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Meta-Analysis of the Efficacy of Surgery Combined with Urokinase in Chronic Subdural Hematoma

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Abstract...

Objective: To compare the clinical efficacy of urokinase in the treatment of chronic subdural hematoma after surgery with that of no urokinase.

Methods: Pubmed, CNKI, VIP, Wanfang Data Knowledge Service platform and other databases were searched by computer from January 2013 to June 2022.Randomized controlled trials related to surgical treatment of chronic subdural hematoma and postoperative use of urokinase were searched, in which patients treated with urokinase after surgery were used as the experimental group. patients who did not receive urokonase served as a control group.

Result: Finally, fifteen articles were included, including 1417 patients. Meta-analysis results showed that the effective rate of the experimental group (96.60%) was higher than that of the control group (82.44%), with statistical significance (P<0.05). The incidence of postoperative adverse events in the experimental group (9.20%) was lower than that in the control group (41.01%),with statistical significance(P<0.05).

Conclusion: Patients with chronic subdural hematoma who receive urokinase after surgery had a better prognosis and a lower incidence of postoperative adverse events.

Keywords: Chronic subdural hematoma; Urokinase; Meta-analysis.

Introduction

Chronic subdural hematoma is defined as an enveloped hematoma located between the dura and arachnoid membranes that begins to show symptoms more than 3 weeks after trauma. They account for 10% of intracranial hematomas and 25% of subdural hematomas. According to statistics, in the general population, the annual incidence is about 14.1 in 100,000 [1]. At present, surgical treatment is the first choice for patients with symptomatic CSDH or large volume of hematoma, which mainly includes endoscopic surgery, drilling and drainage, craniotomy and hematoma removal [2-4]. Urokinase is an enzyme protein that catalyzes the cleavage of plasminoge, so it is often used in CSDH patients after surgery to promote hematoma clearance. However, urokinase also carries a risk of bleeding. At present, there are only some single-center small sample studies on the use of urokinase in CSDH patients after surgery, and no system-

atic studies have been conducted. This study aims to systematically evaluate the clinical effect of surgery combined with urokinase in the treatment of CSDH by methodological analysis and quality evaluation of published relevant literature through evidence-based medicine, so as to provide reliable basis for guiding the treatment of CSDH.

Data and methods

Retrieval methods and strategies

Pubmed, CNKI, Wanfang Data knowledge service platform and VIP were searched by computer system. The retrieval period was from January 2013 to June 2022. The Chinese database was searched with "chronic subdural hematoma" and "urokinase". Outside the network using"((((((Subdural Hematoma, Chronic) OR (Chronic Subdural Hematoma)) OR (Chronic Subdural Hematomas)) OR (Hematoma, Chronic Subdural)) OR (Hematomas, Chronic Subdural)) OR (Subdural Hematomas, Chronic)) AND ((((((((((Urokinase Type Plasminogen Activator[Title/Abstract]) OR (Urokinase Type Plasminogen Activator)) OR (U-Plasminogen Activator)) OR (U Plasminogen Activator)) OR (U-PA)) OR (Urinary Plasminogen Activator)) OR (Urokinase)) OR (Renokinase)) OR (Abbokinase)) OR (Kidney Plasminogen Activator)) OR (Single-Chain Urokinase-Type Plasminogen Activator)) OR (Single Chain Urokinase Type Plasminogen Activator))"to retrieve. At the same time, the relevant free words are combined for retrieval.

Inclusion criteria

①All patients underwent head CT or MRI examination, which met the diagnostic criteria of CSDH [5]; ②The group was divided by random number method or blind method, and the main purpose was to observe the clinical effect; ③In the treatment group, surgery combined with urokinase was used as the intervention measure; ④The control group was treated by operation alone; ⑤There was no significant difference in the basic conditions between the two groups. ⑥Clinical efficacy refers to CSDH evaluation criteria in the Criteria for Cure and Improvement of Clinical Disease Diagnosis [6]. Curative efficacy indicators such as cure, obvious effect, effective and ineffective are used in the literature.

