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REVIEW ARTICLE - BRAIN INJURY

Dexamethasone for chronic subdural haematoma: a systematic review and meta-analysis

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Abstract
Background Chronic subdural haematoma is a common but retractable neurological disease in the elderly with a high rate of recurrence. Dexamethasone (DX) either as monotherapy or adjuvant therapy has been applied clinically, but its effectiveness and feasibility remain controversial. We conducted this review to clarify this issue.
Methods With a systematic review through multiple databases, we retrieved eligible English language publications and extracted relevant data to perform meta-analyses. The respective risk ratio (RR) and its 95% confidence interval (CI) were pooled to evaluate the overall effect.
Results Our meta-analysis showed overall that DX (alone or adjuvant) resulted in a lower recurrence rate when compared with non-DX therapy (RR, 0.54; 95% CI, 0.33-0.88; $p = 0.01$), but sensitivity analysis by excluding the most influential study achieved inconsistent results. The pooled effect revealed no statistical difference on recurrence rate between DX alone and non-DX therapy or surgical therapy (RR, 0.86; 95% CI, 0.43-1.71; $p = 0.66$) (RR, 0.89; 95% CI, 0.43-1.85; $p = 0.76$). Comparison between DX alone with the surgical therapy demonstrated no difference on the poor outcome (RR, 0.40; 95% CI, 0.15-1.04; $p = 0.06$).
Conclusions We had no enough evidence to support DX use as an effective alternation to surgical therapy. But adjuvant DX use may facilitate the surgical therapy by reducing recurrence. Further study focusing on adjuvant DX was required.

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Keywords Dexamethasone · Subdural haematoma · Chronic · Meta-analysis

Introduction

Chronic subdural haematoma (CSDH) is a common neurological disease in the elderly, and has shown an increase in incidence due to the extended life expectancy [19, 20]. Despite the mature surgery modality, patient outcomes have remained less optimistic owing to the high rate of recurrence. An alternative or adjunctive therapy is required, especially for patients with poor baseline functions. The rationale of dexamethasone (DX) treatment for CSDH was based on its property to preclude inflammation and angiogenesis, presumed to be the underlying mechanisms of CSDH recurrence [12, 14, 16]. Though DX had been applied clinically as the monotherapy or perioperative adjuvant therapy in some institutions [27], its effectiveness and feasibility are still controversial [2, 25, 29]. Considering the existing results remain divergent and optimal treatment strategy is required, we conducted this systematic literature review so as to clarify the effectiveness and applicability of DX for the treatment of CSDH.

Methods

Search strategy

Searching through the Cochrane Library, PubMed, Ovid and Web of Science from starting dates to June 2017, we reviewed related English language publications. Keywords and MeSH were used in combination as follows: “glucocorticoid”, “dexamethasone”, “steroid”, “corticosteroid”, “nonsurgical”, “conservative”, “subdural”, “hematoma”, “haematoma”,

"bleeding", "hemorrhage" and "haemorrhage." Reference lists of retrieved articles were manually searched. We tried to report this review in according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Selection criteria

We included studies if they fulfilled the following criteria: (1) described patients aged 18 years or older, with a confirmed diagnosis of CSDH; (2) oral or intravenous DX was used as monotherapy or adjuvant therapy; (3) the control group without application of DX; (4) sample size over ten patients; (5) with definite documentation of outcomes as mortality, morbidity, recurrence rate and complications. Recurrence was defined as the relapse of haematoma confirmed by clinical symptoms or radiological signs, warranting further treatment. Here we arbitrarily excluded small sample size studies because too small a sample size resulted in no endpoint and biased the analysis.

The primary endpoint was a poor outcome defined as a score of 3-4 on the Markwalder Grading Score (MGS) [22], a 1-3 score on the Glasgow Outcome Scale or clinical symptoms which could not recover to the premorbidity condition. Secondary events concluded the recurrence rate, the time of hospital stay and complications.

Data extraction

Two investigators (Z.Y. and C.Y.) independently evaluated the inclusion criteria for relevant publications. Divergent findings were resolved by discussion or consensus. Data extraction forms were used to collect information about the author(s), year of publication, treatment modalities, poor outcomes, recurrence rates and complications. We also tried to contact the authors of primary articles to obtain acute data.

