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Review

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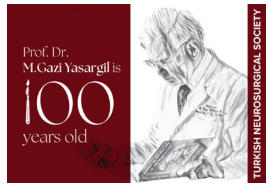

Chronic Subdural Hematoma and Tranexamic Acid: A Systematic Review

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ABSTRACT

AIM: To systematically evaluate the existing literature regarding adjuvant or primary treatment of chronic subdural hematoma (cSDH) with tranexamic acid (TXA).

MATERIAL and METHODS: This systematic review followed the parameters set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A search in the available literature was conducted up to February 2024 in five databases using the keywords “chronic subdural hematoma” and “tranexamic acid.” Randomized clinical trials, prospective or retrospective cohorts, systematic reviews, and case series (> five patients) relevant to the analysis were included.

RESULTS: In total, 10 studies were included, encompassing a total of 912 patients diagnosed with cSDH who underwent treatment with TXA. Seven studies evaluated the use of TXA as an adjunctive to surgical treatment, and three articles investigated the effect of TXA as primary therapy.

CONCLUSION: TXA can be considered a safe and effective option in adjunct to surgical management. Further studies are needed to establish its role as primary treatment.

KEYWORDS: Tranexamic acid, Chronic subdural hematoma, Systematic review

ABBREVIATIONS: AT: Antithrombotics, **CI:** Confidence Interval, **cSDH:** Chronic Subdural Hematoma, **CSF:** Cerebrospinal Fluid, **CT:** Computed Tomography, **GCS:** Glasgow Coma Scale, **KKS:** Kallikrein-Kinin System, **MRI:** Magnetic Resonance Imaging, **NOS:** Newcastle-Ottawa Scale, **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **OR:** Odds Ratio, **RR:** Relative Risk, **SEPS:** Subdural Evacuation Port System, **TBI:** Traumatic Brain Injury, **t-PA:** Tissue Plasminogen Activator, **TRACS:** Tranexamic Acid in Chronic Subdural Hematomas, **TORCH:** Tranexamic Acid to Prevent Operation in Chronic Subdural Hematoma, **TXA:** Tranexamic Acid: **VEGF:** Vascular Endothelial Growth Factor

INTRODUCTION

Chronic subdural hematoma (cSDH) is an encapsulated collection of blood in various stages of coagulation, accumulating at the dural border cell layer. Symptoms vary and are typically insidious, including headache, gait instability, mental confusion, fluctuating hemiparesis, and seizures (11,30,32). However, patients can remain asymptomatic, and cSDH may only be detected as an incidental finding on imaging.

The sometimes-subclinical course of the disease may contribute to the imprecise reported incidence, estimated at 1.72 to 20.6 cases per 100.000 population per year (46). As it predominantly affects the elderly population, there is an expectation of a significant increase in surgical approaches for cSDH, following the trend of increasing life expectancy and the use of antiplatelet and anticoagulant medications (17,32). It is estimated that by 2030, approximately 60.000 cases of cSDH will occur annually in the United States alone (2).

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Despite its significant prevalence, there is currently no consensus on treatment, adjunct therapy, or pre- and post-surgical care. Surgical management is considered the gold standard for symptomatic cSDH treatment (34). Among various indications, large hematomas (> 10 mm) or midline shifts (> 5 mm) on computed tomography (CT) scans, combined with the presence of symptoms, are often cited (20). Although the surgical procedure is considered safe with a low mortality rate (approximately 2%) (3), recurrence is estimated at 10 to 20% (17). Considering a primarily elderly population with multiple comorbidities, less invasive therapeutic proposals assume significance, especially in asymptomatic or oligosymptomatic patients.

Current research suggests that the constitution of cSDH is more complex than theorized by Virchow in 1857 (14), who attributed hematoma formation to traumatic injury and subsequent rupture of tributary veins of the dural venous sinuses. The pathophysiology of cSDH involves the coexistence of various predisposing factors, such as sustained inflammation, angiogenesis, and fibrinolysis (11). The cascade of inflammatory and fibrinogenic processes leads to the formation of internal, thin, avascular membranes and external, highly vascularized membranes, forming a thick capsule (6). This capsule, in turn, promotes the processes that generated it through the production of substances such as tissue plasminogen activator (t-PA) and vascular endothelial growth factor (VEGF) (11).

