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Research Article

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The pharmacological landscape of chronic subdural hematoma: a systematic review and network meta-analysis of randomized and non-randomized controlled studies

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Abstract

Background: There are various treatment modalities for chronic subdural hematoma (CSDH) and there is extensive debate surrounding pharmaceutical interventions. There is no consensus regarding the relative efficacy and safety of multiple treatment modalities. This study aims to investigate this issue and offer potential clinical recommendations.

Methods: We searched PubMed, Web of Science, Embase and the Cochrane Library from January 2000 to May 2023 to identify randomized and nonrandomized controlled studies reporting one or more outcomes associated with the pharmacologic management of CSDH. The primary outcomes of interest included recurrence, favorable prognosis and adverse events, while the secondary outcomes included a reduction in hematoma volume and mortality. Pooled estimates, credible intervals and odds ratios were calculated for all outcomes using a fixed effects model. Confidence in network meta-analysis judgments were employed to stratify the evidential quality. This study was registered with PROSPERO: CRD42023406599.

Results: The search strategy yielded 656 references; ultimately, 36 studies involving 8082 patients fulfilled our predefined inclusion criteria. The findings suggested that statins + glucocorticoids (GCs) ranked highest for preventing recurrence, improving prognosis and facilitating hematoma absorption. Tranexamic acid ranked second highest for preventing recurrence. Statins were found to be the preferred drug intervention for decreasing mortality and preventing adverse events. Antithrombotic agents ranked lowest in terms of decreasing mortality and improving prognosis.

Conclusions: Our findings indicate that statins + GCs may be the most effective treatment modality for preventing recurrence, improving patient prognosis and facilitating hematoma absorption. In terms of reducing mortality and preventing adverse events, statins may be superior to other pharmacological interventions. Routine use of GCs is not suggested for patients with CSDH.

Further prospective research is needed to directly compare the efficacy and superiority of various pharmaceutical interventions targeting CSDH to reinforce and validate our findings.

Key words: Chronic subdural hematoma, Pharmacological interventions, Recurrence, Statins, Glucocorticoids, Meta-analysis, Randomized controlled studies

Highlights

- The inaugural network meta-analysis aimed at appraising the efficacy and safety of various traditional and emerging non-surgical interventions for the treatment of CSDH.
- Statins + glucocorticoids may be the most effective pharmacological intervention in preventing recurrence, improving prognosis and facilitating hematoma absorption.
- Tranexamic acid emerges as a promising option for CSDH recurrence prevention, ranking second in effectiveness, suggesting its potential adjunct role in treatment strategies.
- Statins are favored for lowering mortality and adverse events in CSDH patients, emphasizing their significance in treatment. Conversely, antithrombotic agents show inferior outcomes, urging careful treatment selection.

Background

Currently, the primary therapeutic approach for symptomatic chronic subdural hematoma (CSDH) is surgical evacuation of the hematoma [1,2]. Despite the significant efficacy of surgery in terms of alleviating symptoms arising from cerebral parenchymal compression, the postoperative recurrence rate of hematoma is reported to be ~10.9 to 26.3% [3–5]. In certain elderly patients, the mortality rate can reach up to 24 to 32% [6,7]. Previous research has suggested that in CSDH patients with brain atrophy who undergo hematoma evacuation, the brain undergoes delayed recovery to its initial state, resulting in delayed occlusion within the subdural space and subsequent cerebral displacement. This phenomenon, in turn, could trigger bridging-vein rupture and hemorrhage, thereby augmenting the risk of postoperative recurrence [8,9]. Furthermore, due to factors such as advanced age, comorbidities, financial constraints and religious beliefs, a significant number of CSDH patients are ineligible for surgical interventions and thus resort to conservative treatment. Consequently, it is necessary to explore pharmacological approaches that can serve as a substitute for surgical intervention [10].

To date, numerous clinical trials have been undertaken to investigate the efficacy of pharmacological interventions for CSDH, including agents such as glucocorticoids (GCs), statins, statins combined with glucocorticoids (statins + GCs), Goreisan and tranexamic acid (TXA) [11]. However, there is no consensus regarding the optimal clinical therapy, and there has been no comprehensive assessment of the efficacy and safety of diverse pharmacological interventions. The current study aims to comprehensively compare pharmacological interventions for CSDH in terms of recurrence, favorable prognosis, adverse events, reduction in hematoma volume and mortality to identify the optimal treatment modality.