Quality assessment

Randomised studies underwent quality assessment with the Cochrane collaboration's tool for assessing the risk of bias, observational studies with the Newcastle Ottawa scale.

Statistical analyses

Overall effect was shown with the risk ratio (RR) and its 95% confidence interval (95% CI). Comparisons between overall DX (alone or adjuvant) versus non-DX therapy, DX alone versus non-DX therapy and DX alone versus the surgical therapy were made to identify the effectiveness of different forms of DX therapy. A two-tailed $p < 0.05$ was considered significantly different. A fixed effects model was used when no substantial

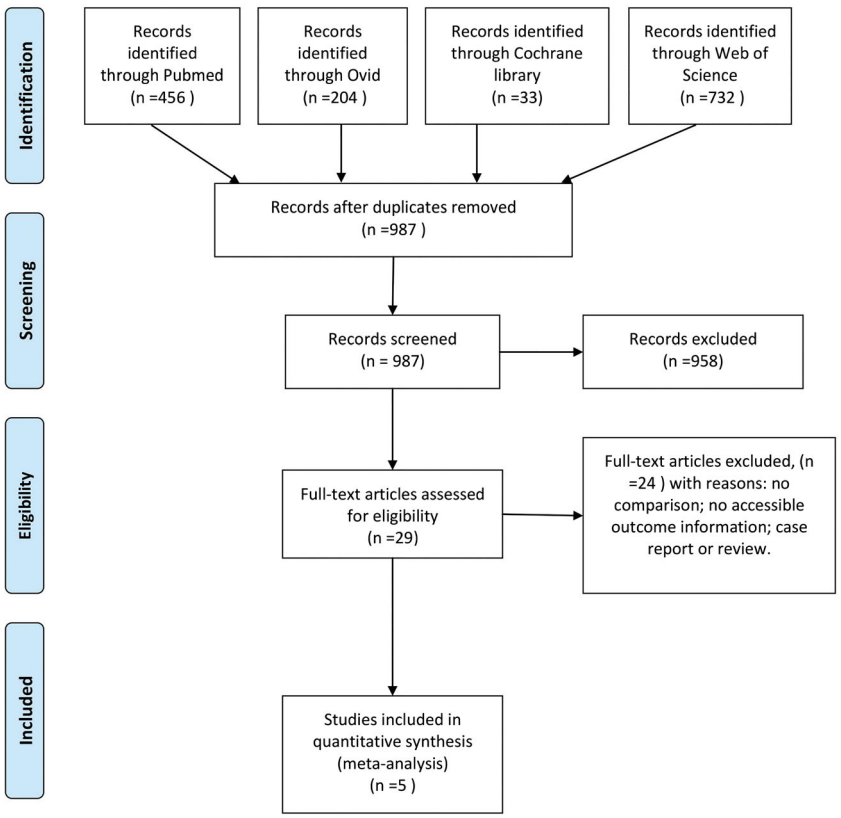

Fig. 1 Flow diagram of literature research

heterogeneity existed, otherwise a random effects model was employed. Heterogeneity was assessed by Cochrane Q test and I^2 test, with a threshold of $p < 0.10$ or $I^2 > 50\%$ indicating substantial heterogeneity. Sensitivity analyses were conducted by excluding any single study one time to test whether results were robust. Publication bias was measured by funnel plot. Statistical tests were implemented with Review Manager software (version 5.3, Cochrane Collaboration).

Results

Literature search

Through literature review, we retrieved five related studies consisting of one randomised trial and four observational studies. Additionally, there were six related randomised controlled trials underway in the WHO International Clinical Trials Registry Platform. A search flow diagram is shown in Fig. 1. Owing to severe complications and incomplete outcome data, the randomised study took a high risk of bias. The other four observational studies were moderate-quality evidence according to the Newcastle Ottawa scale. No significant new information was achieved through contacting the authors of primary studies.

