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REVIEW ARTICLE - BRAIN TRAUMA

Corticosteroid treatment compared with surgery in chronic subdural hematoma: a systematic review and meta-analysis

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Abstract

Background There is an ongoing debate on the role of corticosteroids in the treatment of chronic subdural hematoma (CSDH). This study aims to evaluate the effectiveness of corticosteroids for the treatment of CSDH compared to surgery.

Method A systematic search was performed in relevant databases up to January 2019 to identify RCTs or observational studies that compared at least two of three treatment modalities: the use of corticosteroids as a monotherapy (C), corticosteroids as an adjunct to surgery (CS), and surgery alone (S). Outcome measures were good neurological outcome, need for reintervention, mortality, and complications. Effect estimates were pooled and presented as relative risk (RR) with 95% confidence interval (95%CI).

Results Of 796 initially identified studies, 7 were included in the meta-analysis. Risk of bias was generally high. There were no differences in good neurological outcome between treatment modalities. The need for reintervention varied between 4 and 58% in C, 4–12% in CS, and 7–26% in S. The need for reintervention was lower in CS compared with C (RR 3.34 [95% CI 1.53–7.29]; $p < 0.01$) and lower in CS compared with S (RR 0.44 [95% CI 0.27–0.72]; $p < 0.01$). Mortality varied between 0 and 4% in C, 0–13% in CS, and 0–44% in S. Mortality was lower in CS compared with S (RR 0.39 [95% CI 0.25–0.63]; $p < 0.01$). There were no differences in complications between treatment modalities.

Conclusions This meta-analysis suggests that the addition of corticosteroids to surgery might be effective in the treatment of CSDH. However, the results must be interpreted with caution in light of the serious risk of bias of the included studies. This study stresses the need for large randomized trials to investigate the use of corticosteroids in the management of CSDH.

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Introduction

Chronic subdural hematoma (CSDH) is one of the most common neurosurgical conditions with an overall incidence rate of 1.72–79.6 per 100,000 persons per year and the incidence is increasing over time [2, 7, 19, 29, 32, 36]. Consensus on the best standard treatment of symptomatic CSDH is lacking. Worldwide, the most commonly performed intervention in symptomatic CSDH is surgery through burr hole craniostomy (BHC), with or without insertion of a closed-system drainage [3, 13, 23, 43, 45]. Postoperative recurrence rates range from 2 to 37% [18, 21, 22, 28, 33, 39, 44, 49, 52] and postoperative complications may occur, including rebleed, tension pneumocephalus, cerebral infarction, subdural empyema, and wound infection. Death occurs in 1.5 to 6% of the patients operated for a CSDH [4, 6, 31, 38, 53]. The esthetic outcome after surgery may be unsatisfactory for some patients [51], which may be avoided with medical treatment.

To determine the best treatment for each individual CSDH patient, knowledge of the pathophysiology of the CSDH is indispensable. The exact mechanism of CSDH formation is not fully understood, but likely relies on a complex intertwined pathway of angiogenesis, inflammation, recurrent microbleeds, exudates, and local coagulopathy [10, 17, 25]. In light of this hypothesis, other treatment options, such as the use of corticosteroids, as monotherapy or as an adjunct to surgery might be worthwhile to investigate. Surveys among neurosurgeons show that nearly a quarter of them use corticosteroids in the conservative management of CSDH [8, 11]. Steroids are known to have an anti-inflammatory and an anti-angiogenic effect. However, the administration of corticosteroids in patients diagnosed with CSDH is also associated with complications such as hyperglycemia, infections, mental disturbances, and even mortality in 0.8 to 4% of patients [10, 11]. The aim of this meta-analysis is to study the effectiveness of corticosteroids for the treatment of CSDH—as a monotherapy or as an adjunct to surgery—compared with surgery alone. The present meta-analysis is a reiteration of a previous article published in 2012 by our group [10]. From 2012 on, new data have been published regarding the use of corticosteroids in the treatment of CSDH. Upon aiming to update the meta-analysis, we have also improved the methodology.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for the evaluation and analysis of this meta-analysis [37].

Protocol

This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [26] and followed guidelines from the Centre for Reviews and Dissemination (University of York, UK).

Literature search

Medline Ovid, Embase, Web of Science, Cochrane Central, and Google Scholar were systematically searched from their starting dates to January 2019 (Supplementary Material). Titles and abstracts of these studies were independently screened by three investigators (DCH, VV, RD) to identify potential relevant studies after which the full text was screened. Any discrepancies were discussed and resolved through consensus. All articles in English, French, German, Dutch, Spanish, or Italian languages were included.

Inclusion criteria

Studies were included if they included at least 10 adults (aged 18 years or older) with a newly diagnosed supratentorial CSDH. These patients should have received a surgical treatment (group S) or a treatment with corticosteroids as a monotherapy (group C) or as an adjunct to surgery (group CS). Studies needed to report on at least 2 of these treatment modalities. Also, studies needed to report on mortality, neurological outcome, need for reintervention, and/or complications. In case data on mortality, neurological outcome, recurrence, and complications were missing or unclear, authors of studies were contacted.

Outcome measures

Good neurological outcome

Good outcome was defined as a Glasgow Outcome Score [27] (GOS) of 4–5 and/or Markwalder Grading Scale [35] (MGS) 0–1 (Table 1). Articles without a defined GOS or MGS were excluded from this part of the meta-analysis.

Need for reintervention

Need for reintervention was defined as the need for an additional treatment of CSDH with corticosteroids or surgery, based on neurological deterioration and/or radiological recurrence.

Table 1 Criteria on good neurological outcome

Glasgow Outcome Scale (GOS) [27]		Markwalder Grading Scale (MGS) [35]	
1. Death	Severe injury or death without recovery of consciousness.	Grade 4	Comatose with absent motor responses to painful stimuli, decerebrate or decorticate posturing.
2. Persistent vegetative state	Severe damage with prolonged state of unresponsiveness and a lack of higher mental functions.	Grade 3	Stuporous, but responding appropriately to noxious stimuli, several focal signs such as hemiplegia.
3. Severe disability	Severe injury with permanent need for help with daily living.	Grade 2	Drowsy or disorientated, or variable neurological deficit such as hemiparesis.
4. *Moderate disability*	*No need for assistance in everyday life, employment is possible but may require special equipment.*	*Grade 1*	*Alert and orientated: absence of mild symptoms such as headache, or mild neurological deficit such as reflex asymmetry.*
5. *Low disability*	*Light damage with minor neurological and psychological deficits.*	*Grade 0*	*Neurologically normal.*

Italicized words are in good neurological outcome

Mortality

Mortality was defined as death from the moment treatment was started until the end of the follow-up period.