Exclusion Criteria

①The control group received intervention measures other than surgery; ②Lack of control group or missing data; ③Simple descriptive research; ④Clinical studies with unclear description of specific efficacy indicators; ⑤Non-clinical trials.

Quality evaluation and data extraction

The Cochrane Collaboration risk bias assessment tool was used to evaluate the quality of the literature that met the inclusion criteria, including random sequence generation, performance bias, detection bias, attrition bias, reporting bias and other biases. Two researchers independently screened the literature, extracted the data, and then cross-checked. In case of disagreements, they discussed together. If no agreement was reached after the discussion, the third researcher decided whether to include them.

Method of statistics

RevMan 5.4 statistical software was used for data analysis. Odds ratio (OR) was used for postoperative efficacy, and hazard ratio (RR) was used for postoperative adverse events.95% confidence interval (CI) was used for both. All included studies were tested for heterogeneity and I2 was used to evaluate the magnitude of heterogeneity. Fixed-effect model (P≧0.10, I2<50%) or random effect model (P<0.10, I2≧50%) for meta-analysis. Invered funnel plots were drawn to analyze whether publication bias existed in the included literature.

Results

Retrieval Results

This study finally included 15 articles [7-21] in accordance with the literature, a total of 1417 patients, 705 cases in the experimental group and 714 cases in the control group. The flow chart of literature screening is shown in Figure 1.

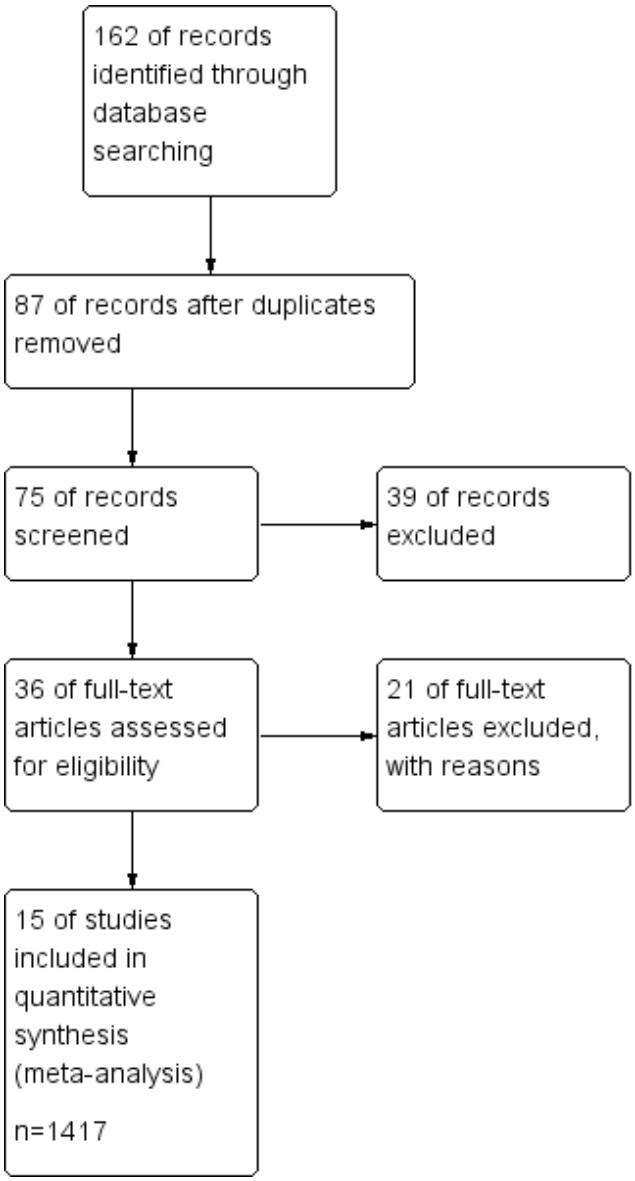

Figure 1: Flow chart.

Quality evaluation of included literature

Among all the 15 literatures, 8 [7-9,11,13,16,17,20] articles adopted the numerical random method, 1 [10] article adopted the double-blind method, the rest of the studies did not mention the specific grouping method, all the studies did not mention the allocation hiding, did not describe the detection bias, loss bias, it is unclear whether there is reporting bias and other bias. All studies were assessed with a risk bias assessment tool (Figures 2,3).

