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Early Application of Citicoline in the Treatment of Acute Stroke: A Meta-analysis of Randomized Controlled Trials

Pei-yu SHI (石佩玉)[1], Xiao-cui ZHOU (周小翠)[1], Xiao-xue YIN (尹晓雪)[2], Liang-liang XU (许亮亮)[3], Xing-ming ZHANG (张兴明)[4], Hong-ying BAI (白宏英)[1#]
[1]*Department of Neurology, the Second Affiliated Hospital of Zhengzhou University, Zhengzhou 450000, China*
[2]*Department of Pathology,* [3]*Department of General Surgery,* [4]*Department of Urology, West China Medical Center of Sichuan University, Chengdu 610000, China*

Summary: This study was to evaluate the efficacy and safety of early application of citicoline in the treatment of patients with acute stroke by meta-analysis. Randomized controlled trials published until May 2015 were electronically searched in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, WHO International Clinical Trial Registration Platform, Clinical Trial.gov, and China Biology Medicine disc. Two reviewers independently screened the articles and extracted the data based on the inclusion and exclusion criteria. The quality of included articles was evaluated by using Revman5.0, and meta-analysis was performed. The results showed that 1027 articles were obtained in initial retrieval, and finally 7 articles, involving a total of 4039 cases, were included for analysis. The meta-analysis showed that no significant differences were found in the long-term mortality (OR=0.91, 95% CI 0.07 to 1.09, *P*=0.30), the rate of dependency (OR=1.02, 95% CI 0.87 to 1.24, *P*=0.85), and the effective rate (OR=0.98, 95% CI 0.84 to 1.14, *P*=0.82) between citicoline group and control group. The overall rate of adverse events in citicoline group was not significantly different from that in control group (*P*=0.30). The quality of included articles reached moderate-low level. In conclusion, citicolne cannot reduce long-term mortality and dependence rate in the treatment of acute stroke, and the effective rate of citivoline may be not better than that of controls but with reliable safety.
Key words: cytidine diphosphate choline; acute stroke; meta-analysis; randomized controlled trials

Acute stroke is a common and frequently-occurring disease in the nervous system with high morbidity, mortality and disability. It has became the third most common cause of death in developed countries, exceeded only by coronary heart disease and cancer[1, 2]. The prevalence of stroke is about 3.0% (7 million) in the US[3] and between 1.8% (rural areas) and 9.4% (urban areas) in China[4]. Worldwide, 15 million people suffer stroke each year; and one-third die and one-third are left permanently disabled[5]. In China, stroke imposes an economic burden of 30 billion Yuan in terms of treatment and rehabilitation, bringing a heavy financial and psychological stress on families and on society[6].

Citicoline consists of ribose, pyrophosphate, nitrogenous base and choline, an intermediate in the biosynthesis of cell membrane[7]. It has been investigated as a therapy for stroke patients for its neuroprotective function. In a very long period of time, citicoline has been extensively studied in most animal and clinical trials to confirm its efficacy and safety in patients with acute stroke, and some clinical trials showed remarkable short-term benefits when citicoline was used for patients with acute ischemic stroke[8, 9]. In addition, a retrospective meta-analysis conducted in 2002 showed its superiority upon placebo[10]. What's more, other studies reported that oral citicoline within the first 24 h after stroke onset improved neurological deficit function and increased the probability of complete recovery at 3 months in patients with moderate to severe stoke[11, 12]. However, a recent randomized controlled trial published on the Lancet revealed the opposite conclusion[13]. In the present study, we attempted to assess the efficacy and safety of citicoline applied within the first 24 h after onset of acute stroke by using a meta-analysis.

1 SUBJECTS AND METHODS

1.1 Inclusion and Exclusion Criteria

Randomized controlled trials (RCTs) published until May 2015 were searched from MEDLINE, Embase through OvidSP and Embase.com, the Cochrane Central Register of Controlled Trials (CENTRAL), WHO International Clinical Trial Registration Platform (ICTRP), Clinical Trial.gov, and China Biology Medicine disc (CBMdisc). The inclusion criteria for RCTs were as follows: therapeutic window within 24 h after stroke onset; no restriction on the age, gender, race and nationality; diagnosis criteria from the second Chinese academic conference of cerebrovascular disease, or the 4th national cerebrovascular disease conference in China[14], or the WHO definition of stroke[15]; ischemic or hemorrhagic stroke; clinical trials lasting at least 12 weeks (three months); language in articles restricted to English or Chinese. Relevant researches, reviews, reports, clinical trials with only abstract published were excluded. Exclusion criteria of RCTs were as follows: patients with systemic complications occurring in the liver, kidney, lungs and heart, for instance, ventricular fibrillation, acute

Pei-yu SHI, E-mail: shipy520@163.com
#Corresponding author, E-mail: hybai@126.com

myocardial infarction, or severe cardiovascular diseases, or with severe coexisting systemic diseases that limited life expectancy, or with other brain organic diseases, such as CT/MRI evidence of brain tumor, significant cerebral edema.