Complications

Complications, possibly related to the use of corticosteroids and/or surgery, were extracted from the included articles.

Data extraction

From every paper, the number of patients, the median or mean age, sex, intervention, and the complications, in absolute numbers or relative risks (when available) were extracted in a database. If the relative risks were not available, Review Manager 5.3 (RevMan) was used to calculate them based on the absolute numbers.

Risk of bias analysis

A risk of bias analysis was then performed for each of the included papers using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [24] and the ROBINS-I (risk of bias in non-randomized studies - of interventions): a tool for assessing risk of bias in non-randomized studies of interventions [46]. Each paper was graded (by DCH and VV) and assigned a risk of bias, either low, moderate, high, or critical. The conclusions are also interpreted in this light.

Statistical analysis

RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform the meta-analyses. The following comparisons were made as follows: corticosteroids versus surgery, corticosteroids and surgery versus surgery, and corticosteroids alone versus corticosteroids and surgery. For all three comparisons, the outcomes mortality, good outcome, need for reintervention, and complications were assessed. The Mantel-Haenszel method was used to provide a summary relative risk. The I^2 measure was used to determine the level of statistical heterogeneity, with a cut-off of 50%. When heterogeneity was moderate to high (> 50%), we used a random effects model, if heterogeneity was low (< 50%), we used a fixed effects model. The results are presented as relative risks with 95% confidence intervals. A p value of 0.05 was considered statistically significant.

Results

Included publications

The initial search identified 1082 studies of which 796 remained after removal of double references. A total of 785 records were excluded based on title/abstract and four articles were excluded based on full text. Finally, seven papers met the inclusion criteria. These studies were included in this meta-analysis (Fig. 1, Table 2).

Quality

The included studies were assessed on risk of bias. All non-randomized studies had a critical risk of bias (Table 3). The randomized controlled trial was of poor quality as well (Table 4). Authors of three studies were contacted in order to clarify missing data on outcome [20, 42, 48] and mortality [42] but did not respond.

Treatments

A total of 1119 patients were included. Group C (treatment with corticosteroids as a monotherapy) consisted of 138 patients; group CS (corticosteroids as an adjunct to surgery)

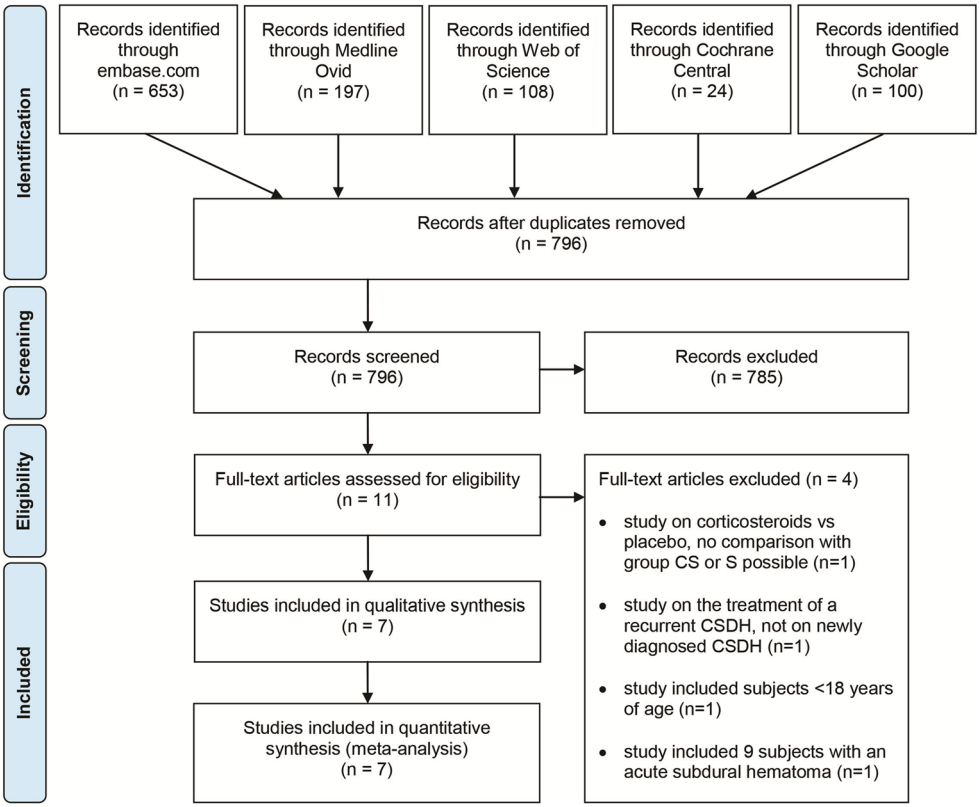

Fig. 1 PRISMA 2009 Flow Diagram [37]

contained 461 patients, and group S (surgical treatment only) consisted of 507 patients. Thirteen patients could not be classified in one of these treatment groups (e.g., because of bed rest treatment). Patients treated with corticosteroids received dexamethasone (starting dose 12–24 mg/day) or [14, 15, 20, 42, 47, 48] methylprednisolone (starting dose 0.5 mg/kg/day) [16] as a monotherapy or as an adjunct to surgery. Three out of 7 studies described group C, CS, and S [15, 20, 47]. Also, 3 out of 7 studies compared group CS versus S [14, 16, 42] and 1 out of 7 studies described group CS versus group C [48] (Table 2).

Outcome measures

Good neurological outcome

Of the 7 included publications, 3 described neurological outcome [14, 15, 47]. To indicate the outcome at any time point, some authors used the GOS [14, 47] while others used the MGS [15]. A favorable outcome (GOS 4–5 or MGS 0–1) was reported in 88–91% of patients of group C, 72–91% of patients of group CS, and in 77–88% of the patients of group S (Table 5).