Figure 2: Cochrane assessment result for risk of bias.

Efficient

Fifteen articles [7-21] reported the effective rate and heterogeneity test (P=0.93, I^2=0%), suggesting that there was no heterogeneity among the literatures, as shown in Figure 3. The fixed effect model was used for analysis. Odds ratio (*OR*) test showed that the effective rate of the experimental group (96.60%, 681/705) was higher than that of the control group (82.44%, 587/712), and the difference was statistically significant (*OR*=5.96, 95% *CI*:3.83,9.29, *P*<0.00001) (Figure 4).

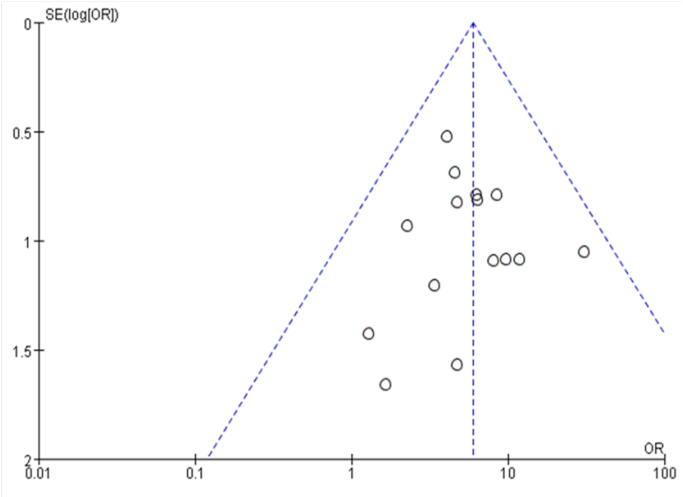

Figure 3: Heterogeneity test.

Incidence of postoperative adverse events

Total incidence of adverse events

All postoperative adverse events of different types in all literatures were analyzed. Heterogeneity test (*P*=0.19, *I*2=24%< 50%), and the fixed effects model was used for analysis. Relative Risk (*RR*) test showed that the incidence of adverse events in experimental group (9.22%, 65/705) was lower than that in control group (41.01%, 292/712), and the difference was statistically significant (*RR*=0.24, 95%*CI*:0.19,0.31, P<0.00001). As shown in Figure 5.

Incidence of intracranial gas accumulation

9 articles [7-11,13,18,19,21] reported the occurrence of intracranial pneumatosis, and the results of meta-analysis showed that: The incidence of intracranial gas in the experimental group (5.35%, 20/374) was lower than that in the control group (32.32%, 128/396), and the difference was statistically significant (*RR*=0.20, 95%*CI*:0.14,0.30, P<0.00001). As shown in **Figure 6**.

Incidence of subdural effusion

7 [8,10,12,13,17,19,20] articles reported the occurrence of subdural effusion, and meta-analysis showed that: The incidence of subdural effusion in the experimental group (6.47%, 20/309) was lower than that in the control group (14.24%, 44/309), and the difference was statistically significant (*RR*=0.46, 95%*CI*:0.28,0.75, *P*=0.002). As shown in Figure 7.

Incidence of infection

4 articles [9,11,15,16] reported the occurrence of postoperative infection, and meta-analysis showed that: The incidence of infection in the experimental group (3.56%, 9/253) was lower than that in the control group (11.86%, 30/309), and the difference was statistically significant (*RR*=0.30, 95%*CI*:0.15,0.62, *P*=0.001). As shown in Figure 8.

Incidence of brain injury

4[7,9-11] articles reported the occurrence of postoperative brain injury, and meta-analysis results showed that: The incidence of brain injury in the experimental group (0.47%, 1/215) was lower than that in the control group (7.91%, 17/215), and the difference was statistically significant (*RR*=0.14, 95%*CI*:0.04,0.50, *P*=0.003). As shown in Figure 9.