Hyperfibrinolysis plays a prominent role in the liquefaction and expansion of the hematoma between the internal membrane and the capsule. At the biomolecular level, the degradation of fibrin clots primarily occurs through the activity of plasmin, converted from plasminogen by tPA (4).

Given this panorama, tranexamic acid (TXA) may be an alternative to reduce the volume of surgical procedures. It is an antifibrinolytic agent that competitively inhibits plasmin activation and interrupts the fibrinolysis process (27). Its use has been shown to be safe for patients with intracranial bleeding post-traumatic brain injury (TBI), reducing the risk of TBI-related death when treatment is initiated within 3 hours after moderate traumas (8).

Although treatment with TXA holds promise, evidence regarding its use in cSDH cases remains insufficient. Larger-scale clinical trials such as "Tranexamic Acid in Chronic Subdural Hematomas" – TRACS (Canada) (19) and "Tranexamic Acid to Prevent Operation in Chronic Subdural Hematoma" – TORCH (Netherlands) (18) are underway, with publication expected within the next 3 years.

MATERIAL and METHODS

This study consists of a systematic review of international medical literature using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines published in 2020 (28).

The following databases were selected for consultation: Embase, Lilacs, PubMed/MEDLINE, Scopus, and Web of Science. Searches were conducted on March 18, 2023, and again on February 14, 2024, by two independent researchers (B.R.M. and J.P.M.B.), with no initial restrictions on language and/or publication date. A manual search of the references of selected papers and systematic reviews published on the same topic was also conducted to identify additional studies. To add information on ongoing clinical trials, the Cochrane Library and ClinicalTrials.gov databases were consulted in February 2024.

The search terms used to identify studies regarding the use of TXA for cSDH were "chronic subdural hematoma" and "tranexamic acid" [MeSH], combined with Boolean operators ("AND" and "OR"). Eligible articles included those in which participants were adults (age ≥ 18 years) with a confirmed diagnosis of cSDH, regardless of severity, for which TXA was used as either the primary or adjunctive therapy to surgical treatment in any dosage or administration scheme.

Letters to the editor, comments, editorials, narrative or literature reviews, and case reports were excluded. Ongoing clinical trials with unknown status or no updates in the last year were also excluded. Trials with expired end dates and no published results were searched by title on PubMed/MEDLINE and Google to ensure no related publication was unreported in the databases (Cochrane Library and ClinicalTrials.gov).

Initially, two authors (B.R.M and J.P.M.B.) independently assessed all retrieved articles for eligibility based on title and abstract. For studies not fully available, the author whose email was listed in the publication was contacted to assess the availability of the full text. Duplicates and articles accessible only partially were then removed. Finally, the full text of eligible studies was examined for inclusion. Any doubts or discrepancies were discussed and resolved with the project supervisor (A.F.G).

Data from the selected references for this systematic review were extracted in a structured manner: article characteristics, including lead investigator, year of publication, study design, and country of origin; demographic and clinical data of patients, such as mean age, male-to-female ratio, and sample size; description of administered treatment (TXA dose and duration, surgical necessity, placebo control); and evaluated outcomes.

Bias risk was independently assessed by two authors (B.R.M and J.P.M.B.) for each included study, using three tools depending on the evaluated article's methodology: Newcastle Ottawa Scale (NOS) (43) for non-randomized clinical trials and prospective or retrospective cohorts; ROB 2 Risk of Bias Tool for randomized clinical trials (36); and AMSTAR 2 (33) for systematic reviews.