Table 2 Publications screened for full text

	N	Design	Male	Treatment	Age	Starting dose	Tapering course	Follow-up
INCLUDED								
Sun et al., 2005 [47]	112	P	63	C, CS, S	Median 75 (range 37–91)	DXM 16 mg/day	2–21 days	6 months
Dran et al., 2007 [16]	198	R	142	CS, S	Mean 75 (± 13)	MPRD 0.5 mg/kg/day	Minimum 1 month	17.5 months
Delgado-Lopez et al., 2009 [15]	122	R	84	C, CS, S	Median 78 (range 25–97)	DXM 12 mg/day	36 days	25 weeks
Chan et al., 2015 [14]	248	P	177	CS, S	Mean 71.3	DXM 16 mg/day	10 days	6 months
Thotakura et al., 2015 [48]	26	P	20	C, CS	Mean 60.25 (range 32–77)	DXM 12 mg/day	31 days	2–25 months
Qian et al., 2017 [42]	242	R	148	CS, S	Median 66.3 (± 10.9)	DXM 12 mg/day	40 days	6 months
Fountas et al., 2019 [20]	171	R	120	C, CS, S	Mean 76.4 (± 9.3)	DXM 24 mg/day	14 days	> 3 months

N, number of patients; *R*, retrospective; *P*, prospective; *C*, corticosteroids as monotherapy; *CS*, corticosteroids as an adjunct to surgery; *S*, surgery; *DXM*, dexamethasone; *PRD,* prednisone; *MPRD*, methylprednisolone; *n.a.*, not available

Table 3 Risk of bias in non-randomized studies - of Interventions (ROBINS-I) assessment tool

	Sun et al., 2005 [47]	Dran et al., 2007 [16]	Delgado-Lopez et al., 2009 [15]	Thotakura et al., 2015 [48]	Qian et al., 2017 [42]	Fountas et al., 2019 [20]
Bias due to confounding	CRI	CRI	CRI	CRI	CRI	CRI
Bias in selection of participants into the study	CRI	CRI	CRI	CRI	CRI	CRI
Bias in classification of interventions	LOW	MOD	LOW	MOD	LOW	CRI
Bias due to deviations from intended intervention	UNK	UNK	UNK	UNK	UNK	UNK
Bias due to missing data	UNK	UNK	UNK	UNK	UNK	UNK
Bias in measurement of outcomes	LOW	LOW	LOW	LOW	LOW	LOW
Bias in selection of the reported result	LOW	UNK	MOD	MOD	LOW	LOW
Overall interpretation	CRI	CRI	CRI	CRI	CRI	CRI

LOW, low risk of bias; *MOD*, moderate risk of bias; *SER*, serious risk of bias; *CR*, critical risk of bias; *UNK*, unknown

When comparing the three groups on good neurological outcome the pooled relative risks did not show any differences between treatment groups (Fig. 2).

Need for reintervention

Of the included publications, 6 out of 7 discussed the need for reintervention. In group C, the percentages ranged from 4 [47] to 58% [48], in group CS 4 [20, 47] –12% [15] and in group S 7 [20] –26% [15] (Table 5). The need for reintervention was lower in group CS compared with group C (RR 3.34 [95% CI 1.53–7.29]; $p < 0.01$; $I^2 = 7\%$) and lower in CS compared with S (RR 0.44 [95% CI 0.27–0.72]; $p < 0.01$ $I^2 = 0\%$) (Fig. 3).

Mortality

Mortality was described in 6 out of 7 publications. It was not possible to provide the six-month mortality data, because it was not reported as such in the included publications. The percentages range from 0 [15, 20, 48]to 4% [47] in group C, 0 [48] –13% [16] in group CS, and 0 [15] –44% [16] in group S (Table 5). The causes of death are clearly described in 3 out of these 7 studies [14, 20, 47]. Two other studies [15, 16] published numbers on mortality without specifying the cause of death (Table 6). Mortality was lower in group CS compared with group S (RR 0.39 [95% CI 0.25–0.63]; $p < 0.01$; $I^2 = 15\%$) (Fig. 4).

Complications

A total of 63 complications were described in the included publications (Table 7), but definitions of complications varied or were not provided. In some articles, it was not clear if and in which treatment group a complication had occurred [15, 16, 20, 42, 48]. Sun et al. and Chan et al. described the complications in each treatment group. In group C, hyperglycemia was the most common complication. In group S, infection (0.8–7.7%) and pneumocephalus (12.5%) occurred most frequently. Hyperglycemia (6.7–14.8%) and infection (1.5–12.5%) were the most common complications in the CS group. The only comparison for which a pooled relative risk could be calculated was the risk of infection between the CS and S groups, which was not significantly different (Fig. 5).

Publication bias

We aimed to assess publication bias using funnel plot symmetry, but the number of included studies precluded proper interpretation and was therefore abandoned.

Table 4 Cochrane risk of bias tool for randomized controlled trials

	Chan et al., 2015 [14]
Biased allocation to interventions	LOW
Biased allocation to interventions	LOW
Bias due to selective outcome reporting	HIGH
Bias due to problems not covered elsewhere in the table	HIGH
Performance bias due to knowledge of the allocated interventions by participants and personnel	HIGH
Detection bias due to knowledge of the allocated interventions by outcome assessors	LOW
Attrition bias due to amount, nature, or handling of incomplete outcome data	LOW
Overall interpretation	Poor quality

LOW, low risk of bias; *HIGH*, critical risk of bias; *UNK*, unknown

Table 5 Effects of corticosteroids and/or surgery on good neurological outcome, need for reintervention, and mortality

	Good neurological outcome‡			Need for reintervention			Mortality		
	C	CS	S	C	CS	S	C	CS	S
Sun et al., 2005 [47]	23/26 (88%)	63/69 (91%)	10/13 (77%)	1/26 (4%)	3/69 (4%)	2/13 (15%)	1/26 (4%)	2/69 (3%)	2/13 (15%)
Dran et al., 2007 [16]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	17/131 (13%)	20/45 (44%)
Delgado-Lopez et al., 2009 [15]	69/76 (91%)	18/25 (72%)	15/17 (88%)	28/101 (28%)	3/25 (12%)	5/19 (26%)	0/76 (0%)	1/25 (4%)	0/17 (0%)
Chan et al., 2015 [14]	n.a.	104/122 (85%)	105/126 (83%)	n.a.	8/122 (7%)	17/126 (13%)	n.a.	3/122 (2%)	3/126 (2%)
Thotakura et al., 2015 [48]	n.a.*	n.a.*	n.a.	15/26 (58%)	1/15 (7%)	n.a.	0/11 (0%)	0/15 (0%)	n.a.
Qian et al., 2017 [42]	n.a.	n.a.*	n.a.*	n.a.	6/75 (8%)	33/167 (20%)	n.a.	n.a.*	n.a.*
Fountas et al., 2019 [20]	n.a.*	n.a.*	n.a.*	3/10 (30%)	1/24 (4%)	10/137 (7%)	0/10 (0%)	1/24 (4%)	8/137 (6%)

C, corticosteroids as a monotherapy; *CS*, corticosteroids as an adjunct to surgery; *S*, surgery; *n.a.*, not available; *n.a.**, not available after attempt to contact the authors

‡ GOS 4–5 and/or MRS 0–1 (Table 2)

Discussion

We updated our previous meta-analysis on the effects of corticosteroids compared with surgery in patients with a CSDH. Four studies were added [14, 20, 42, 48] to our previous review and two were abandoned and the methodology was improved [10]. We found no significant difference between treatment modalities with regard to good neurological outcome. In terms of reinterventions, patients who were treated with corticosteroids as an adjunct to surgery had significantly less reinterventions compared with patients who were treated with corticosteroids or surgery alone. Also, patients who were