Methods

The research methodology has been registered in PROSPERO (CRD42023406599). This study was performed in accordance with the Cochrane handbook and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Network Meta-Analysis extension guidelines (Appendix 1, see online supplementary material) [12,13].

Search strategy and selection criteria

The PubMed, Embase, Web of Science and Cochrane Library databases were searched on 31 May 2023. Literature screening was carried out independently by two researchers (TL, ZZ) and disagreements were resolved by consulting a third reviewer (RJ). The complete search strategy is presented in Appendix 2.1 (see online supplementary material).

Outcome assessment

The primary outcomes included recurrence, favorable prognosis and adverse events. The secondary outcomes included a reduction in hematoma volume and mortality. Herein, recurrence, favorable prognosis and reduced hematoma volume served as indicators of the efficacy of pharmacologic management interventions, while adverse events and mortality rates provided insights into the safety of the interventions. The details of the outcome definitions are presented in Appendix 2.2 (see online supplementary material).

Data extraction, quality assessment and risk of bias

Two independent investigators systematically extracted data from the eligible studies and entered the data into standardized electronic spreadsheets using Microsoft Excel. Any disagreements that arose during the data extraction process were resolved through internal consensus or by consulting a third independent reviewer. Jadad scores between 4 and 7 and Newcastle–Ottawa Scale (NOS) scores between 7 and 9 were considered to indicate high-quality research for randomized controlled trials (RCTs) and non-RCTs, respectively [14]. Moreover, we utilized the Cochrane risk of bias tool (version 2) to assess the risk of bias of the included RCTs [15].

Additionally, the Confidence in Network Meta-Analysis (CINeMA) framework, which is based on the Grading of

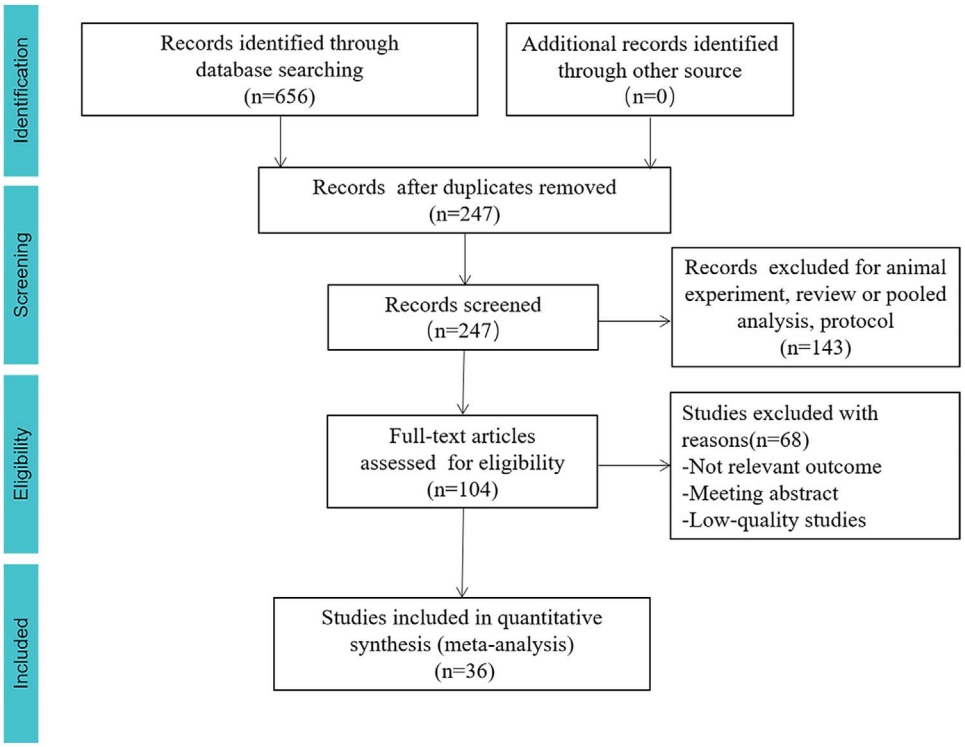

Figure 1. Flowchart of selected trials included in this study

Recommendations, Assessment, Development, and Evaluations framework, was employed to conduct a comprehensive appraisal of the evidence quality in the context of network meta-analysis (NMA) [16].