Postoperative recurrence rate

4 articles [11,13,14,17] reported the occurrence of postoperative recurrence, and meta-analysis showed that: The recurrence rate of the experimental group (2.21%, 6/271) was lower than that of the control group (14.45%, 37/256), and the difference was statistically significant (*RR*=0.17, 95%*CI*:0.07,0.38, P< 0.0001). As shown in Figure 10.

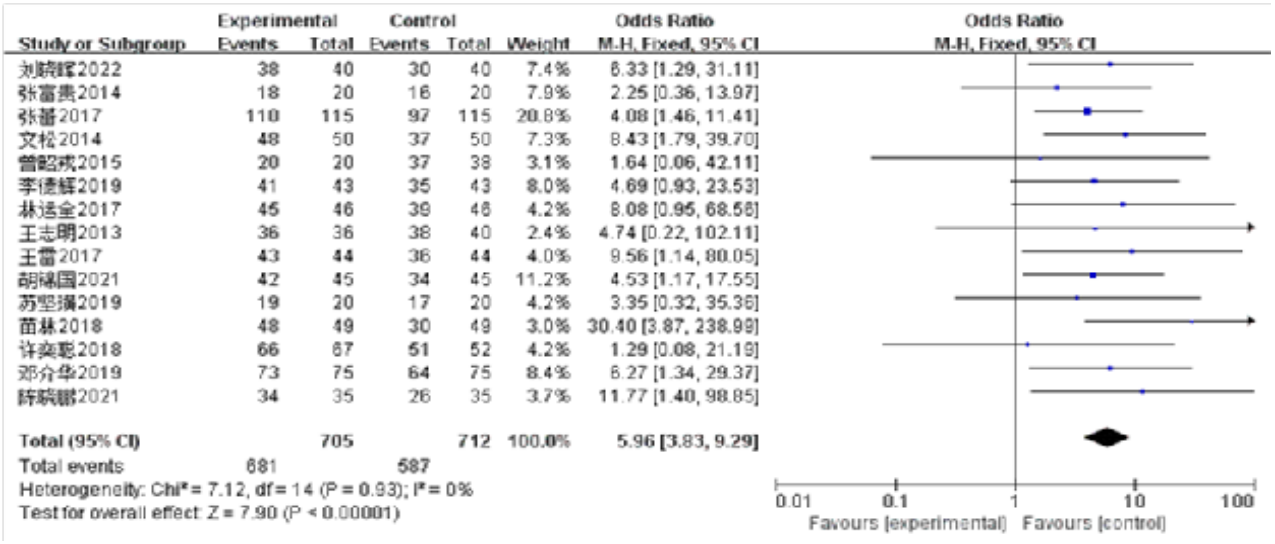

Figure 4: Efficiency.