Main characteristics of included studies

There was a total of 523 patients involving 332 men and 191 women in the review. Most patients aged more than 60 years, with an age range from 25 to 97 years old. Doses of DX used in different studies were close with a mean dose of 12 mg per day. The most common complication was hyperglycaemia, followed by various infections. Also, there existed lethal complications of pulmonary embolus and suicide, which might be attributable to the effects of DX [25]. There were ten cases of death due to all causes reported, making the mortality 1.9% in this review. Among the included citations, three studies conducted in China, one in Spain and the other one in Canada. The main characteristics were summarised in Table 1.

Overall DX (alone or adjuvant) versus non-DX therapy

Five studies reported the overall effect of any form of DX use (alone or adjuvant) on the CSDH recurrence, compared with the non-DX therapy. The pooled effect (RR, 0.54; 95% CI, 0.33-0.88; $p = 0.01$) indicated a lower recurrence rate in the overall DX (alone or adjuvant) therapy compared with the non-DX therapy group (Fig. 2). However, the difference became insignificant in sensitivity analysis: the pooled RR ranged from 0.61 (95% CI, 0.36-1.05) when the study of Sun et al. [29] was excluded to 0.68 (95% CI, 0.37-1.25) when

Table 1 Main characteristics of included studies

Study	M/F	Age	Duration	Country	Dose of DX	Complications	Treatment modality (number of patients)			
							DX alone	Adjuvant DX	Surgery	Observation
Delgado-López 2009 [10]	84/38	25-97, median 78	2001-2006	Spain	12 mg/day, with slow tapering	Hyperglycaemias, infections and gastrointestinal bleeding	101		19	2
Prud'homme 2016 [25]	18/2	55-82, mean 70.9	2007-2009	Canada	12 mg/day for 3 weeks	4 hyperglycaemias, each one for hypertension, pulmonary embolus, cellulitis, pulmonary oedema, suicide	10			10
Qian 2017 [26]	148/94	36-93, median 66.3	2010-2015	China	13.5 mg/day, with slow tapering	5 hyperglycaemias		75	167	
Sun 2005 [29]	63/49	37-91, median 75	1998-1999	China	16 mg/day for 21 days	2 hyperglycaemias	26	69	13	4
Zhang 2017 [30]	19/8	46-92, mean 68.3	2010-2014	China	12 mg/day for 3 days	1 hyperglycaemia, 1 urinary tract infection, and 1 pneumonia	24		3	