Statistical analysis

For binary variables, the outcomes are expressed as odds ratios (ORs) and 95% credible intervals (CrIs). For continuous variables, the outcomes are expressed as mean differences (MDs) and 95% CrIs. The details are presented in Appendix 2.3 (see online supplementary material). For all analyses, $p < 0.05$ indicated statistical significance. The statistical analyses were conducted using R (4.2.2), Stata (17.0) and RevMan (5.4).

Results

The search strategy initially yielded 656 references. Following the elimination of duplicate entries (n = 409), we screened the titles and abstracts to exclude studies that did not meet the inclusion criteria (n = 143). Subsequently, 104 articles remained for full-text screening. Ultimately, 36 studies fulfilled our predefined inclusion criteria (Figure 1), encompassing seven distinct pharmacological management interventions and 8082 patients. The detailed citations and characteristics of the selected studies are presented in Appendices 3 and 4 (see online supplementary material).

Characteristics of the included studies

The included studies were published between 2000 and 2023 across multiple nations and regions. The 36 included articles involved eight distinct pharmacologic intervention approaches: GCs, statins, antithrombotic agents (ATBs), Goreisan, TXA, statins + GCs, antiseizure prophylaxis (ASP) and celecoxib (CLX).

Quality evaluation and risk of bias assessment

The results of the quality evaluation and risk of bias assessment are provided in Appendices 5 and 6 (see online supplementary material). Among the 13 RCTs, 6 studies did not incorporate blinding protocols. Additionally, 2 studies had a potential risk of bias with respect to result selection due to the lack of pre-established analytical plans. Furthermore, 1 study exhibited some risk of bias in the domain of missing outcome data, as it lacked adequate descriptions concerning withdrawals and dropouts. Consequently, the overall risk of bias of 2 RCTs was classified as high. Among the 23 non-RCTs, 3 studies had a risk of bias due to inadequate follow-up duration, while the majority of the remaining studies were deemed to be of high methodological quality.

NMA

A network map of primary and secondary outcomes depicting the comparative relationships between various intervention measures included in the literature is presented in Appendix 7

(see online supplementary material). The assessment of network model fit is summarized in Appendix 8 (see online supplementary material). The fixed-effects model had the best fit for modeling primary and secondary outcomes. Therefore, this model was used for all analyses. A comparison-adjusted funnel plot is presented in Appendix 9 (see online supplementary material), revealing a predominantly symmetrical distribution of data points and suggesting a low likelihood of bias. The results of the I^2, Harbord and Egger tests for heterogeneity among all direct comparisons of intervention measures are presented in Table 1. All I^2 values were <60%, indicating that there was no significant heterogeneity. Additionally, the *p* values for the Harbord and Egger tests for direct comparisons were >0.05, indicating the absence of publication bias. To ensure the veracity of the evidence, we employed CINeMA judgments to stratify the quality of evidence (Appendix 10, see online supplementary material). The results indicated varying levels of evidence quality ranging from low to high, with mostly moderate or high-quality evidence.

Primary outcomes

In 30 studies involving seven pharmacologic interventions (n = 6802), GCs, statins and TXA were associated with decreases in recurrence compared with placebo (GCs, OR 0.38 [0.26, 0.54]; statins, OR 0.33 [0.18, 0.58]; TXA, OR 0.25 [0.07, 0.90]) (Table 1; and Appendix 11, see online supplementary material). The results of the NMA (Figure 2a) underscore the efficacy of GCs, statins, statins + GCs and TXA for reducing the risk of recurrence in contrast to the reference group (GCs, OR 0.35 [0.24, 0.51]; statins, OR 0.57 [0.37, 0.87]; statins + GCs, OR 0.10 [0, 0.9]; TXA, OR 0.21 [0.04, 0.66] (Figure 2a; and Appendix 12, see online supplementary material).

In 18 studies involving five pharmacologic interventions (n = 3556), the use of statins alone significantly improved the prognosis of CSDH compared with placebo (OR, 2.33 [1.55, 3.49]) (Table 1, Appendix 11). Furthermore, direct comparative analysis revealed that the combination of statins with GCs markedly improved the prognosis compared with the use of statins alone (OR 11.67 [3.38, 40.22]). According to the NMA (Figure 2b), statins alone as well as the combination of statins + GCs significantly improved the prognosis of CSDH compared to the placebo (statin, OR 2.35 [1.57, 3.55]; statin + GCs, OR 30.28 [8.45, 126.69]). Moreover, the combination of statins + GCs was superior to other pharmacological interventions in terms of improving the prognosis (GCs *vs* statins + GCs, OR 0.03 [0.01, 0.11]; statins *vs* statins + GCs, OR 0.08 [0.02, 0.26]; statins + GCs *vs* Goreisan, OR 24.24 [5.37, 122.92]; statins + GCs *vs* ATB, OR 40.33 [10.85, 173.32]; Figure 2b; Appendix 12).