1.2 Outcome Measures

Outcome measures mainly consisted of mortality, dependency, functional independence and adverse events at the end of long-term follow-up (at least 12 weeks). Dependency was described as Barthel index (BI) scores of 60 or less, or the modified Rankin scale (mRS) graded 3 to 5. Functional independence (the effective rate) was defined as BI score>60, or mRS<3. Neurological function was measured by other stroke scales, e.g. National Institutes of Health Stroke Scale (NIHSS score≤1).

1.3 Data Extraction

The following data were extracted: (1) general information: title, the author's name, study sites, the name of funding source; (2) the characteristics of studies: inclusion and exclusion criteria, participants' general characteristics, interventions, study duration, baseline comparability; (3) outcome measures: mortality, BI scores, mRS scores, NIHSS scores and adverse events.

1.4 Assessment of Quality of Included Articles

Two independent reviewers assessed the risk bias of the included articles according to the tool recommended by the Cochrane Handbook by using RevMan 5.0 software[16, 17]. Items were assessed as follows: (1) adequate sequence generation; (2) allocation concealment; (3) blinding of participants, personnel, and assessors; (4) incomplete outcome data; (5) free of selective reporting; and (6) free of other bias. The judgments were categorized as "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (unclear about the risk of bias).

1.5 Data Synthesis and Analysis

RevMan 5.0 software was used for the meta-analysis. For continuous outcomes, mean difference (MD) or standardized mean difference (SMD) was calculated, with 95% confidence intervals (95% CIs), and likewise, relative risk (RR) or odds ratio (OR), with 95% CI for categorical variables.

Fixed-effect model or random-effect model was used depending on the result of test of the heterogeneity. χ^2 and I^2 tests were applied to examine the heterogeneity between studies. Fixed-effect model could be adopted when studies were non-homogeneous (P>0.1, I^2<50%). Random-effect model was used when heterogeneity was considered to be significant (P<0.1, I^2>50%). The source of heterogeneity was analyzed and subgroup analysis conducted if necessary.

2 RESULTS

2.1 Selection and Characteristics of Eligible studies

A total of 1027 articles were retrieved by our initial search strategy. After removing duplicates and receiving the titles and abstracts according to the inclusion and exclusion criteria, we identified 157 eligible studies for full-text screening. Of those, 150 articles which didn't satisfy the criteria for inclusion were excluded. No additional articles were found after thoroughly screening the reference lists. Finally, 7 RCT studies were included for both the meta-analysis and the qualitative analysis in this study. Table 1 summarizes the characteristics of the included articles and outcomes of interest. The seven eligible articles comprising 4039 cases were included in the meta-analysis. The daily dose ranged from 500 to 2000 mg. In the type of acute stroke, just one study included examined hemorrhagic stroke[21], and the rest were on ischemic stroke. The baseline characteristics showed comparability between included studies.

2.2 Mortality

Five studies[13, 18–21] were included for analysis of the mortality, among which 500, 1000, or 2000 mg citicoline was administrated. A pooled analysis of the five studies was conducted at 12 weeks or at 3 months. As shown in fig. 1, there was no statistical difference in total heterogeneity among the studies (P=0.83, I^2=0%), and a fixed effect model was used to perform meta-analysis. Our analysis indicated that there was no significant difference between citicoline and control groups in terms of the mortality (OR=0.91, 95% CI: 0.07–1.09, P=0.30). In addition, the subgroup analysis also revealed no significant differences between the citicoline group and the control group (500 mg citicoline: OR=0.86, 95% CI: 0.53–1.40, P=0.54; 2000 mg citicoline: OR=0.89, 95% CI: 0.74–1.08, P=0.24).