DX dexemathasone, *M/F* male/female

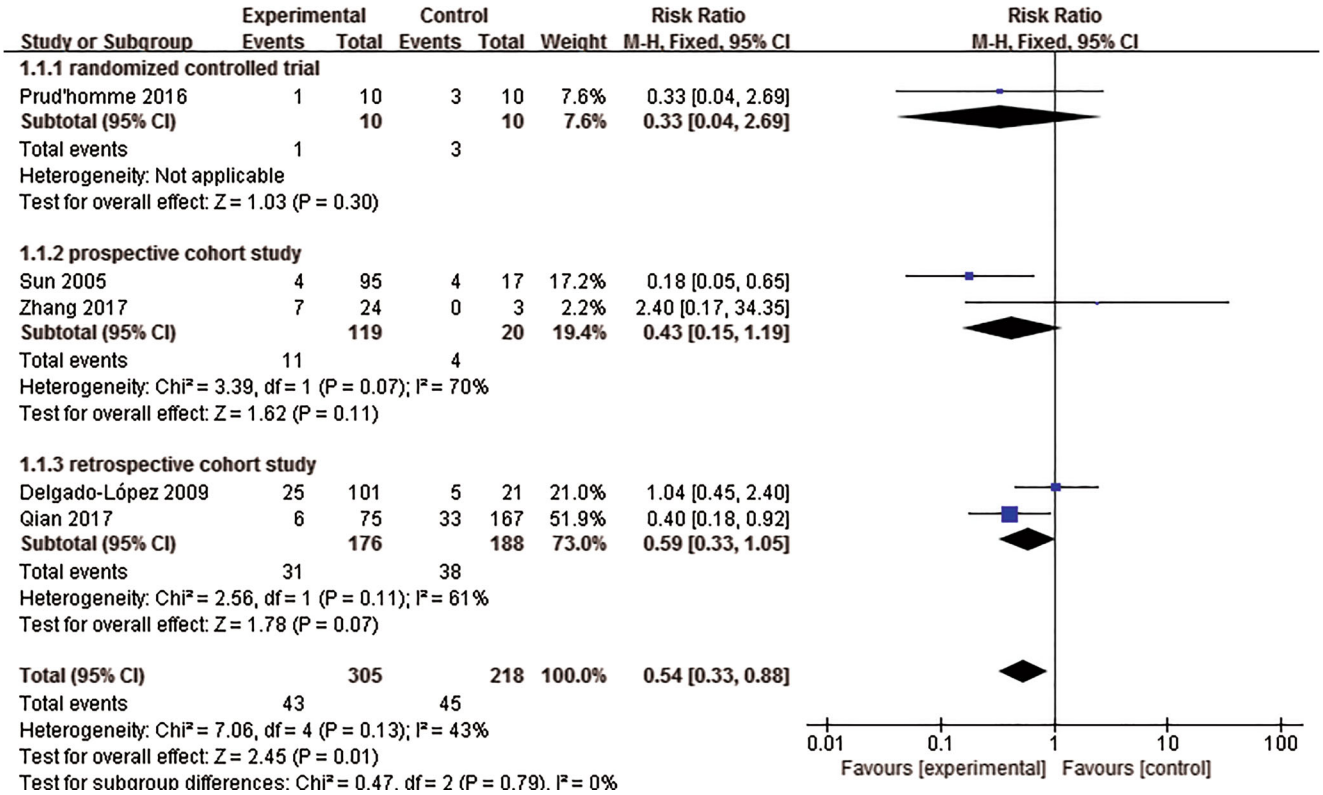

Fig. 2 Forest plot of studies comparing overall DX (alone or adjuvant) with non-DX therapy with their respective risk ratio (RR) and 95% confidence interval (CI), events (recurrence). DX, dexamethasone

the study of Qian et al. [26] was excluded. The heterogeneities between different studies ($\chi^2 = 7.06$, $p = 0.13$, $I^2 = 43\%$) and between different subgroups ($\chi^2 = 0.47$, $p = 0.79$, $I^2 = 0$) were acceptable. Funnel plot was visually symmetric, indicating no obvious publication bias (Fig. 3).

DX alone versus non-DX therapy

There were four studies comparing the effect of DX alone with that of non-DX therapy on the recurrence rate; overall effect (RR, 0.86; 95% CI, 0.43-1.71; $p = 0.66$) showed no significant difference, with rare heterogeneity existing ($\chi^2 = 1.89$, $p = 0.60$, $I^2 = 0$) (Fig. 4). Sensitivity analyses when excluding any single study at a time did not change the result statistically. The result demonstrated comparable recurrence rates between DX alone therapy and non-DX therapy for CSDH.

DX alone versus surgical therapy

With regard to the poor outcome and the recurrence rate, three observational studies reported comparable effects between DX alone therapy and surgical therapy.

Comparing the effects between DX alone therapy and surgical therapy on poor outcomes, overall effect (RR, 0.40; 95% CI, 0.15-1.04; $p = 0.06$) revealed no significant difference, accompanied by rare heterogeneity ($\chi^2 = 0.25$, $p = 0.88$, $I^2 = 0$)(Fig. 5). There was a trend towards more poor outcomes in the surgical therapy group, though insignificant. After excluding any single study one time, sensitivity analyses remained the consistent statistical result.

With reference to the overall effect on the recurrence rate, the difference reached no significance between DX alone therapy and the surgical therapy (RR, 0.89; 95% CI, 0.43-1.85; $p = 0.76$). The heterogeneity was acceptable ($\chi^2 = 1.72$, $p = 0.42$, $I^2 = 0$) and sensitivity analyses did not change the result statistically (Fig. 5).