In 18 studies involving seven pharmacologic interventions (n = 4398), direct comparison revealed that GCs and ATB significantly increased the incidence of adverse events compared to the control treatment (GCs, OR 2.32 [1.16, 4.63]; ATB, OR 2.07 [1.43, 3.00]; Table 1, Appendix 11). In the NMA (Figure 2a; Appendix 12), GCs, ATB, CLX and TXA led to a marked increase in the incidence of treatment-related adverse events throughout treatment (GCs, OR 2.54 [1.88, 3.47]; ATB, OR 2.09 [1.44, 3.05]; CLX, OR 17.51 [1.75, 585.06]; TXA, OR 9.2 [1.04, 291.7]). Additionally, the incidence of treatment-related adverse events was significantly lower in the statins group than in the GCs, ATB and CLX groups: (OR 0.42 [0.23, 0.77]; OR 0.51 [0.27, 0.97]; and OR 0.06 [0, 0.65], respectively).

The surface under the cumulative ranking curve (SUCRA) score depicts the overall rankings for each pharmacologic intervention (Figure 3; Appendix 13 see online supplementary material). In terms of reducing CSDH recurrence, statins + GCs had the strongest effect (statins + GCs, SUCRA = 90.11%), followed by TXA, GCs and statins (TXA, SUCRA = 83.35%; GCs, SUCRA = 71.51%; statins, SUCRA = 50.48%). Among the seven interventions, ATBs ranked lowest (ATBs: SUCRA = 13.16%). Statins + GCs were ranked first in terms of improving the prognosis of CSDH (SUCRA = 89.99%), while ATBs were ranked lowest (SUCRA = 5.97%). Regarding adverse events, statins + GCs as well as statin monotherapy demonstrated a favorable safety profile. Conversely, CLX had the lowest ranking for safety (SUCRA = 8.61%).

Secondary outcomes

Five studies involving 912 patients reported alterations in hematoma volume after pharmacological interventions for CSDH. The results of pairwise meta-analysis revealed that GCs, statins and TXA were more likely to facilitate the absorption of hematomas than placebo (GCs, MD = 7.30 [3.18, 11.42]; statins, MD = 12.55 [3.09, 22.01]; TXA, MD = 9.39 [3.41, 15.36]; Table 1, Appendix 11). The results of NMA revealed that GCs, statins, statins + GCs and TXA had the potential to augment hematoma absorption compared with placebo (GCs, MD = 7.33 [3.16, 11.4]; statins, MD = 12.55 [3.05, 22]; statins + GCs, MD = 32.53 [17.29, 47.56]; TXA, MD = 9.39 [3.34, 15.28]; Appendix 12). Furthermore, statins + GCs demonstrated notable superiority over statins, GCs, Goreisan and TXA in terms of hematoma absorption (statin + GCs *vs* GCs, MD = 25.23 [9.4, 40.81]; statin + GCs *vs* statin, MD = 19.96 [8.19, 31.46]; statin + GCs *vs* Goreisan, MD = 32 [15.62, 48.55]; statin + GCs *vs* TXA, MD = 23.15 [6.85, 39.61]; Appendix 12). No discernible disparities in mortality rates were observed between pharmaceutical interventions in either direct or indirect comparative analyses (Appendix 12).

Seventeen studies involving 3375 patients reported the effects of pharmacological interventions on all-cause mortality among CSDH patients. Regarding the efficacy in promoting hematoma absorption, statins + GCs exhibited the highest efficacy (SUCRA = 87.92%), followed by statins (SUCRA = 70.37%), TXA (SUCRA = 60.02%), GCs (SUCRA = 48.24%) and Goreisan (SUCRA = 12.76%). The efficacy of pharmacological interventions in terms of reducing mortality was as follows, from most effective to least effective: statins, ASP, GCs and ATBs (Appendix 13).