2.3 Dependency

There were 4 articles[13, 18, 19, 21] involved in the analysis of outcome dependency. As shown in fig. 2, no heterogeneity was found between the studies (P=0.30, I^2=18%) and the pooled effect size was analyzed in a fixed model. The result disclosed that for dependency at 12 weeks, no significant difference was noted between the citicoline group and the control group (OR=1.02, 95% CI: 0.87– 1.24, P=0.85).

2.3 Effectiveness

2.3.1 Dichotomous Variables Six studies presented information concerning the effectiveness of citicoline[13, 18–21, 23]. Twelve-week follow-up revealed that the overall pooled OR for effectiveness was 0.98 (95% CI: 0.84–1.14; P=0.82) with no statistically significant heterogeneity between studies. In subgroup analysis, significant heterogeneity seen in 2000 mg citicoline group (P=0.07, I^2=58%, fig. 3) at 12 weeks was obviously declined (P=0.26, I^2=26%) when we eliminated one study[20]. As a result, there was no significant difference in the effectiveness between citicoline and control groups (fig. 3).

2.3.2 Continuous Variables As for continuous variables, a total of 2 studies[21, 22] recorded the outcome of NIHSS. No significant heterogeneity between the studies (P=0.52, I^2=0%) and no statistically significant difference between the citicoline group and the control group were found in terms of NIHSS scores (MD=–1.56, 95% CI: –4.50 to 1.38, P=0.30) (fig. 4).

2.4 Safety

Four studies described adverse events in detail[13, 19–21]. As shown in fig. 5, the overall effect of adverse events in citicoline group was not statistically significantly different from that in control group with no discrepant heterogeneity found (OR=1.04, 95% CI: 0.96– 1.13, P=0.36). Additionally, we conducted subgroup analysis and revealed no significant difference in adverse events between the citicoline group and the control group in terms of different body systems (cardiovascular system, central nervous system, respiratory system, digestive/gastrointestinal system, nutrition and metabolism, urinary system, heme/lymphatic system, skin/appendages).