Articles whose bias was analyzed using the NOS tool had their evidence quality classified as "good," "fair," or "poor," based on the criteria adopted by Mascolo et al. (25). It was considered "good" if NOS had 3 or 4 stars for the "selection" domain, 1 or 2 stars for the "comparability" domain, and 2 or 3 stars for the "outcome" domain; "fair" if 2 stars in "selection," 1 or 2 stars in "comparability," and 2 or 3 stars in "outcome"; and "poor" if 0 or 1 star in "selection," or 0 stars in "comparability," or 0 or 1 star in "outcome."

Randomized clinical trials were evaluated for evidence quality using the ROB 2 Risk of Bias tool, based on the following domains: bias risk in the randomization process, deviations from the intended intervention, incomplete/missing data, bias risk in outcome assessment, and bias risk in result reporting. Each domain was subsequently classified as having a low risk of bias, some concerns, or a high risk of bias. The results were then presented in a figure constructed using the robvis (Risk-of-Bias VISualization) instrument (26).

AMSTAR 2 includes 16 items to assess the reliability of results in systematic reviews. In this study, based on Shea et al.'s recommendations (33), the analyzed studies were classified with a confidence grade: 1) high if no or one non-critical flaw was detected, 2) moderate if more than one non-critical flaw, 3) low if one critical flaw, and 4) critically low if more than one critical flaw.

RESULTS

Systematic Search

From the initial systematic search, 365 articles were retrieved from seven databases. Duplicates (n=161) and ongoing clinical trials without available results (n=8) were excluded. The remaining 196 publications were evaluated based on title and abstract, resulting in 36 references selected for full-text analysis. Eight studies whose full text was not retrieved were excluded. Of the remaining 28 articles, 18 were excluded for not meeting the inclusion criteria of this research, namely: five case reports with a sample size of fewer than five patients, six narrative reviews, six systematic reviews and/or meta-analyses that included multiple drug therapies for cSDH, and one systematic review with methodological flaws. Finally, 10 articles were included in this article, including one non-randomized clinical trial, four retrospective analyses, three randomized clinical trials, one prospective study, and one systematic review. All included articles were published between 2013 and 2023. Figure 1 below summarizes the