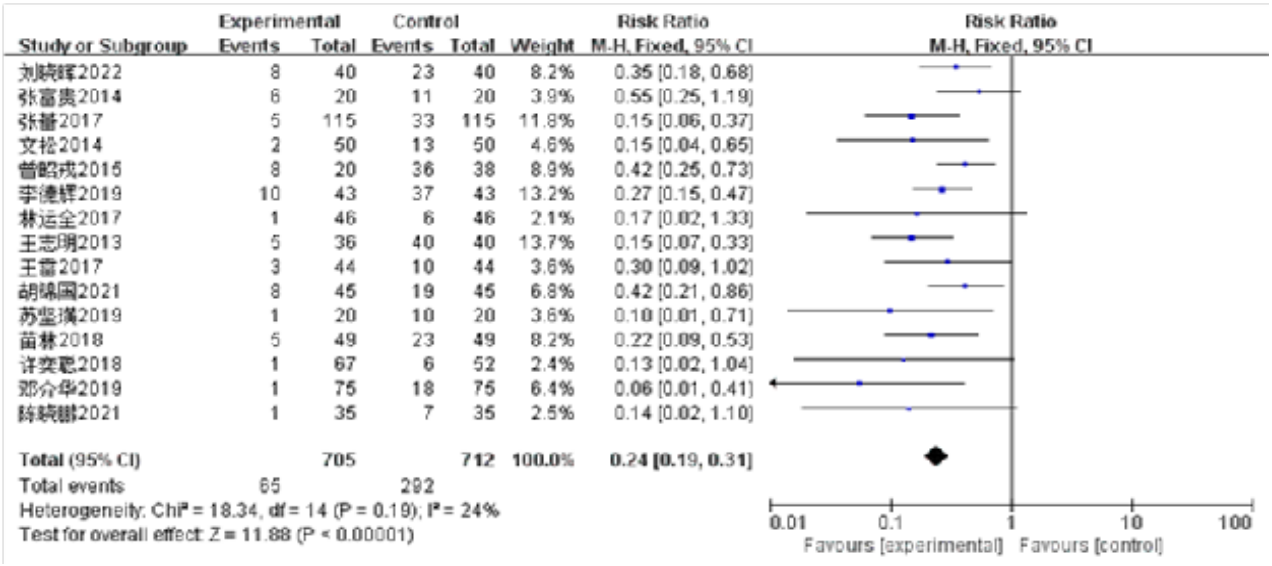

Figure 5: Adverse event rate.

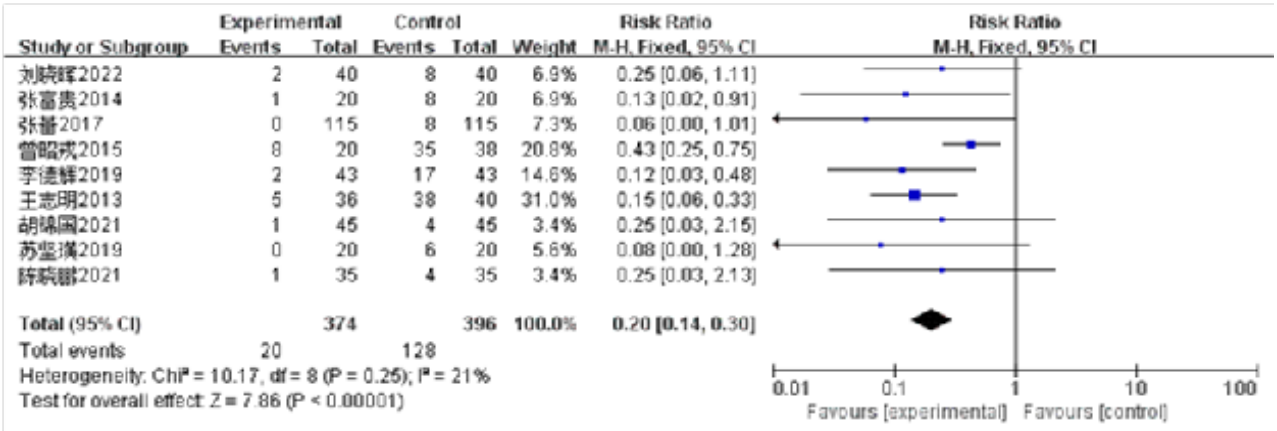

Figure 6: Incidence of pneumocephalus.