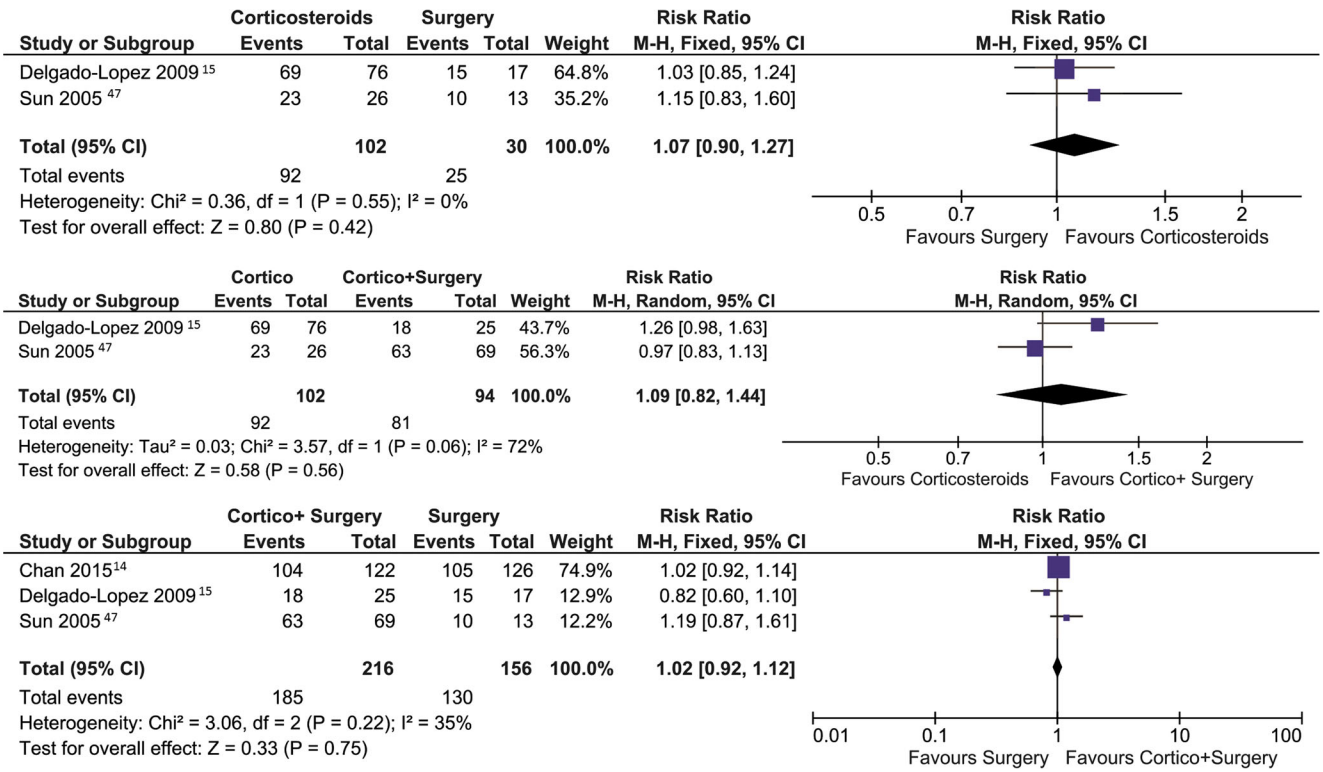

Fig. 2 Forest plots on good neurological outcome; defined as a GOS [27] of 4–5 and/or MGS [35] 0–1 (Table 2)

