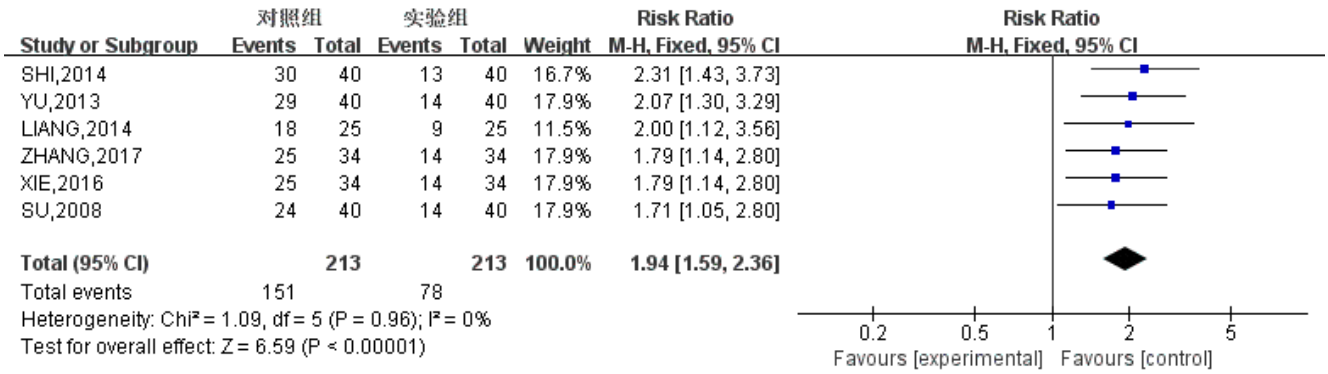

Figure 6. Meta-analysis forest plot of the degree of cerebral edema after14 days of treatment