Table 1. Direct comparisons of each pharmacologic intervention with placebo or different pharmacologic intervention and publication bias

Comparison	Results	Harbord/Egger test
Intervention comparison of recurrence		
Glucocorticoids *vs* placebo	n = 1815, I^2 = 23%, OR (95%CrI) = 0.38 (0.26, 0.54)	0.302/0.256
Statins *vs* placebo	n = 465, I^2 = 0%, OR (95%CrI) = 0.33 (0.18, 0.58)	0.634/0.546
Goreisan *vs* placebo	n = 770, I^2 = 0%, OR (95%CrI) = 0.71 (0.45, 1.12)	0.820/0.630
Antithrombotic *vs* placebo	n = 3272, I^2 = 0%, OR (95%CrI) = 1.05 (0.83, 1.32)	0.963/0.737
Celecoxib *vs* placebo	n = 26, I^2 = NA, OR (95%CrI) = 1.00 (0.06, 17.90)	NA/NA
Tranexamic acid *vs* placebo	n = 244, I^2 = 0%, OR (95%CrI) = 0.25 (0.07, 0.90)	NA/NA
Drugs *vs* placebo	n = 6592, I^2 = 85%, OR (95%CrI) = 0.73 (0.62, 0.85)	0.323/0.269
Statins + glucocorticoids *vs* statins	n = 60, I^2 = NA, OR (95%CrI) = 0.22 (0.02, 2.14)	NA/NA
Tranexamic acid *vs* Goreisan	n = 150, I^2 = NA, OR (95%CrI) = 0.14 (0.02, 1.19)	NA/NA
Intervention comparison of good outcome		
Glucocorticoids *vs* placebo	n = 1353, I^2 = 53%, OR (95%CrI) = 0.93 (0.69, 1.26)	0.104/0.881
Statins *vs* placebo	n = 665, I^2 = 40%, OR (95%CrI) = 2.33 (1.55, 3.49)	0.242/0.266
Goreisan *vs* placebo	n = 222, I^2 = NA, OR (95%CrI) = 1.24 (0.57, 2.69)	NA/NA
Antithrombotic *vs* placebo	n = 1256, I^2 = 17%, OR (95%CrI) = 0.75(0.56, 1.00)	0.193/0.202
Drugs *vs* placebo	n = 3496, I^2 = 80%, OR (95%CrI) = 1.10 (0.93, 1.30)	0.481/0.485
Statins + glucocorticoids *vs* statins	n = 60, I^2 = NA, OR (95%CrI) = 11.67 (3.38, 40.22)	NA/NA
Intervention comparison of adverse events		
Glucocorticoids *vs* placebo	n = 1146, I^2 = 51%, OR (95%CrI) = 2.32(1.16, 4.63)	0.863/0.669
Statins *vs* placebo	n = 552, I^2 = 0%, OR (95%CrI) = 1.07 (0.63, 1.81)	0.99/0.97
Goreisan *vs* placebo	n = 368, I^2 = 0%, OR (95%CrI) = 1.61 (0.41, 6.26)	NA/NA
Antithrombotic *vs* placebo	n = 2006, I^2 = 18%, OR (95%CrI) = 2.07 (1.43, 3.00)	0.998/0.876
Celecoxib *vs* placebo	n = 26, I^2 = NR, OR (95%CrI) = 7.50 (0.73, 76.77)	NA/NA
Tranexamic acid *vs* placebo	n = 90, I^2 = NR, OR (95%CrI) = 11.88 (0.62, 227.52)	NA/NA
Drugs *vs* placebo	n = 4188, I^2 = 67%, OR (95%CrI) = 1.58 (0.97, 2.58)	0.500/0.521
Statins + glucocorticoids *vs* statins	n = 60, I^2 = NA, OR (95%CrI) = 1.00 (0.26, 3.89)	NA/NA
Tranexamic acid *vs* Goreisan	n = 150, I^2 = NA, OR (95%CrI) = 0.36 (0.01, 8.89)	NA/NA
Intervention comparison of mortality		
Glucocorticoids *vs* placebo	n = 1608, I^2 = 50%, OR (95%CrI) = 1.34 (0.87, 2.09)	0.141/0.214
Statins *vs* placebo	n = 441, I^2 = 0%, OR (95%CrI) = 0.48 (0.09, 2.66)	NA/NA
Antithrombotic *vs* placebo	n = 1206, I^2 = 0%, OR (95%CrI) = 1.63 (0.81, 3.27)	0.187/0.186
Antiseizure prophylaxis *vs* placebo	n = 120, I^2 = NA, OR (95%CrI) = 1.52 (0.13, 17.35)	NA/NA
Drugs *vs* placebo	n = 3375, I^2 = 0%, OR (95%CrI) = 1.34 (0.94, 1.91)	0.568/0.509
Intervention comparison of reduction of HV		
Glucocorticoids *vs* placebo	n = 92, I^2 = NA, MD (95%CrI) = 7.30 (3.18, 11.42)	NA/NA
Statins *vs* placebo	N = 196, I^2 = NA, MD (95%CrI) = 12.55 (3.09, 22.01)	NA/NA
Goreisan *vs* placebo	n = 160, I^2 = NA, MD (95%CrI) = 1.20(−5.26, 7.66)	NA/NA
Tranexamic acid *vs* placebo	n = 244, I^2 = 0, MD (95%CrI) = 9.39 (3.41, 15.36)	NA/NA
Drugs *vs* placebo	n = 692, I^2 = 32%, MD (95%CrI) = 7.06 (4.12, 9.93)	NA/0.957
Statins + glucocorticoids *vs* statins	n = 60, I^2 = NA, MD (95%CrI) = 19.95 (8.31, 31.59)	NA/NA
Tranexamic acid *vs* Goreisan	n = 160, I^2 = NA, MD (95%CrI) = 9.50 (2.89, 16.11)	NA/NA