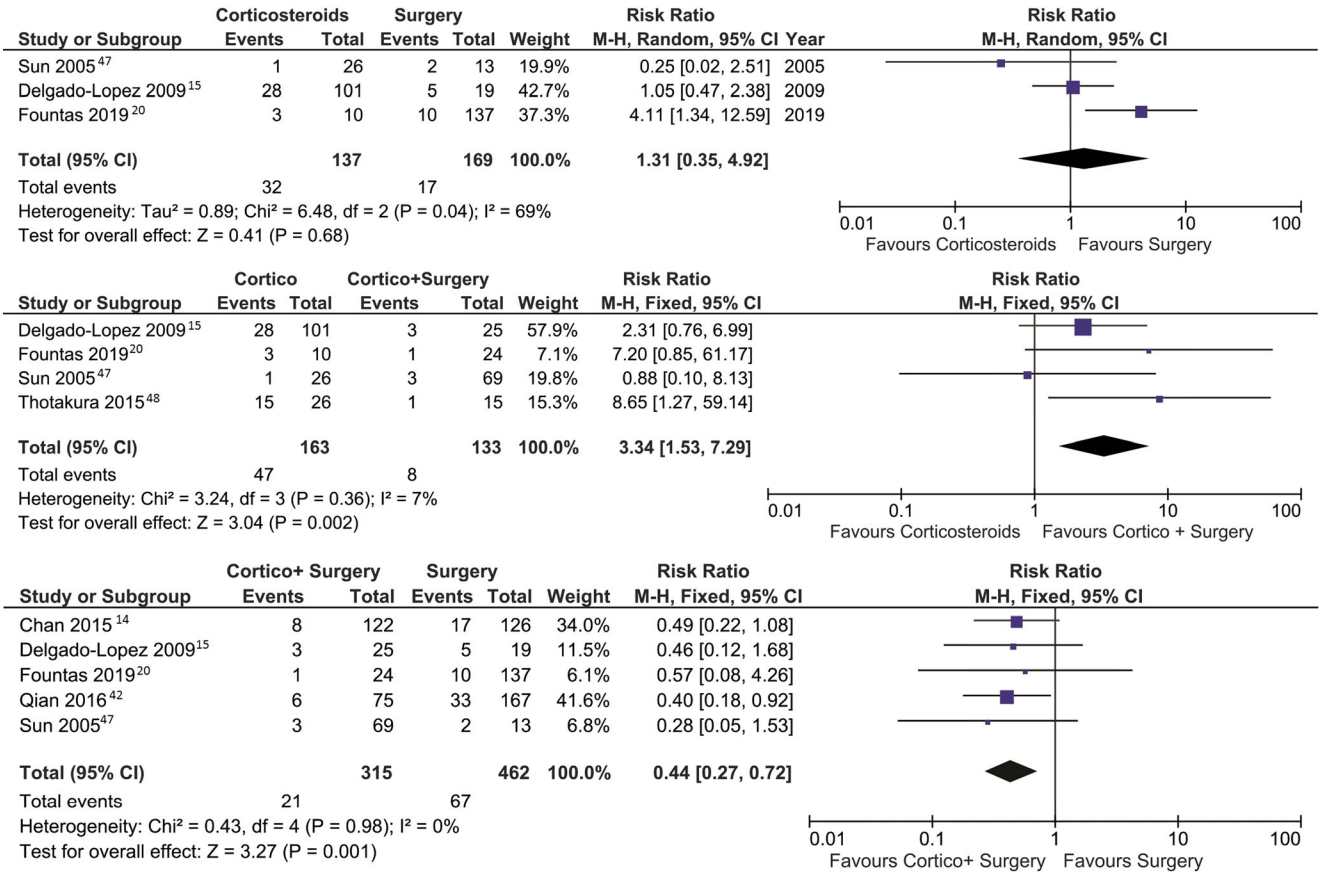

Fig. 3 Forest plots on need for reintervention; the need for an additional treatment of CSDH with corticosteroids or surgery

treated with corticosteroids as an adjunct to surgery had a significantly lower mortality rate compared with patients who were treated with surgery alone.

However, all studies included had a critical risk of bias. No class I studies on the use of corticosteroids in CSDH were available. This provides major concerns about the validity of the pooled results and the limitations of the included studies should be taken into account when interpreting the outcomes of this meta-analysis. The main limitation of the 6 observational studies was the non-random treatment allocation resulting in a critical risk of bias. When treatment is allocated based on the neurological condition, groups become incomparable. Such confounding by indication results in biased treatment effect estimates and can never be fully adjusted

Table 6 Causes of death

	Follow-up	C	CS	S
Sun et al., 2005 [47]	6 months	1 Subarachnoid hemorrhage	1 Intracerebral hemorrhage 1 Urinary tract and chest infection	1 Chest infection 1 Rectum carcinoma
Dran et al., 2007 [16]	17.5 months	n.a.	17 Unknown causes	20 Unknown causes
Delgado-Lopez et al., 2009 [15]	25 weeks	None	1 Unknown	None
Chan et al., 2015 [14]	6 months	n.a.	1 Subdural empyema 1 Chest infection 1 Unknown	1 Intracranial hemorrhage 1 Chest infection 1 Unknown
Thotakura et al., 2015 [48]	2–25 months	None	None	n.a.
Qian et al., 2017 [42]	6 months	n.a.	n.a.	n.a.
Fountas et al., 2019 [20]	> 3 months	None	1 Infection*	2 Status epilepticus* 1 Hemorrhage and edema* 5 Cardiac arrest*

C, corticosteroids as a monotherapy; *CS*, corticosteroids as an adjunct to surgery; *S*, surgery; *n.a.*, not available

*Obtained by contacting the authors

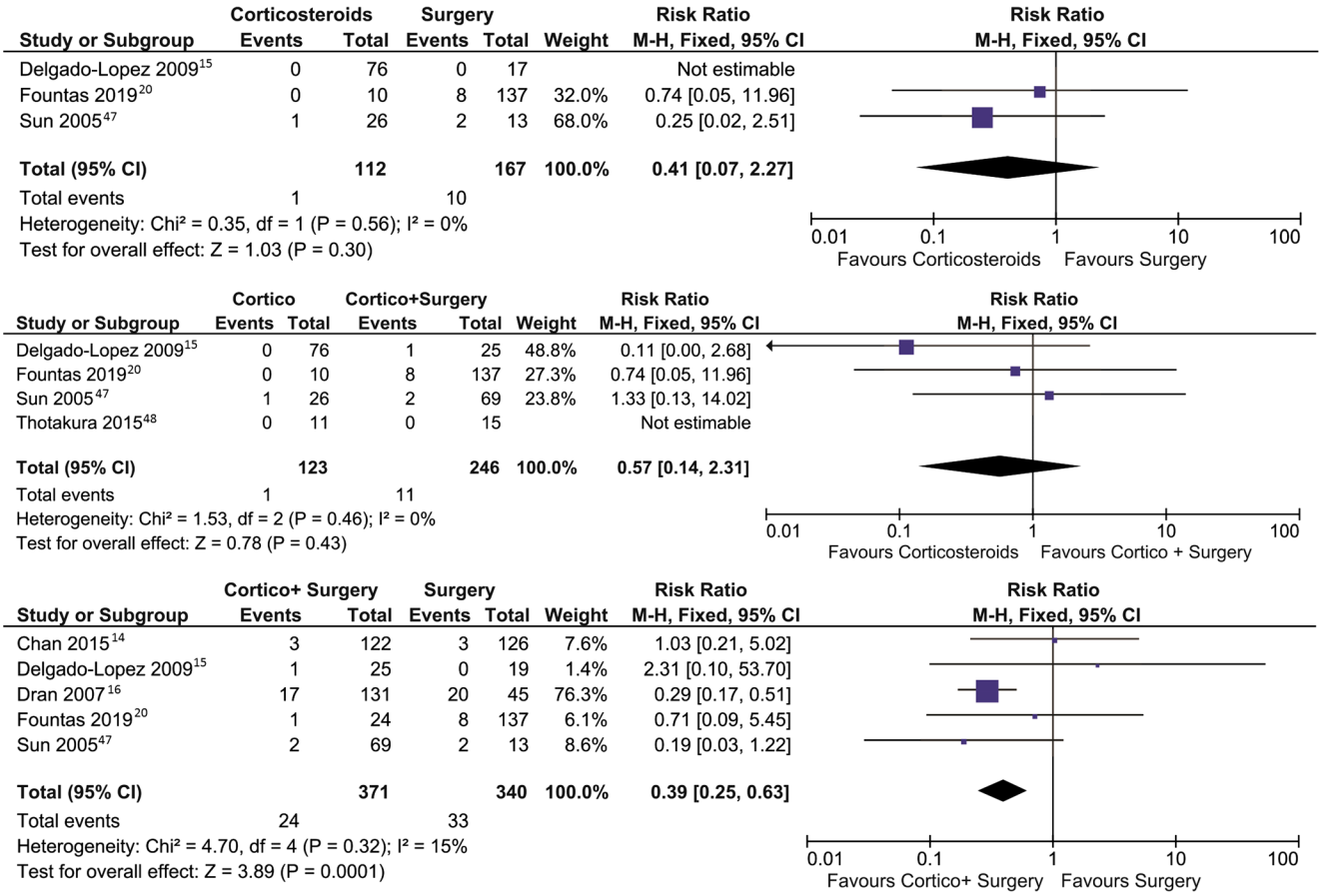

Fig. 4 Forest plots on mortality; death from the moment treatment was started until the end of the follow-up period