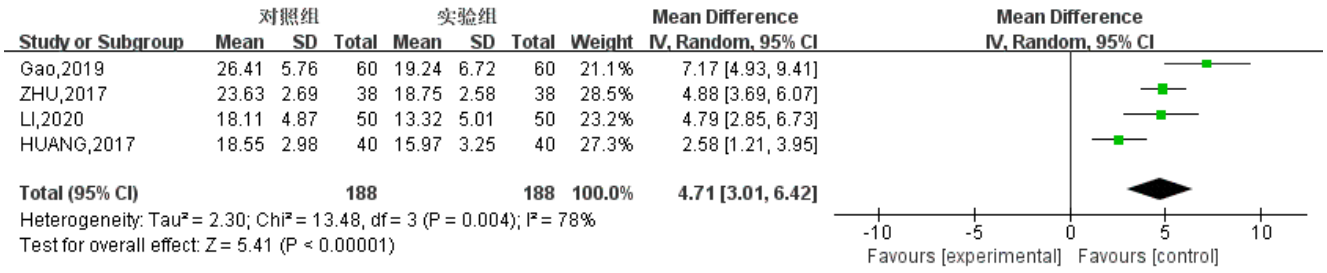

Figure 7. Meta-analysis forest plot of NHISS scores after treatment

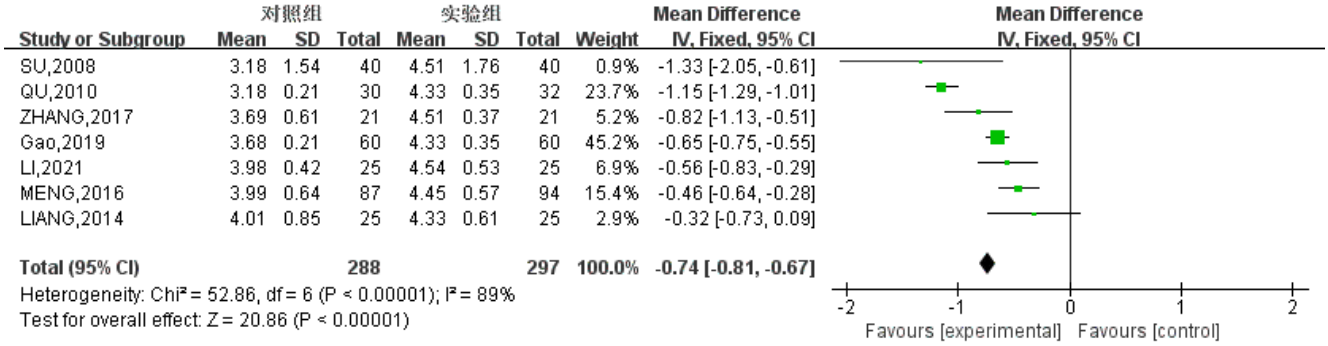

Figure 8. Meta-analysis forest plot of GOS scores after treatment

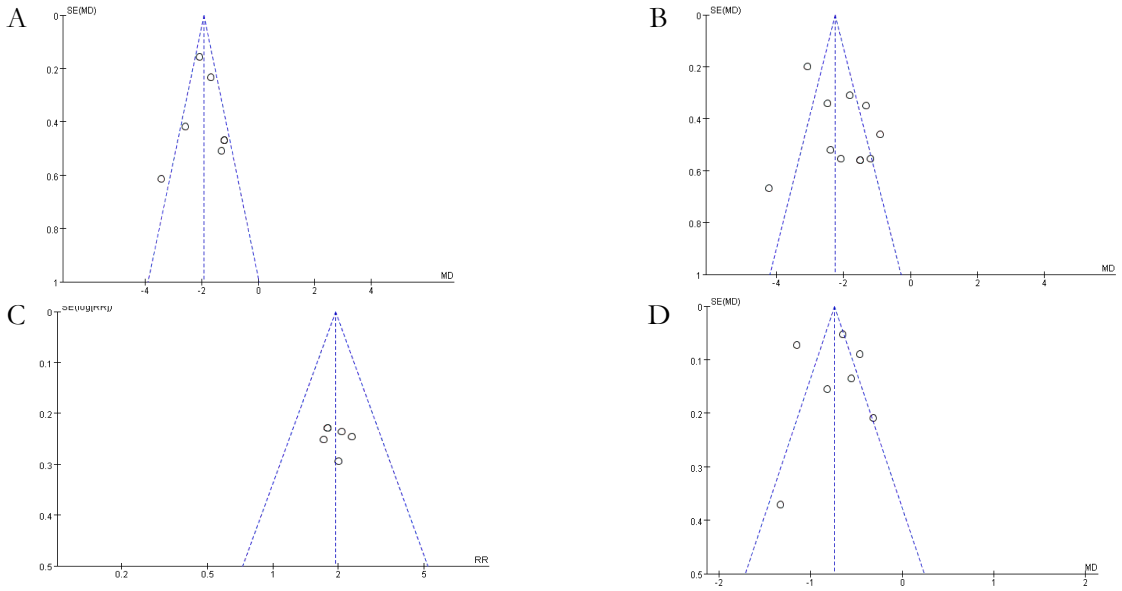

Figure 9-12. Funnel plot

(A.based on GCS score after 7 days of treatment; B. based on GCS score after 14 days of treatment; C. based on the degree of cerebral edema after14 days of treatment; D. based on GOS score aftertreatment)

4. Publication bias

A corrected funnel plot was drawn to test for publication bias, and the results showed that the study points were approximately evenly and symmetrically distributed on both sides of the vertical axis, with a low likelihood of publication bias, Figures 9-12.

Discussion

Craniocerebral injury is often rapid in onset and complex in condition. Therefore, a combination of multiple modalities is often used in clinical treatment. Despite the continuous improvement of medical treatment, the problem of a high death rate and poor prognosis of craniocerebral injury patients still exists. Brain ischemia, hypoxia, neurotransmitter depletion, and accumulation of toxic substances caused by craniocerebral injury [19] are the main reasons for the occurrence of secondary brain damage after craniocerebral injury. Therefore, reducing post-traumatic intracranial oxygen consumption, removing toxic substances, and promoting cerebral blood perfusion are essential to reduce the morbidity and mortality rate of craniocerebral injury, and disability and to improve the prognosis and life treatment of patients.

Related studies have confirmed that mild hypothermia can significantly reduce the oxygen consumption of brain tissues, decrease the energy metabolism of brain tissues, and result in the reduction of lactic acid accumulation in brain tissues [20]. Meanwhile, mild hypothermia can effectively protect the blood-brain barrier and further reduce the oxygen consumption and metabolic rate of brain tissues. It has a very important significance to reduce intracranial pressure and reduce cerebral edema. And edaravone, as a new type of brain tissue protector and free radical scavenger, has the clinical characteristics of high lipid solubility, strong antioxidants, and high blood-brain barrier passage rate [21], which can effectively scavenge free radicals, thus reducing oxidative damage to vascular endothelial cells and tissues, thus improving the degree of brain edema after craniocerebral injury. It can also effectively inhibit the activity of xanthine oxidase and hypoxanthine oxidase, resulting in a decrease in the production of inflammatory mediators such as leukotrienes [22], inhibiting delayed neuronal death and ultimately reducing neurological damage [4].

Although previous studies have shown that mild hypothermia treatment and edaravone treatment can improve the efficacy and prognosis of patients with craniocerebral injury. However, there is still a lack of efficacy for the combination of the two in the treatment of craniocerebral injuryIn this study, we evaluated the efficacy of mild hypothermia combined with edaravone in the treatment of craniocerebral injury using GCS scores, NHISS scores, GOS scores, and the degree of cerebral edema as outcome indicators at 7 and 14 days after treatment. According to the results of this study, based on emergency surgery and drug conventional treatment, mild hypothermia treatment combined with edaravone drug treatment had better efficacy compared with the control group who only underwent conventional treatment. The GCS scores of patients in the experimental group were higher than those in the control group after 7 and 14 days of treatment, and the level of the coma of patients was improved. In terms of controlling the degree of cerebral edema, the degree of cerebral edema in patients treated withmild hypothermia combined with edaravone was lighter than that in the control group, and the difference was statistically significant. The outcome indicators of the NHISS score, which reflects the degree of neurological deficits of patients, and the GOS score, which reflects the degree of prognosis, showed that patients in the treated group had a lower degree of neurological deficits and an improved prognosis.

There are some limitations of this meta-analysis: (1) there are few RCT studies of suboxic combined with suboxone for craniocerebral injury and the sample size is small; (2) the design of the clinical trial does not have a good follow-up tracking of patients, a poor account of blinding, allocation concealment, etc. ③ The type of injury and degree of injury of craniocerebral injury patients are different, so there are some individual differences in the included study subjects, and the results are somewhat biased; ④ The literature selected for this study are from China, and there is some regional bias. Therefore, in future studies, more high-quality, large-sample, randomized, double-blind, multicenter, controlled clinical studies should be conducted on the efficacy of mild hypothermia combined with edaravone, with joint multi-institutional and cross-institutional cooperation, and the studies should involve patients of all ages to evaluate the clinical efficacy of this treatment method as comprehensively as possible. This will provide better treatment modalities and improve the prognosis of patients with craniocerebral injuries.

Conclusions

Based on the results of the Meta-analysis, mild hypothermia combined with edaravone treatment can reduce the degree of cerebral edema in patients with craniocerebral injury, improve the recovery of patients from the coma, effectively reduce the degree of postoperative neurological deficits, and can improve the quality of life of patients after discharge from hospital. After a large-scale clinical study, it has a certain value for promotion and application.

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