HV hematoma volume, *OR* odds ratio, *CrI* credible interval, *MD* mean difference, *NA* not available.

Discussion

This NMA synthesized 36 studies involving 8082 patients. The included studies were performed in various countries and regions. The findings suggest that the use of statins + GCs may be the most effective approach for preventing recurrence, improving prognosis and facilitating hematoma absorption among CSDH patients. Furthermore, statin monotherapy may be the most effective pharmaceutical intervention for reducing mortality and preventing adverse events.

In light of the contemporary understanding of its pathophysiology, CSDH remains a formidable clinical challenge. Despite sustained endeavors to elucidate therapeutic modalities for CSDH, the intricate underpinnings of its pathogenesis have impeded notable advancements in treatment outcomes, culminating in mortality rates ranging from 0 to 32% [3,5,17]. Various pharmacological agents, including GCs, statins and TXA, have been proposed as potential interventions, which are predicated on divergent pathogenic mechanisms [11]. The primary complication of CSDH is recurrence necessitating repeat surgery, with reported rates varying widely from 0 to 76% in the literature [18]. Owing to the paucity of high-quality clinical evidence or promising results, the routine incorporation of such pharmaceutical agents into clinical practice has not garnered widespread acceptance. Drawing upon the premise that dexamethasone has the capacity to mitigate inflammation within the subdural compartment, thereby impeding the

Figure 2. Comparison of pharmacological interventions for patients with chronic subdural hematoma. (**a**) NMA estimates (recurrence,blue;adverse events, yellow); (**b**) NMA (green) and direct pairwise meta-analysis(red) estimates on improved prognosis.The column treatment was compared with the row treatment. The numbers in parentheses are the 95% confidence intervals. Odds ratios with a Bayesian $p < 0.05$ are in bold. *GCs* glucocorticoids, *ATB* antithrombotic agent, *CLX* celecoxib, *TXA* tranexamic acid, *ATB* antithrombotic agent, *PLB* placebo, *ND* no direct evidence available. Confidence of evidence: §high, ‡moderate, †low and *very low

persistence and expansion of hematomas, Hutchinson *et al*. assessed the efficacy of dexamethasone in patients with CSDH [19].

Their findings revealed that dexamethasone showed no significant superiority over placebos in terms of improving patient outcomes, and some of their findings even suggested dexamethasone may lead to a worse prognosis than surgical intervention [19,20]. Nonetheless, other investigations have shown that GCs may be independently correlated with a reduced risk of CSDH recurrence [21,22].

A recent study published in the *New England Journal of Medicine* involved a comparative evaluation of dexamethasone *vs* surgical interventions for CSDH [23]. This trial was prematurely terminated at the behest of the ethics committee due to pronounced safety concerns. The discerned outcomes revealed that the therapeutic efficacy of dexamethasone did not surpass that of surgery. In the dexamethasone group, 55.1% of patients transitioned to surgical intervention within a 3-week interval following the initiation of their initial therapeutic regimen [23]. It is undeniable that GCs do manifest a certain degree of efficacy in preventing recurrence in our NMA, ranking third among all pharmacological interventions examined herein. However, their performance in other aspects is notably subpar, particularly in terms of prognosis improvement, and potentially even inferior to that of the control group (GCs, SUCRA = 0.2830; placebo, SUCRA = 0.3878). These findings raise the possibility that dexamethasone may be an ineffective treatment for CSDH.