Table 7 Complications

	Complications in group C	Possible surgery and/or corticosteroid related complications	Complications in group S
Sun et al., 2005 [47]	2 Hyperglycemias (7.7%) 1 Subarachnoid hemorrhage (3.8%)	1 Urinary tract and chest infection (1.5%) 1 Intracerebral hemorrhage (1.5%)	1 Chest infection (7.7%)
Dran et al., 2007 [16]	–	n.a.	3 Subdural empyema (5.4%) 7 Pneumocephalus (12.5%)
Delgado-Lopez et al., 2009 [15]	n.a.	18 Hyperglycemias (14.8%)11 Infections (9.0%) 3 Thromboembolism (2.5%) 3 Cardiac impairment (2.5%) 1 Stroke in patient with AF (0.8%) 1 GI-bleeding (0.8%) 1 ADH inappropriate secretion responding to water restriction (0.8%) 1 Self-limited hyponatremia (0.8%)	n.a.
Chan et al., 2015 [14]	–	5 Chest infections (4.1%)	1 Intracerebral hemorrhage (0.8%) 1 Chest infection (0.8%) 1 Urinary tract infection (0.8%) 1 Wound infection (0.8%) 1 Subdural empyema (0.8%)
Thotakura et al., 2015 [48]	1 Hyperglycemia (9.1%) 1 Gastritis (9.1%)	n.a.	–
Qian et al., 2017 [42]	–	5 Hyperglycemias (6.7%)3 Sleeplessness (4.0%)	n.a.
Fountas et al., 2019 [20]	n.a.*	n.a.*	n.a.*

C, corticosteroids as a monotherapy; *S*, surgery; *AF*, atrial fibrillation; –, group not included in article; *n.a.*, not available; *n.a.**, not available after contact with the authors

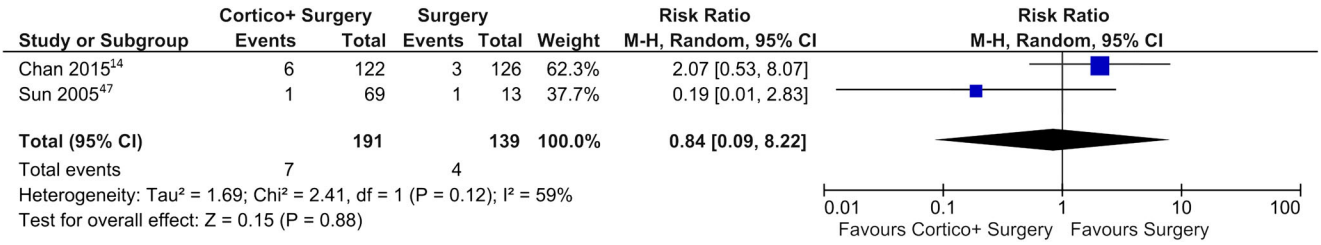

Fig. 5 Forest plot on complications; evaluation of infections

for. An attempt was made to compare the patient characteristics of the different treatment arms (group C, CS, and S). However, this information was incomplete and could not be reconstructed from the included papers.

In addition, there were inconsistencies regarding data on functional outcome, need for reintervention, and/or mortality. Some data was missing or unclear and could not be obtained by contacting the authors. Also, heterogeneous outcome measures were used. For example, different measuring scales were used in describing good neurological outcome (e.g., GOS or MGS); various timeframes were used when reporting mortality (e.g., follow-up 2 months up to 25 months). Finally, different types and doses of corticosteroids were used in the included studies.

Dran et al. described a recurrence rate of 8% [16]. However, it was unknown in which treatment modality these recurrences occurred and it was unclear if there was a need for reintervention. Therefore, the exact impact of the different treatment modalities on complications is unclear. Complications were not always clearly mentioned for the treatment groups within a study [15, 16, 20, 42, 48]. For example, Delgado et al. mention a total of 39 different complications in their cohort. It could however not be deduced which complication occurred in which treatment group. When complications were mentioned, they were often difficult to interpret. Hyperglycemia is the most prevalent complication and is commonly seen in patients using corticosteroids as a monotherapy and as an adjunct to surgery. The cases of hyperglycemia in these studies had optimal blood sugar controls after insulin administration [15, 42, 47]. Once the corticosteroid tapering course ended, patients returned to baseline diabetic control. Other complications, such as infections and thromboembolic events, were reported but it was unclear in which treatment group they occurred. Certain causes of death (e.g., rectum carcinoma in the surgery group) could not be attributed to the intervention itself. Also, it was not possible to provide the six-month mortality data, because it was not reported as such in the included publications and could not be retrieved from the manuscript itself or its figures and tables. These limitations have undoubtedly biased the effect estimates.

When comparing our meta-analysis to the meta-analysis of Yao et al. [55], certain differences have to be noted. First of all, Yao focused on recurrence, not on mortality or good neurological outcome. A letter to the editor from Brotis et al. [12] discusses the conclusion of Yao on the dexamethasone "overall effect" on recurrence. Brotis et al. state that various treatments (group C and CS) cannot be combined into one dexamethasone "overall effect" group. In their letter, a network meta-analysis is performed, based on the data extracted by Yao et al. When comparing our meta-analysis to Brotis' network meta-analysis, both show a lower recurrence rate in patients using adjuvant dexamethasone. Because of the critical risk of bias of the included studies, we decided not to perform a network meta-analysis.

In our meta-analysis, we found a statistical difference in recurrence when comparing adjuvant dexamethasone with surgery alone and with corticosteroids alone. Based on the data extracted by Yao, Brotis did not find a statistically significant difference among these different treatment options. The articles used by Yao et al. differ from the articles included in our meta-analysis. Yao included the articles of Prud'homme [41] and Zhang [56]. Prud'homme et al. compared the use of dexamethasone with the use of placebo. There is no comparison with any form of surgical treatment. Zhang et al. compared dexamethasone treatment with surgical intervention in patients with a recurrent CSDH, not in patients with a newly diagnosed CSDH. We therefore excluded the articles of Prud'homme and Zhang from this meta-analysis after full-text review. However, these two articles should not be omitted from the discussion on the use of corticosteroids in CSDH.

Like Yao, we excluded the article of Bender et al. since patients with an acute subdural hematoma (ASDH) were included [9]. This article was published in 1974 and states that 9 out of 185 patients were considered to have an ASDH because the injury took place within 48 h of admittance. At that time, no additional imaging could be performed to differentiate between an ASDH and CSDH and CT-imaging was not available in the follow-up of potential recurrences.

Yao excluded the manuscript of Pichert because language restrictions [40]. We also excluded the study of Pichert, although not because of the German language, but because of the inclusion of at least 1 patient under the age of 18 years.