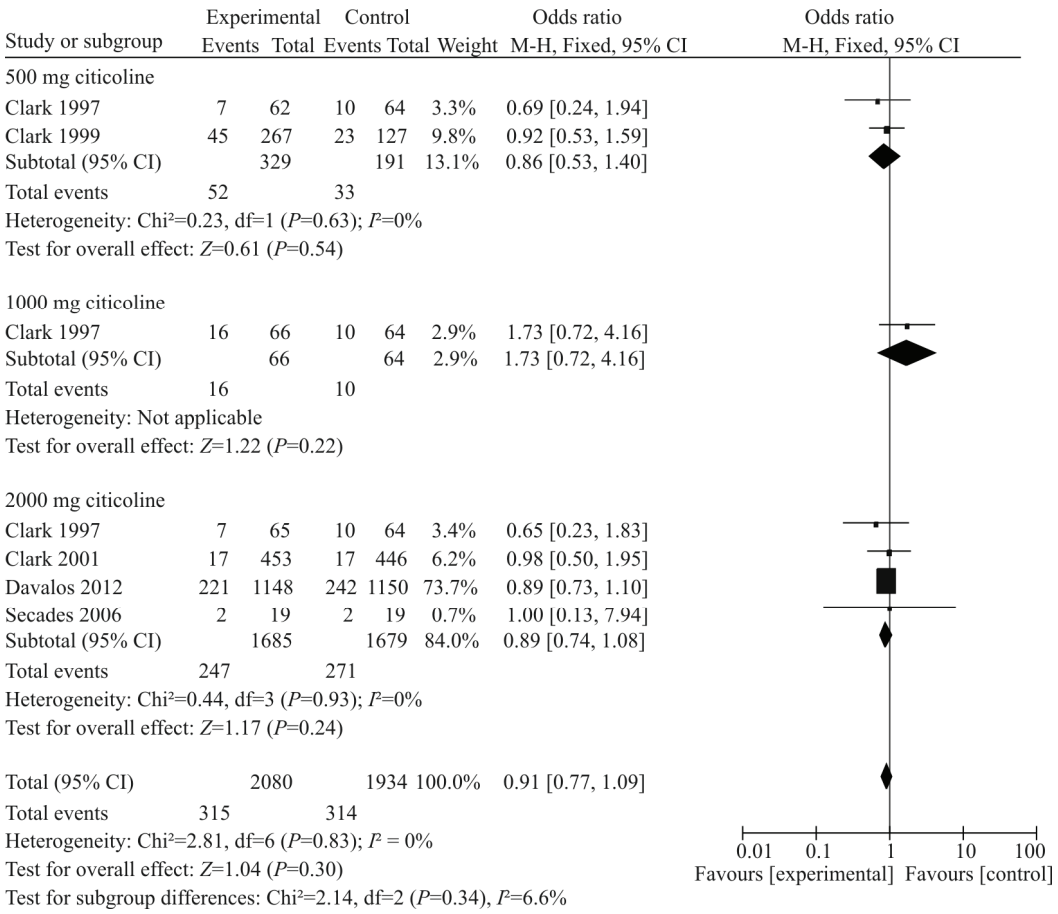

Fig. 1 Analysis of the mortality between the citicoline group and the control group

Table 1 Characteristics of included studies

	Intervention measures			Type	Patients' characteristics (intervention/comparison)			Baseline NIHSS (intervention/comparison) (score, mean)	Outcome measurements
	Comparisons	Delivery manner	Dosage (mg/daily)		Number	Age (year, mean)	Female (%)		
Davalos 2012[13]	Citicoline *vs*. placebo	Orally	2000 mg	Ischemic	1148 /1150	72.9 /72.8	48.8 /51.8	**	D1, D2, D3, D4, A
Clark 1997[18]	Citicoline *vs*. placebo	Orally	500 mg 1000 mg 2000 mg	Ischemic	62 66 66 /65	66 67 68 /70	51.60 47.00 59.10 /55.39	11.6 13.2 13.6 /13	D1, D2
Clark 1999[19]	Citicoline *vs*. placebo	Orally	500 mg	Ischemic	267 /127	70 /71	54 /51	13.3 /12.7	D1, D2, D3, A
Clark 2001[20]	Citicoline *vs*. placebo	Orally	2000 mg	Ischemic	453 /446	68 /67	50 /46	13.9 /14.5	D1, D2, D3, C2, A
Secades 2006[21]	Citicoline *vs*. placebo	Orally or intravenously	2000 mg	Hemorrhagic	19 /19	74.5 /67.0	71 /79	10.6 /13.7	D2, D4, C3, A
Mittal 2012[22]	Citicoline *vs*. edaravone	Orally or intravenously	1000 mg	Ischemic	24 /22 /25	54.83 /57.36 /55.6	43.5 /41 /36	3.91 /4.0 4.2	C3, C4
Lin 2007[23]	Citicoline *vs*. edaravone	Intravenously	500 mg	Ischemic	40 /40	55.9 /56.1	35 /37.5	*	D1, C1

D: dichotomous outcome; C: continuous outcome; A: adverse events; 1: Barthel index (BI); 2: mortality; 3: NIHSS; 4: modified rankin scale (mRS); *not reported. **Davalos 2012[13] NIHSS score, (1) 8–14 scores: 540/538; (2) 14–22 scores: 552/556; (3) >22 scores: 56/56