Discussion

Current research of the CSDH

CSDH, as a benign entity, had perplexed clinicians for years because of its high incidence and high rate of recurrence. The estimated incidence ranged from 8.2/100,000 to 14.0/100,000 per person years [1, 4, 9, 20], and an increase

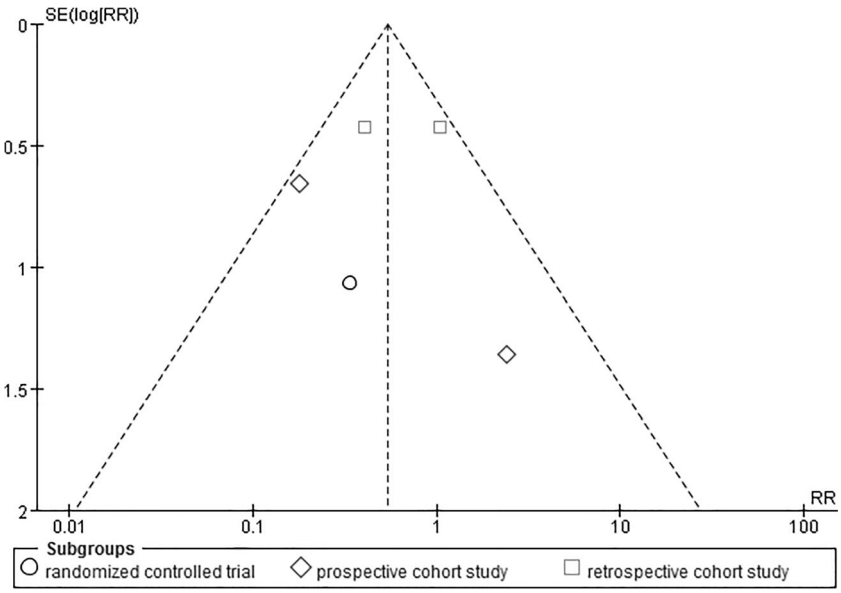

Fig. 3 Funnel plot of studies comparing overall DX (alone or adjuvant) with non-DX therapy. DX, dexamethasone

in incidence was expected in the coming years due to the aged population. The main hurdle in curing CSDH was the high rate of recurrence ranging from 7.6 to 30% in different reports [5, 10, 13, 15, 30]. Researches on the mechanisms of recurrence have speculated that inflammation induced by the erythrocyte breakdown products played a predominant role in this process [28, 29]. Elements like plasminogen and activators concentrated and inhabited blood coagulation in the subdural space where the neo-membrane and neo-capillaries constantly leaked blood to the subdural space [17, 21]. The process of rebleeding and breakdown of erythrocytes exacerbated the inflammation reaction, followed by the formation of the neo-membrane and neo-capillaries. This cycle of the rebleeding-coagulation-fibrinolysis process eventually led the haematoma to enlargement or recurrence. In experimental conditions, Glover et al. [14] found DX inhabited the formation of the neo-membrane and reduced the volume of haematoma.