In contrast to our meta-analysis, Yao did not include the articles of Dran, Thotakura Chan, and Fountas. The study of Dran is written in French and was excluded since Yao included English language publications only. Chan and Thotakura are not mentioned in Yao's systematic review and meta-analysis. A letter to Yao et al. [50] pointed at the missing article of

Chan. Yao replied [54] that Chan's study was excluded because of the focus on the reoperation rate instead of the recurrence rate. Personal correspondence with Yao learned that the study of Thotakura was excluded because, according to Yao, it was a non-comparative study. Thotakura was included in this meta-analysis because, on the contrary, it was felt that Thotakura's study was a comparative study, since they compare the use of corticosteroids as a monotherapy with the use of corticosteroids as an adjunct to surgery. The study of Fountas et al. was not yet published when Yao et al. published their manuscript and was therefore not included in their meta-analysis.

Based on the current knowledge of the pathophysiological mechanism of CSDH, corticosteroids may play a role in the treatment of CSDH. Based on the outcome of this meta-analysis, corticosteroids can be administered as an adjunct to surgery, possibly with a beneficial effect. However, the outcomes of this meta-analysis are based on articles with a critical risk of bias. Well-designed prospective randomized controlled trials are needed to assess which treatment is most beneficial in each individual patient diagnosed with CSDH. Especially given that the incidence of CSDH is predicted to increase and even to have doubled in 2030, because of the continuous rise of life expectancy and the increasing use of anticoagulants and platelet inhibitors [1, 4, 5, 23, 30, 31, 34, 53].

Currently, worldwide multiple randomized controlled clinical trials on the treatment of CSDH with corticosteroids have been set up or are in progress. Among those studies are three studies that will compare the use of corticosteroids with surgery alone (NCT02938468, NCT02111785, EudraCT#2015-001563-39).

Two other studies will compare the use of corticosteroids with the use of placebo (NCT02650609, EudraCT#2014-004948-35). One final study (EudraCT#2011-003544-42) will compare a group receiving corticosteroids as an adjunct to surgery with a group receiving a placebo as an adjunct to surgery.

Conclusion

Although this meta-analysis provides a methodologically sound summary of the currently available data on the effect of different treatments for newly diagnosed CSDH, limited conclusions can be drawn because of serious risk of bias of the included studies. The use of corticosteroids as an adjunct to surgery might be beneficial compared with surgery alone, but large randomized trials are needed to investigate the use of corticosteroids in the management of CSDH.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval For this type of study formal consent is not required. This article does not contain any studies with human participants performed by any of the authors.

References

1. Adhiyaman V, Asghar M, Ganeshram KN, Bhowmick BK (2002) Chronic subdural haematoma in the elderly. Postgrad Med J 78:71–75
2. Adhiyaman V, Chattopadhyay I, Irshad F, Curran D, Abraham S (2017) Increasing incidence of chronic subdural haematoma in the elderly. QJM 110:375–378
3. Almenawer SA, Farrokhyar F, Hong C, Alhazzani W, Manoranjan B, Yarascavitch B, Arjmand P, Baronia B, Reddy K, Murty N, Singh S (2014) Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. Ann Surg 259:449–457
4. Asghar M, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A (2002) Chronic subdural haematoma in the elderly–a North Wales experience. J R Soc Med 95:290–292
5. Aspegren O, Astrand R, Lundgren M, Romner B (2013) Anticoagulation therapy a risk factor for the development of chronic subdural hematoma. Clin Neurol Neurosurg 115:981–984
6. Baechli H, Nordmann A, Bucher HC, Gratzl O (2004) Demographics and prevalent risk factors of chronic subdural haematoma: results of a large single-center cohort study. Neurosurg Rev 27:263–266
7. Balser D, Farooq S, Mehmood T, Reyes M, Samadani U (2015) Actual and projected incidence rates for chronic subdural hematomas in United States Veterans Administration and civilian populations. J Neurosurg 123:1209–1215
8. Baschera D, Tosic L, Westermann L, Oberle J, Alfieri A (2018) Treatment standards for chronic subdural hematoma: results from a survey in Austrian, German, and Swiss neurosurgical units. World Neurosurg 116:e983–e995
9. Bender MB, Christoff N (1974) Nonsurgical treatment of subdural hematomas. Arch Neurol 31
10. Berghauser Pont LM, Dirven CM, Dippel DW, Verweij BH, Dammers R (2012) The role of corticosteroids in the management of chronic subdural hematoma: a systematic review. Eur J Neurol 19:1397–1403
11. Berghauser Pont LM, Dippel DW, Verweij BH, Dirven CM, Dammers R (2013) Ambivalence among neurologists and