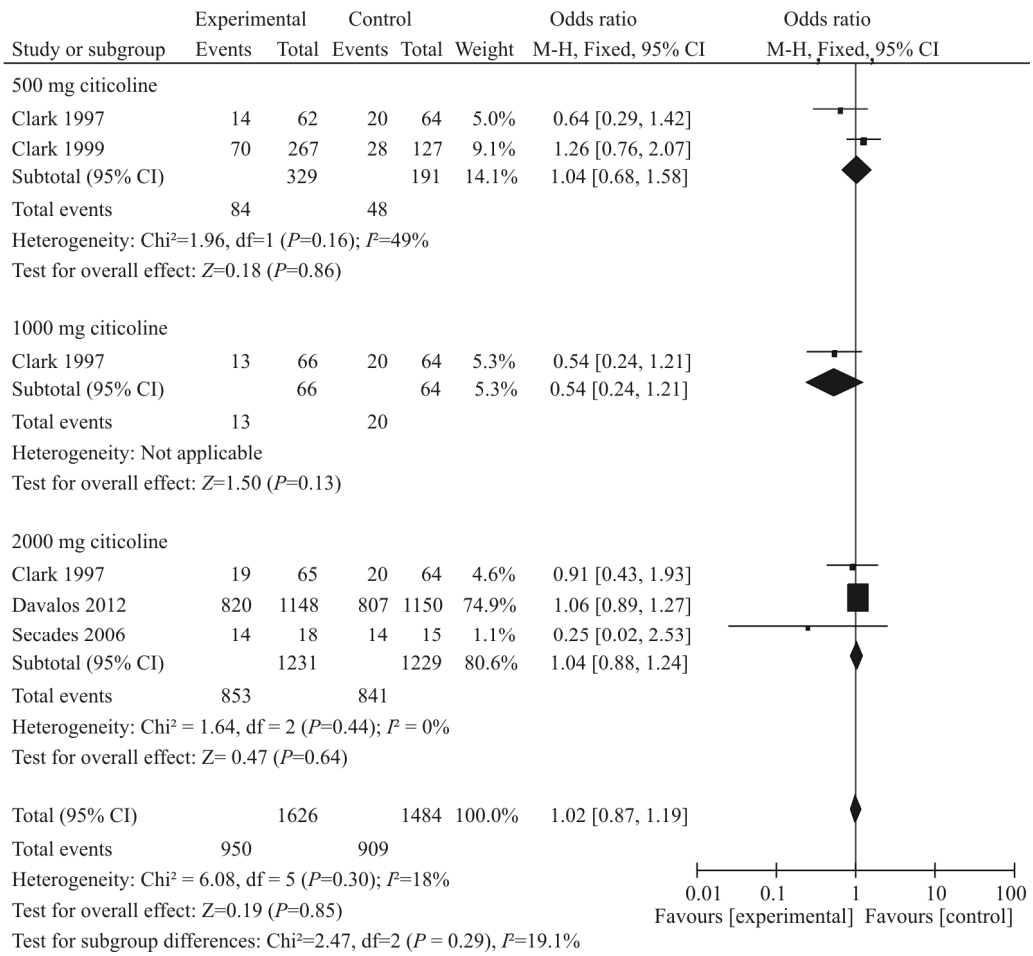

Fig. 2 Analysis of the dependency between the citicoline group and the control group at 12 weeks

2.4 Assessment of Risk of Bias

The risk of bias in 7 included studies is summarized graphically in fig. 6. Five studies[13, 18–21] were multicentral, randomized, double-blind, placebo-controlled trials. The following data were not clearly revealed in the studies: the generation of random sequence in one study[18], allocation concealment in four studies[18, 19, 22, 23], blinding participants in three studies[18, 22, 23], and blinding outcome assessors in five studies[18–20, 22, 23]. The rest of assessed items showed low risk, and all studies had no high risk of bias.

3 DISCUSSION

Stroke is a common condition in the nervous system with devastating complications[24]. In this study, we systematically assessed the efficacy and safety of the early application of citicoline in the treatment of patients with acute stroke. In order to augment the reliability of the systemic review, the therapeutic window was restrained within 24 h and trials that probably disturbed our outcomes, such as those on the combination therapy of citicoline, were excluded. It was a pity that only one study[13] performed subgroup analysis based on the scores of NIHSS and categorized participants into mild, moderate and severe stroke, while most of the included studies just presented the mean value of NIHSS scores; likewise, all studies did not perform subgrouping on the basis of age or gender. As a result, the ambiguity of outcomes and the differences of curative effect were increased. Although the way of delivery (orally or intravenously) was different in these studies, the studies were comparable given the bioavailability of intravenous administration was similar to oral administration[25].

Our meta-analysis showed that citicoline was not effective in treatment of acute stroke, although it was of reliable safety. The present study used the same outcome indicators and consistent scales to decrease the heterogeneity and increase the possibility of pooled analysis and the reliability of results. Our results revealed that no statistical differences in terms of mortality, dependency, adverse events, and effectiveness were found between the citicoline group and the control group. There is a controversy about the appropriate dosage of citicoline used to treat acute stroke. We classified the study subjects into 500 mg group, 1000 mg group and 2000 mg group according to the dose of citicoline, but we could not analyze the pooled indicators of each dosage due to the differences of outcome indicators in each group and the small size of included studies, and thus it was unclear that whether citicoline had different efficacy on the basis of different doses. As only one study[18] reported the related data of 1000 mg citicoline, we could not confirm the pooled effect, and further studies are needed to elucidate the potential efficacy of 1000 mg citicoline. The heterogeneity was possibly caused by the study of Clark *et al*[20]. They defined BI scores >95 points as effectiveness, which was obviously different from others (BI scores ≥60 points). In fact, some studies indicated that

patients with hemorrhage stroke had their muscular strength increased after administration of citicoline, indicating the effectiveness of citicoline in cerebral hemorrhage patients[26]. Among our included studies, only one study[21] examined hemorrhage stroke, and concluded that citicoline is a safe drug for the treatment of human intracerebral hemorrhage. The efficacy of citicoline for hemorrhage stroke still needs further investigation in large-scale clinical trials with large sample sizes. In terms of safety, the overall adverse event rate of citicoline was not significantly different from that of controls (P=0.30), suggesting the reliable safety of citicoline in the treatment of acute stroke.