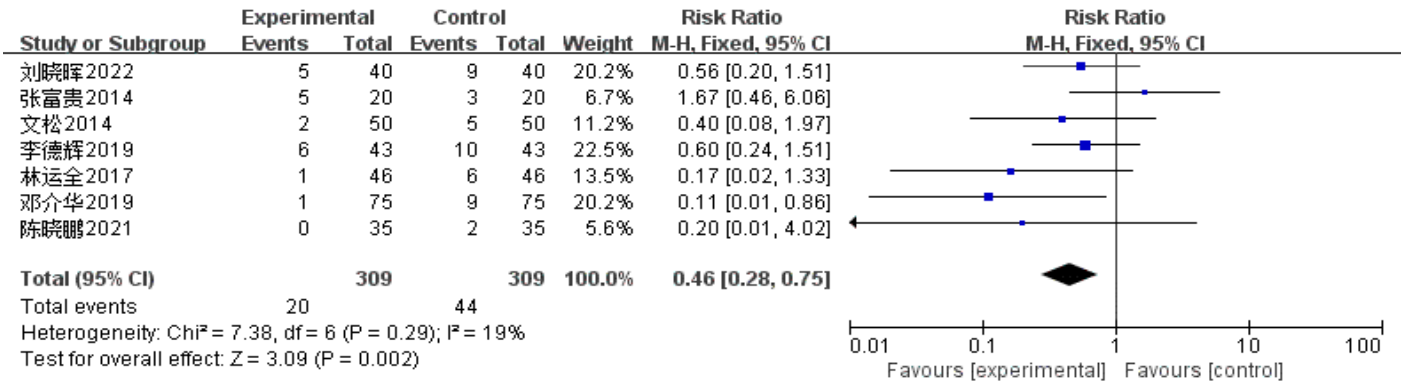

Figure 7: Incidence of subdural effusion.

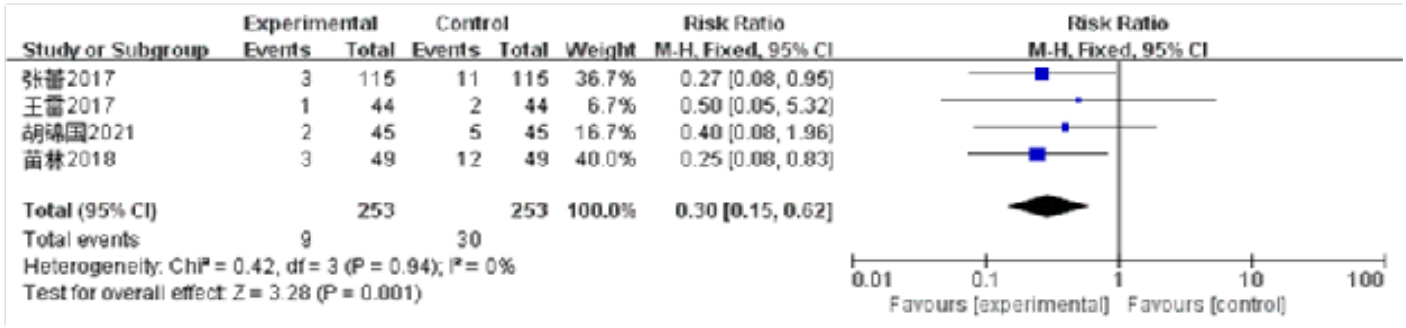

Figure 8: Infection rate.

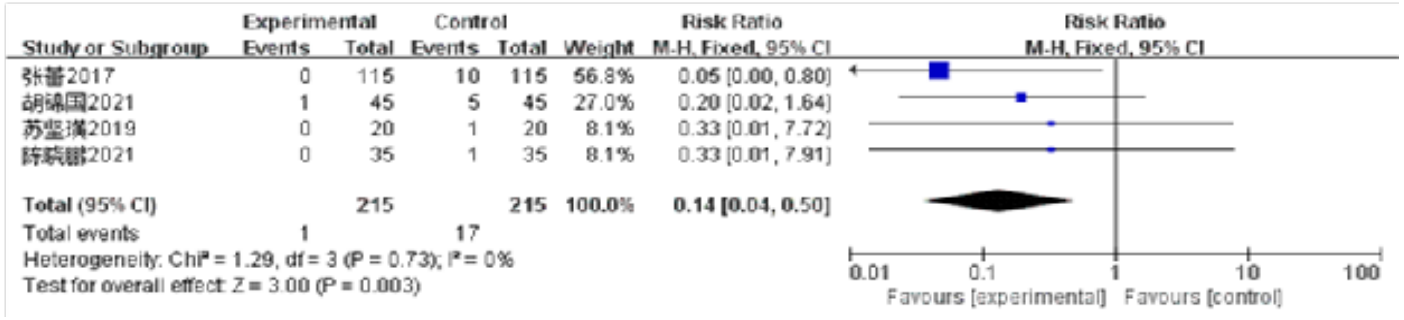

Figure 9: Incidence of brain injury.