neurosurgeons on the treatment of chronic subdural hematoma: a national survey. Acta Neurol Belg 113:55–59
12. Brotis AG, Gatos C, Fountas KN (2018) Letter to the editor regarding "dexamethasone for chronic subdural haematoma: a systematic review and meta-analysis". Acta Neurochir 160:2145–2147
13. Cenic A, Bhandari M, Reddy K (2005) Management of chronic subdural hematoma: a national survey and literature review. Can J Neurol Sci 32:501–506
14. Chan DYC, Sun TFD, Poon WS (2015) Steroid for chronic subdural hematoma? A prospective phase IIB pilot randomized controlled trial on the use of dexamethasone with surgical drainage for the reduction of recurrence with reoperation. Chin Neurosurg J 1:2
15. Delgado-López PD, Martín-Velasco V, Castilla-Díez JM, Rodríguez-Salazar A, Galacho-Harriero AM, Fernández-Arconada O (2009) Dexamethasone treatment in chronic subdural haematoma. Neurocirugía 20:346–359
16. Dran G, Berthier F, Fontaine D, Rasenrarijao D, Paquis P (2007) Efficacité de la corticothérapie dans le traitement adjuvant des hématomes sous-duraux chroniques. Étude rétrospective sur 198 cas. Neurochirurgie 53:477–482
17. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ (2017) Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. J Neuroinflammation 14:108
18. Ernestus R, Beldzinski P, Lanfermann H, Klug N (1997) Chronic subdural hematoma: surgical treatment and outcome in 104 patients. Surg Neurol 48:220–225
19. Foelholm R, Waltimo O (1975) Epidemiology of chronic subdural haematoma. Acta Neurochir 32:247–250
20. Fountas K, Kotlia P, Panagiotopoulos V, Fotakopoulos G (2019) The outcome after surgical vs nonsurgical treatment of chronic subdural hematoma with dexamethasone. Interdiscip Neurosurg Adv Tech Case Manag 16:70–74
21. Gabarrós A, Acebes JJ, Rodríguez R, Cabiol J, Obarrio LL, Mamov A, Isamat F (2000) Resultados del tratamiento quirúrgico del hematoma subdural crónico. Comparación de dos técnicas: minitrépano y drenaje cerrado continuo versus dos trépanos y drenaj e externo abierto. Neurocirugía 11:377–390
22. Gelabert-González M, Fernández-Villa JM, López-García E, García-Allut A (2001) Hematoma subdural crónico en el paciente mayor de 80 años. Neurocirugía 12:325–330
23. Gelabert-Gonzalez M, Iglesias-Pais M, Garcia-Allut A, Martinez-Rumbo R (2005) Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. Clin Neurol Neurosurg 107:223–229
24. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ:d5928
25. Holl DC, Volovici V, Dirven CMF, Peul WC, van Kooten F, Jellema K, van der Gaag NA, Miah IP, Kho KH, den Hertog HM, Lingsma HF, Dammers R, Dutch Chronic Subdural Hematoma Research G (2018) Pathophysiology and non-surgical treatment of chronic subdural hematoma: from past to present to future. World Neurosurg 116:402–411 e402
26. Holl DC, Volovici V, Dirven CM, Van Kooten F, Miah IP, Jellema K, Peul WC, Van der Gaag NA, Kho KH, Den Hertog HM, Dammers R, Lingsma HF (2019) PROSPERO record: corticosteroid treatment compared to surgery in chronic subdural hematoma: a systematic review and meta-analysis. https://www.crd.york.ac.uk/prospero. Registration number CRD42019123594; last edited 27/03/2019
27. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1:480–484
28. Jung Y, Jung N, Kim E (2015) Independent predictors for recurrence of chronic subdural hematoma. J Korean Neurosurg Soc 57:266–270
29. Karibe H, Kameyama M, Kawase M, Hirano T, Kawaguchi T, Tominaga T (2011) Epidemiology of chronic subdural hematomas. No Shinkei Geka 39:1149–1153
30. Kirley K, Qato D, Kornfield R, Stafford R, Alexander G (2012) National trends in oral anticoagulant use in the United States, 2007 to 2011. Circ Cardiovasc Qual Outcomes 5:615–621
31. Ko BS, Lee JK, Seo BR, Moon SJ, Kim JH, Kim SH (2008) Clinical analysis of risk factors related to recurrent chronic subdural hematoma. J Korean Neurosurg Soc 43:11–15
32. Kudo H, Kuwamura K, Izawa I, Sawa H, Tamaki N (1992) Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. Neurol Med Chir (Tokyo) 32:207–209
33. Kwon T, Park Y, Lim D et al (2000) Chronic subdural hematoma: evaluation of the clinical significance of postoperative drainage volume. J Neurosurg 93:796–799
34. Lindvall P, Koskinen L (2009) Anticoagulants and antiplatelet agents and the risk of development and recurrence of chronic subdural haematomas. J Clin Neurosci 16:1287–1290
35. Markwalder TM, Steinsiepe KF, Rohner M, Reichenbach W, Markwalder H (1981) The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. J Neurosurg 55:390–396
36. Mellergard P, Wisten O (1996) Operations and re-operations for chronic subdural haematomas during a 25-year period in a well defined population. Acta Neurochir 138:708–713
37. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097
38. Mori K, Maeda M (2001) Surgical treatment of chronic subdural hematoma in 500 consecutive cases: clinical characteristics, surgical outcome, complications, and recurrence rate. Neurol Med Chir (Tokyo) 41:371–381
39. Oishi M, Toyama M, Tamatani S, Kitazawa T, Saito M (2001) Clinical factors of recurrent chronic subdural hematoma. Neurol Med Chir (Tokyo) 41:382–386
40. Pichert G, Henn V (1987) Conservative therapy of chronic subdural hematomas. Schweiz Med Wochenschr 117
41. Prud'homme M, Mathieu F, Marcotte N, Cottin S (2016) A pilot placebo controlled randomized trial of dexamethasone for chronic subdural hematoma. Can J Neurol Sci 43:284–290
42. Qian Z, Yang D, Sun F, Sun Z (2017) Risk factors for recurrence of chronic subdural hematoma after burr hole surgery: potential protective role of dexamethasone. Br J Neurosurg 31:84–88
43. Robinson R (1984) Chronic subdural hematoma: surgical management in 133 patients. J Neurosurg 61:263–268
44. Santarius T, Hutchinson P (2004) Chronic subdural haematoma: time to rationalize treatment? Br J Neurosurg 18:328–332
45. Santarius T, Lawton R, Kirkpatrick PJ, Hutchinson PJ (2008) The management of primary chronic subdural haematoma: a questionnaire survey of practice in the United Kingdom and the Republic of Ireland. Br J Neurosurg 22:529–534
46. Sterne JAC, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hrobjartsson A, Kirkham J, Juni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schunemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355:i4919
47. Sun TF, Boet R, Poon WS (2005) Non-surgical primary treatment of chronic subdural haematoma: preliminary results of using dexamethasone. Br J Neurosurg 19:327–333

48. Thotakura AK, Marabathina NR (2015) Nonsurgical treatment of chronic subdural hematoma with steroids. World Neurosurg 84: 1968–1972
49. Torihashi K, Sadamasa N, Yoshida K et al (2008) Independent predictors for recurrence of chronic subdural hematoma: a review of 343 consecutive surgical cases. Neurosurgery 63:1125–1129
50. Turgut M, Akhaddar A (2017) Dexamethasone for chronic subdural hematoma: a systematic review and meta-analysis. Acta Neurochir 159:2289–2290
51. Vasella F, Akeret K, Smoll NR, Germans MR, Jehli E, Bozinov O, Regli L, Stienen MN, group CSs (2018) Improving the aesthetic outcome with burr hole cover placement in chronic subdural hematoma evacuation-a retrospective pilot study. Acta Neurochir 160: 2129–2135
52. Victoratos G, Bligh A (1981) A more systematic management of subdural hematoma with the aid of CT scan. Surg Neurol 15:158–160
53. Voelker JL (2000) Nonoperative treatment of chronic subdural hematoma. Neurosurg Clin N Am 11:507–513
54. Yao Z, You C (2017) Reply to letter: "dexamethasone for chronic subdural haematoma: a systematic review and meta-analysis". Acta Neurochir 159:2291
55. Yao Z, Hu X, Ma L, You C (2017) Dexamethasone for chronic subdural haematoma: a systematic review and meta-analysis. Acta Neurochir 159:2037–2044
56. Zhang Y, Chen S, Xiao Y, Tang W (2017) Effects of dexamethasone in the treatment of recurrent chronic subdural hematoma. World Neurosurg 105:115–121

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