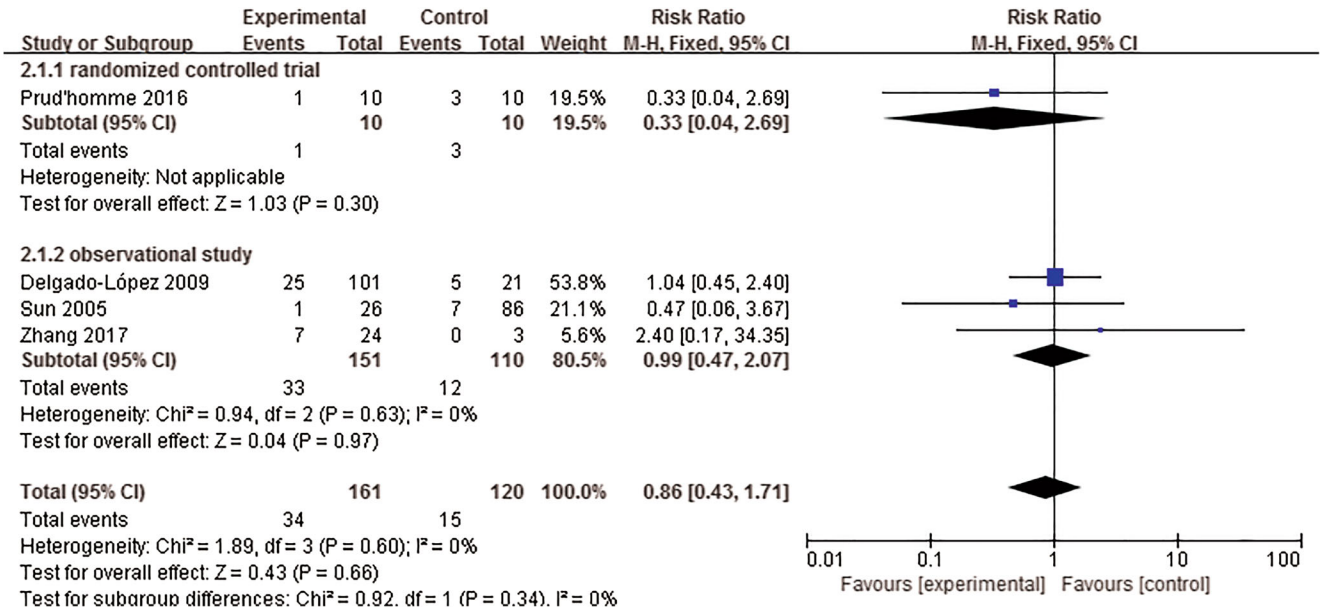

Fig. 4 Forest plot of studies comparing DX alone with non-DX therapy with their respective risk ratio (RR) and 95% confidence interval (CI), events (recurrence). DX dexamethasone

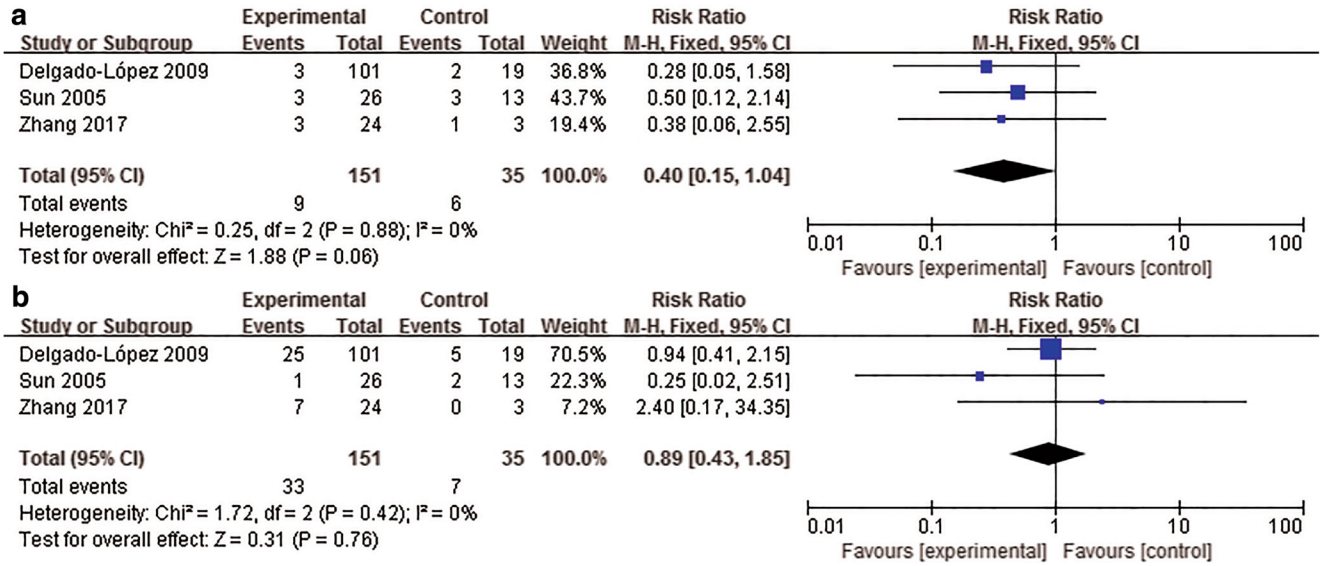

Fig. 5 Forest plot of studies comparing DX alone with the surgical therapy. **a** Studies with events of poor outcome; **b** studies with events of recurrence. *DX* dexamethasone