However, the quest for an optimal pharmaceutical agent remains unabated. Jiang *et al*. discovered that

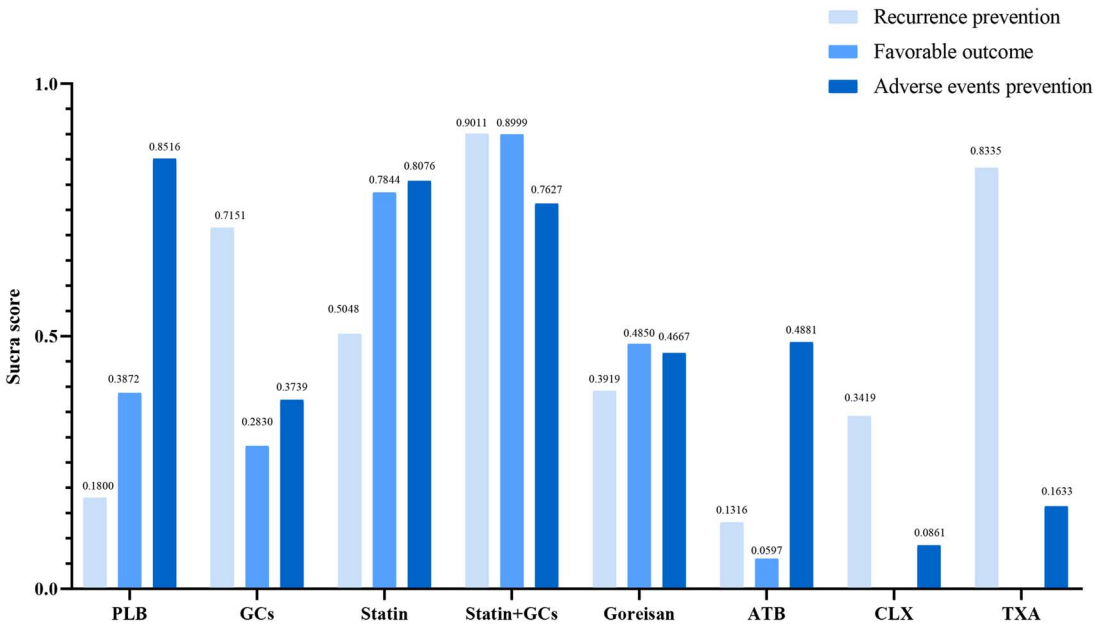

Figure 3. Relative efficacy of different pharmacologic management interventions for recurrence prevention, favorable outcomes and adverse event prevention in patients with CSDH. Larger surface under the cumulative ranking curve (SUCRA) values indicate more effective pharmacologic management. *CSDH* chronic subdural hematoma, *GCs* glucocorticoids, *ATB* antithrombotic agent, *CLX* celecoxib, *TXA* tranexamic acid, *PLB* placebo

atorvastatin significantly improves the prognosis of CSDH patients without any apparent adverse events [24]. As ~11.2% of participants did not respond to atorvastatin treatment, the authors conducted a proof-of-concept study confirming that atorvastatin plus dexamethasone is more effective at reducing hematoma volume and improving neurological function in CSDH patients than is atorvastatin monotherapy [25]. Furthermore, the team's subsequent findings from real-world studies are poised for release, potentially yielding further insights [26]. Our NMA also suggested that statin monotherapy and statins + GCs may be promising pharmaceutical interventions, although the underlying mechanism of atorvastatin treatment for CSDH is still unclear. Previous research has indicated that atorvastatin significantly mitigates local inflammation, promotes angiogenesis and subsequently enhances the absorption of subdural hematomas in rats [27]. Previous studies have also suggested a possible association between atorvastatin and inflammation regulation [28,29], but the pathway connecting the dural lymphatic system to deep cervical lymph nodes may represent a novel avenue for the resolution of CSDH (Appendix 14, see online supplementary material), and the molecular regulatory mechanisms have yet to be fully elucidated [30,31]. Given these encouraging results, the ongoing ATOCH II trial (ChiCTR1900021659) has also garnered increased attention [32].