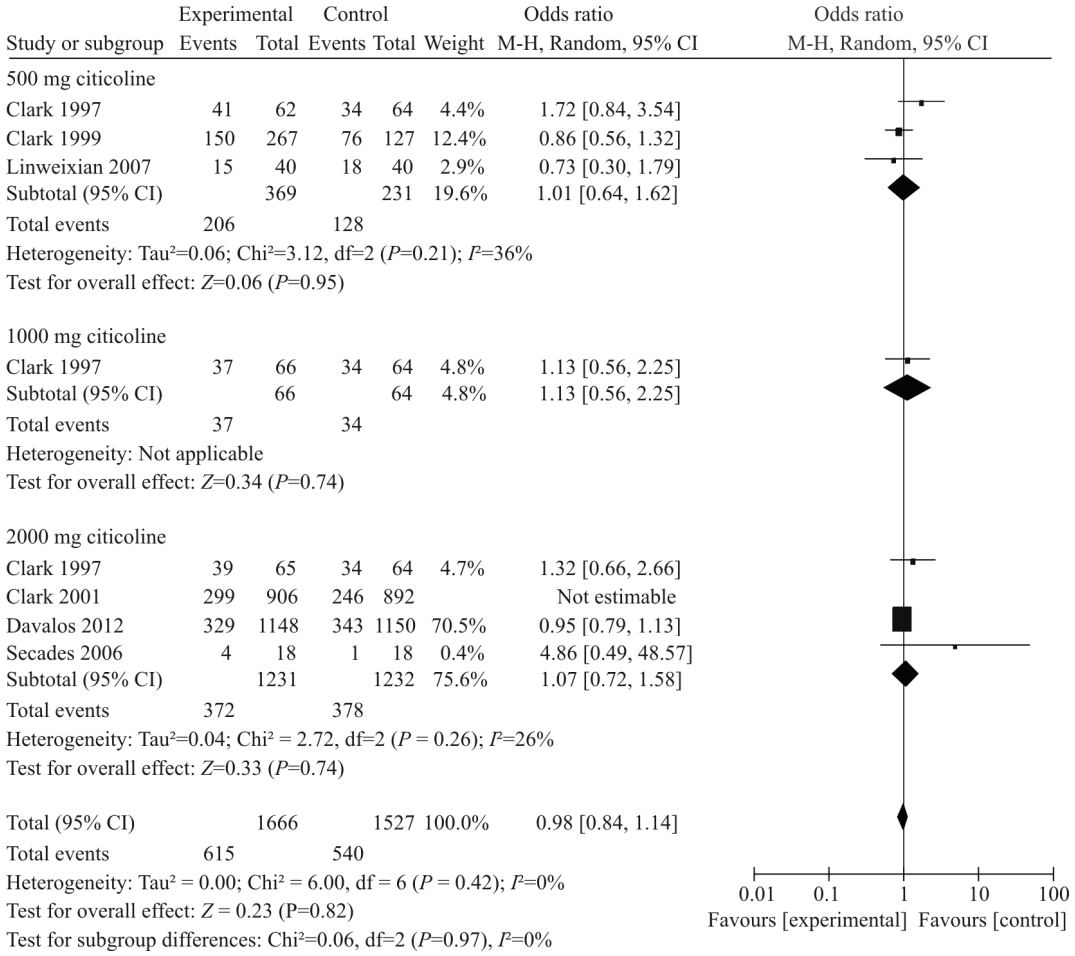

Fig. 3 Analysis of the effective rate between the citicoline group and placebo or edaravine group