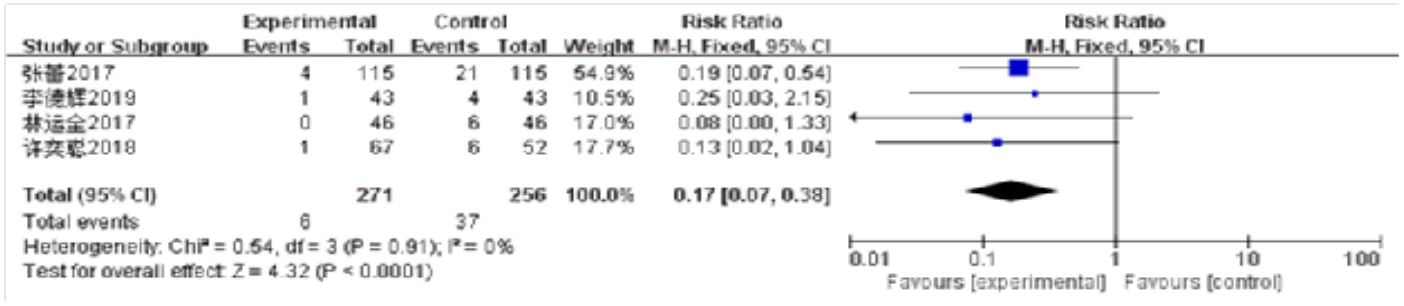

Figure 10: Recurrence rate.

Atorvastatin

Because in some literature in the process of collecting literature in the experimental group with atorvastatin are excluded, but whether atorvastatin can be used as single factor to improve the prognosis of patients with CSDH aroused our attention, we rearrange the data, collecting all of the patients used urokinase, divided into the postoperative use of atorvastatin group and not used in the control group, There were 23[7-29] articles. Compare the efficiency between the two. X^2 test was used, as shown in Table 1. The effective rate of patients treated with atorvastatin after operation (96.98%) was higher than that of the control group (95.26%). Calculate the $X^2 = 1.71 < X^2_{0.05,1} = 3.84$, P>0.05, no statistical significance. This is contrary to the theories of some of our current scholars [30] and may require further verification.

Table 1: Atorvastatin.

Group	Effective	Invalid	Total	Effective rate
Experimental	321	10	331	96.98%
Control	784	39	823	95.26%
Total	1105	49	1154	95.75%

Discussion

CSDH is a common disease in neurosurgery, which is more common in the elderly and often secondary to a history of mild head trauma, leading to bridge vein tearing and bleeding. Some scholars also believe that local inflammation and abnormal blood vessel formation [31], in which angiogenesis reaction causes local repeated micro bleeding. CSDH is often insidious because of its insidious onset, with mild headache and severe coma and cerebral rigidity. Therefore, for patients with indications, surgical treatment should be performed [32]. For the elderly with generally low physical quality, how to remove blood quickly and reduce postoperative adverse reactions is the direction we should study. Urokinase has long been used to promote hematoma exclusion, but more direct evidence is needed to determine whether it is more effective and has a better prognosis for CSDH.

A total of 15 literatures were included in this study, all of which were RCTS. The selected indicators included the effective rate, recurrence rate and various complications, hoping to comprehensively evaluate the therapeutic effect of urokinase on postoperative CSDH patients. The results showed that the experimental group was better than the control group in terms of effective rate and postoperative adverse reactions. Some scholars believe that intraoperative puncture without irrigation may reduce the incidence of pneumocephaly in patients after surgery [11,22], but due to the lack of data, systematic analysis was not conducted in this study.

In this study, X^2 test was also performed on the efficacy of urokinase combined with atorvastatin after surgery, and the results did not show the superiority of atorvastatin in the treatment of CSDH patients. This is contrary to the idea of some scholars. Possible reasons are as follows: 1. The literature related to atorvastatin was not thoroughly searched; 2. 2. Patients with CSDH who did not use urokinase were not searched. Some scholars believe that atorvastatin is only effective for patients with mild-to-moderate CSDH [33]. In conclusion, more trials are needed to confirm whether atorvastatin is a single factor that improves treatment efficacy and prognosis in patients with CSDH.

Conclusion

In conclusion, surgery combined with urokinase is effective in the treatment of CSDH, which is helpful to improve the treatment efficiency of patients and reduce the postoperative complications and recurrence rate of patients.

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