Therefore, methods to block this inflammation process were likely to reduce and avoid haematoma recurrence. In clinical practice, CSDH was divided into five grades (0-4) according to clinical manifestation [22], and four types (homogeneous, laminar, separated and trabecular) according to intensity and internal architecture [23], among which the separated type was inclined to relapse. Despite those experimental and clinical researches, optimal treatment to avoid recurrence was not defined yet.

Summary of different forms of DX use

Corticosteroid, a powerful anti-inflammation and anti-angiogenesis drug, has been used to treat CSDH for a long time [3, 6]. Subsequent case reports and series confirmed its effectiveness [10, 29]. In a previous review of five cohort studies, Berghauser et al. [8] considered the level of evidence for DX as an effective treatment to CSDH still low (class III). In another systematic review of Almenawer et al. [2], comparisons between different treatment modalities found adjuvant DX use resulted in higher morbidity. But this result may be biased by substantial heterogeneity ($I^2 > 50\%$) for the included population covered infantile patients [18] and acute subdural haematoma cases [6].

Different from the previous reviews, two non-English language studies [11, 24] were not retrieved in our work. Also, Bender and Christoff's study [6], despite its inclusion in the previous reviews, was not included in our review because it researched on the mix of CSDH and acute subdural haematoma. Additionally, the medical treatment in Bender and Christoff's study mainly referred to the bed rest accompanied with DX. In our review, a new randomised controlled study and two more observational studies were included. Through pooling the effects, we found the overall effect of DX (alone or adjuvant) therapy resulted in a lower recurrence rate than that of non-DX therapy (Fig. 2). But in sensitivity analysis after excluding the most influential study, the difference reached no significance. Therefore, we could not exclude the likelihood that the single study with large sample size biased the overall effect. Additionally, the comparison between DX alone therapy and non-DX therapy demonstrated comparable effects in CSDH recurrence (Fig. 4). The subsequent sensitivity analyses achieved the consistent result. In view of the poor outcome, pooled analyses showed no statistical difference in the poor outcome and recurrence rate when comparing DX alone therapy with surgical therapy (Fig. 5). There existed a trend towards more poor outcome in the surgical therapy group, but reaching no significance. Speculation was that the trend was due to the inherent bias of observational studies. For example, Delgado-Lopez et al. [10] allocated patients with MGS 1-2 to DX therapy and patients with MGS 3-4 to surgical therapy, which produced obvious biased allocation. Owing to the lack of data, we could not compare adjuvant DX with surgical therapy in treating CSDH. However, studies revealed perioperative use of DX was associated with a lower recurrence rate and mortality [7, 11].

The most common DX-associated side effect was hyperglycaemia, but in our review most cases could be controlled with insulin and recovered to previous levels after withdrawing DX. Two lethal complications as pulmonary embolus and suicide were reported, but the association with DX use was unclear. Doses of DX use were much the same with minimum dose of 12 mg per day and maximun dose of 16 mg per day, but the duration varied, ranging from 3 days to 3 weeks.

Limitations and further research

This review still had some limitations. Firstly, relatively few studies precluded us to further subgroup analysis. Besides, lack of data about outcomes and hospital stay time make it difficult to evaluate those endpoints. Moreover, the inherent limitations of observational study and the relatively moderate quality of included studies made the result less robust. Further study is required to elucidate the effectiveness of adjuvant DX use and optimal duration.

Conclusions

The present review had not enough evidence to support DX use as an effective alternative to surgical therapy. But adjuvant DX use may facilitate the surgical therapy in achieving a lower recurrence rate. Meanwhile, the DX-related side effects merited attention. Hence, a comprehensive treatment modality combining surgery with DX use needs to be built for this common but retractable disease, taking into consideration various factors like optimal duration and complications.

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Compliance with ethical standards

Conflict of interest None

Ethical statements This review required no ethical approval.

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