Previous studies have shown that TXA can inhibit the conversion of plasminogen into plasmin, thus preventing rebleeding in patients with aneurysmal subarachnoid hemorrhage [33]. Our NMA suggested that TXA can reduce the recurrence of CSDH, possibly because the intracranial cavity in CSDH patients also exhibits an excessive fibrinolytic state, leading to ongoing intracranial bleeding and hematoma recurrence [34]. Miyakoshi *et al*. also reported that oral TXA reduces recurrence and the need for reoperation in elderly patients with CSDH after burr hole craniotomy [35]. An RCT also showed that TXA significantly reduced recurrence and promoted hematoma absorption, but it did not differ from Goreisan in terms of reducing recurrence rates [36]. The results of our NMA suggested that in terms of reducing recurrence rates, Goreisan may be inferior to TXA, and there was no statistically significant difference in primary outcomes between the Goreisan group and the control group.

Our study revealed that ATB significantly increased the incidence of adverse events compared to that in the control group. Although there was no statistically significant difference between the ATB group and the control group in preventing recurrence, ATB appeared to be less effective than TXA. Some studies have shown that the use of ATB may be associated with a greater risk of recurrence, especially in elderly patients [37,38]. Our study also confirmed that among all drug interventions, ATB may be the least effective in preventing recurrence (SUCRA = 0.1316). The timing of initiating ATB is of significant importance in balancing the risks of bleeding and vascular occlusion, and these uncertainties still require guidance from RCTs. Interestingly, despite its anti-inflammatory properties, we did not find evidence of the efficacy of CLX in CSDH patients. In contrast, the incidence of adverse events may be greater in this group than in the control group. In our study, there was insufficient evidence to suggest any potential benefits of ASP in CSDH patients.

Our study has several limitations. First, we included some non-RCTs, which inevitably increased the risk of bias. However, we also conducted a quality assessment and risk

of bias assessment using the NOS scale, with the majority being classified as high-quality literature (NOS score ≥ 7). Therefore, the conclusions we drew from our study are still reliable. Second, most of the current research regarding drug treatments for CSDH involves comparisons between drug intervention measures and control groups, and direct comparisons between different drugs are lacking. This means that some of the results could not undergo inconsistency testing. Therefore, the conclusions of this study should be interpreted with caution when analyzing the rankings of the relative efficacy of drugs with similar effects. In the future, it may be necessary to include more prospective clinical trials directly comparing different drugs to further validate our conclusions. Third, we included only English-language and published literature, excluding data in other languages and unpublished literature, which might introduce publication bias. However, we corrected for potential publication bias by generating funnel plots and conducting Harbord and Egger tests, all of which did not detect the presence of publication bias, suggesting a minimal likelihood of this occurring.

Conclusions

The results of our NMA indicate that statins + GCs may be the most effective pharmaceutical intervention for preventing recurrence, improving prognosis and facilitating hematoma absorption. Additionally, statin monotherapy may be the most effective pharmaceutical intervention for reducing mortality and preventing adverse events. Despite the effectiveness of GCs in reducing recurrence, their effect on other outcome measures is notably suboptimal, particularly in terms of prognosis improvement, and may even be inferior to that of the control group. These findings may suggest that dexamethasone may be an ineffective treatment for CSDH and should thus be used cautiously in clinical practice. In the future, additional prospective studies directly comparing the efficacy of different drugs for treating CSDH are needed to further validate and consolidate our conclusions.

Abbreviations

ASP: Antiseizure prophylaxis; ATB: Antithrombotic agent; CINeMA: Confidence in network meta-analysis; CLX: Celecoxib; CrIs: Credible intervals; CSDH: Chronic subdural hematoma; GCs: Glucocorticoids: MDs, Mean differences; NMA: Network Meta-Analysis; NOS: Newcastle–Ottawa Scale; ORs: Odds ratios; RCT: Randomized controlled trial; SUCRA: Surface under the cumulative ranking curve; TXA: Tranexamic acid.

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Author contributions

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Supplementary data

Supplementary data is available at *Burns & Trauma Journal* online.

Conflict of interests

The authors declare no financial affiliations with entities that may hold vested interests in the submitted research; further, no additional associations or engagements have exerted an influence on the content of the submitted work.

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Data availability

The original data are presented in the text and supplementary materials.

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