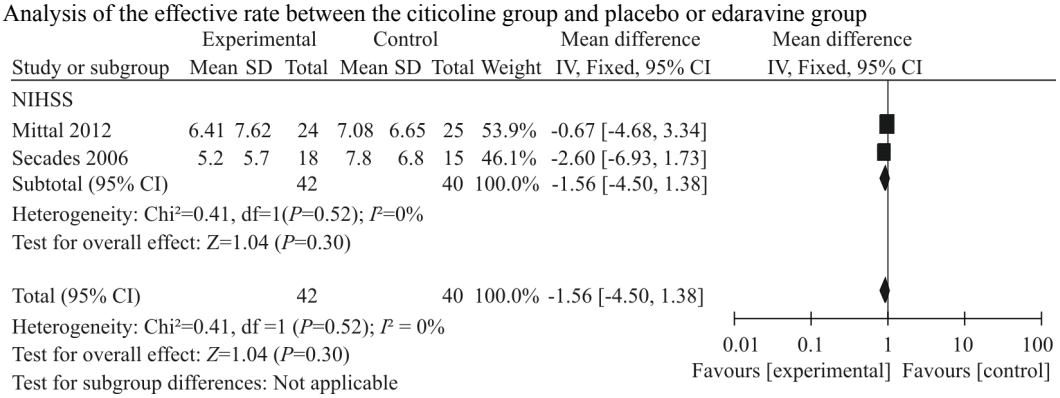

Fig. 4 Analysis of NIHSS between the citicoline group and placebo or edaravine group

We evaluated the quality of the included studies by analyzing risk of bias. Five studies[13, 18–21] were multi-central, randomized, double-blind, placebo-controled trials, reporting the number of patients loss to follow-up and analyzing the missing data, and therefore their outcome had higher reliability. Unfortunately, only two studies[13, 21] described the sequence generation, concealment, and blinding in detail. What's more, the risk of bias (such as concealment and blinding) in some studies[22, 23] was unclear. In conclusion, poor description given by some studies on the trial design, the possible selection bias, the performance bias, the detection bias, and the attrition bias may lead to relatively low quality of included studies. Not only the standards of outcome measures but also the treatment programs of each enrolled studies were roughly similar, which could greatly

reduce the differences of heterogeneity and increase the reliability of results of the systematical review.

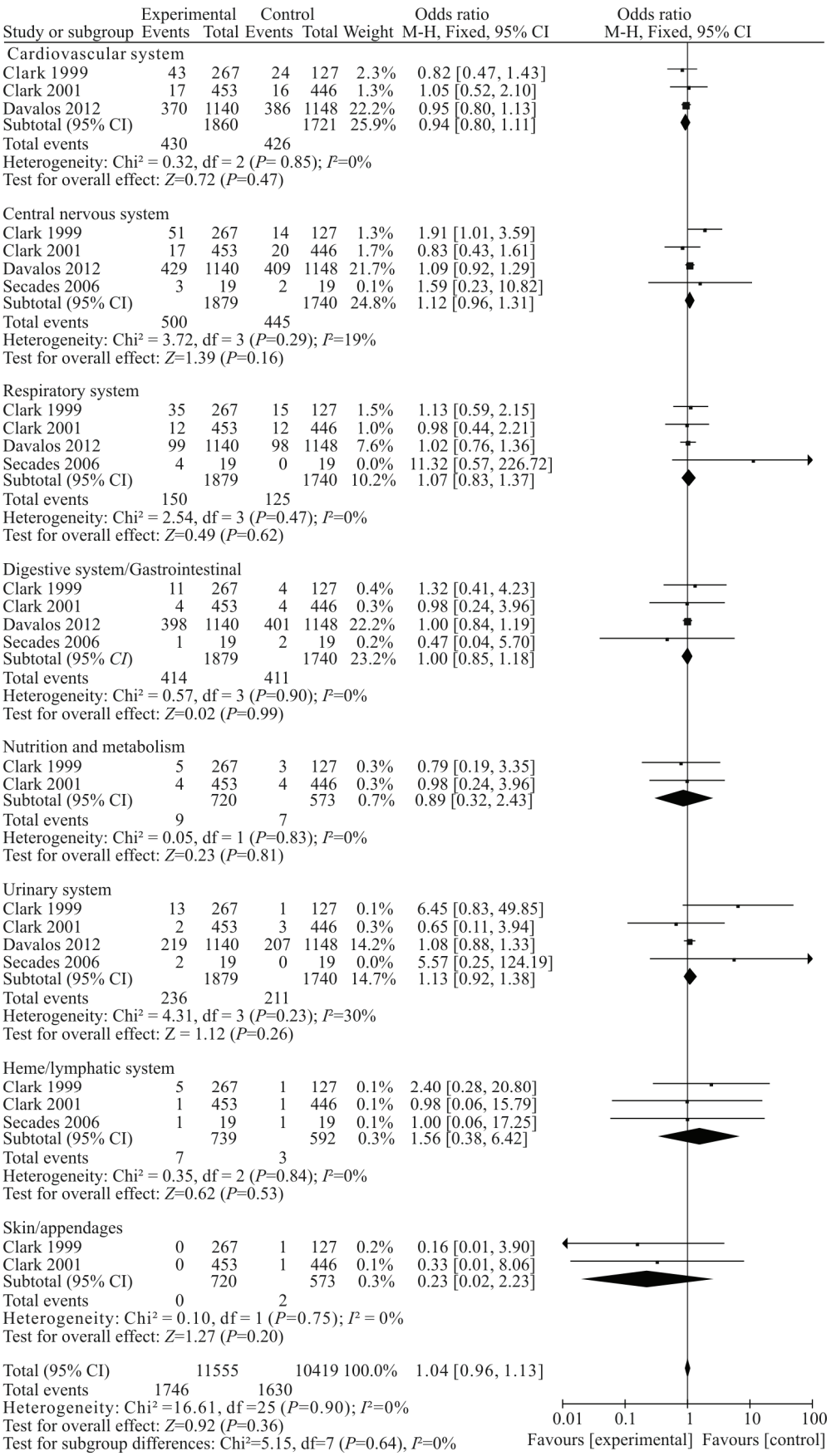

Fig. 5 Comparison of the incidence of adverse events in different body systems between the citicoline group and the placebo or edaravone group for the treatment of acute stroke at 12 weeks

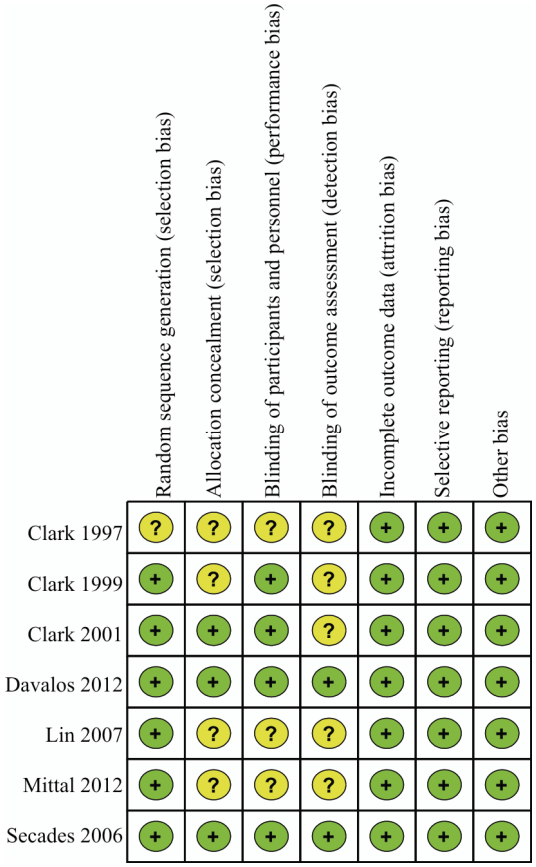

Fig. 6 Risk of bias in included studies
"+": low risk; "–" : high risk; "?": unclear risk

Our research had some advantages over previous studies. Firstly, we strictly imposed restrictions on inclusion criteria, for instance, the therapeutic window, the follow-up duration, and outcome indicators, which to some extent decreased the heterogeneity and improved the credibility of the study. Secondly, all of outcomes presented in eligible studies were represented in detail, and except for 1000 mg citicoline group, we performed subgroup analysis to testify the pooled size. Our review also had some limitations. Since patients were not subgrouped based on the severity of acute stroke, the effect of different doses of citicoline on acute stoke patients was not examined. Additionally, the appropriate treatment dose of citicoline was not concluded due to small samples in our research.

In conclusion, our systematical review demonstrated that citicoline is not better than placebo or edaravone in the treatment of acute stroke, which provides guidance for clinicians on drug choice for acute stroke.

Conflict of Interest Statement

The authors declare that there is no potential conflict of interest in this study.

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