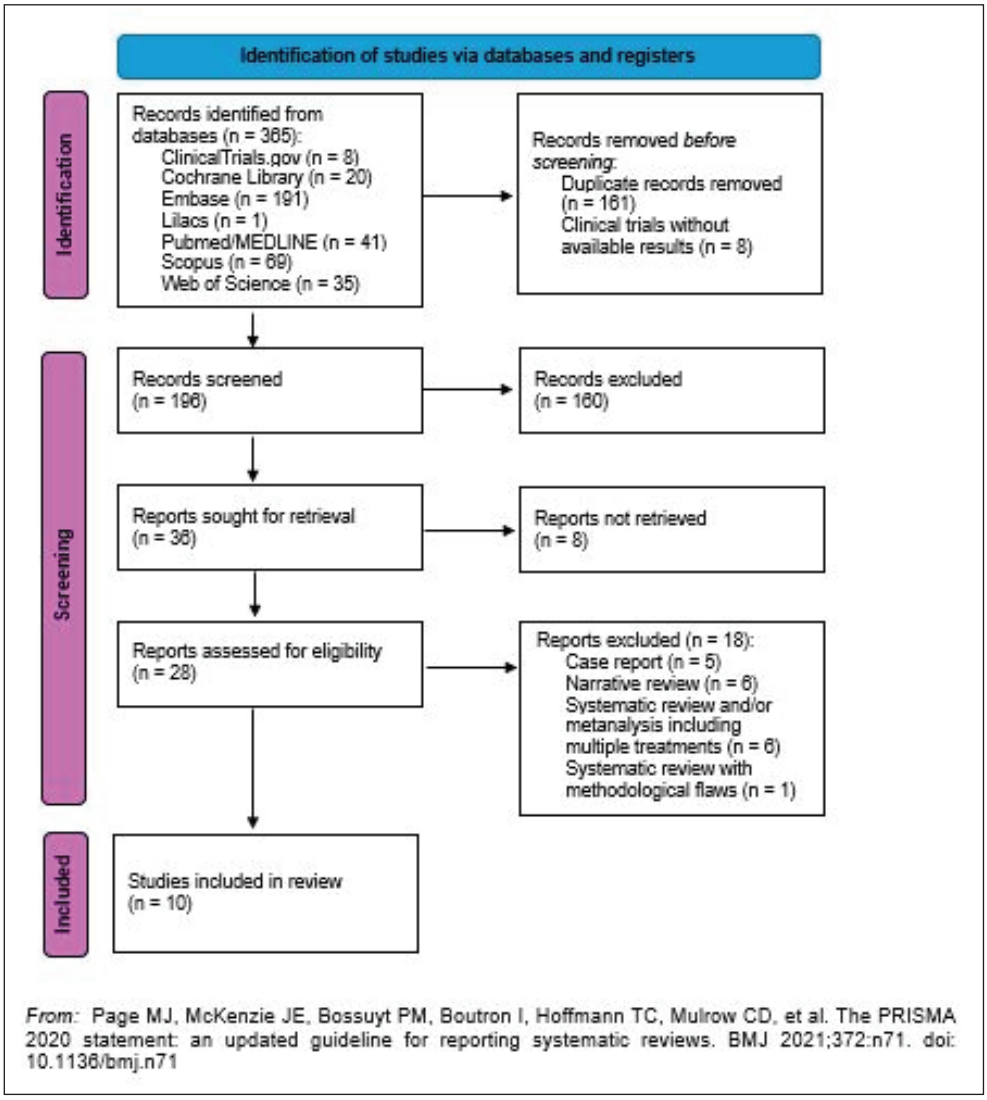

Figure 1: PRISMA flowchart.

study selection process using the flowchart proposed by the PRISMA guidelines (28).

Characteristics of the Included Studies

This systematic review included 912 patients diagnosed with cSDH who underwent treatment with TXA. Seven studies investigated the effect of TXA as an adjuvant therapy to surgical procedures, and one article investigated it as the primary treatment; two cohorts evaluated the use of TXA predominantly as a single intervention. The average age of participants in all studies was over 55 years, predominantly above 70 years in most cases. The follow-up time ranged from 28 days to 10 months. The results are summarized in Table I below.

Table I: Study Characteristics Included in the Systematic Review

Study	Design	Country	Standard treatment (sample size)	Male (%)	Mean age (years ± standard deviation)	TXA dosage	Treatment duration
Albalkhi et al., (1)	Systematic review and meta-analysis	Saudi Arabia	TXA (n=654) *versus* control (n=749)	440 (65.3%) *versus* 493 (65.8%)	75 [71-78.9] *versus* 74.9 [72.4-77.5]‡	Unreported	Unreported
De Paula et al., (9)	Randomized clinical trial	Brazil	TXA (n=24) *versus* control (n=26)◊	15 (62.5%) *versus* 16 (61.5%)	75.8 ± 11.8 *versus* 72.6 ± 11.9	750 mg/day	90 days
Kageyama et al., (22)	Retrospective cohort	Japan	TXA (n=21)	12 (57%)	78.7 ± 10.5	750 mg/day	28-137 days
Kutty et al., (23)	Prospective cohort	India	TXA (n=27)	15 (55.6%)	64.9 ± 11.8	750 mg/day	27-120 days
Lodewijkx et al., (24)	Non-randomized clinical trial	Netherlands	TXA (n=7)	7 (100%)	78.1 ± 4.7	1-2 g/day	5-56 days
Puente Tinoco et al., (29)	Retrospective cohort	Venezuela	TXA (n=11) *versus* Jackson-Pratt drain (n=11)◊	11 (100%) *versus* 10 (90.9%)	32-87 years¥	2 g/day	4 days
Tanweer et al., (38)	Retrospective cohort	United States	TXA (n=14)※	12 (86%)	56.4 ± 16.3	650 mg/day	180 days¶
Wan et al., (41)	Randomized clinical trial	Singapore	Control (n=49) *versus* TXA (n=41)*	36 (73.5%) *versus* 24 (58.5%)	69.6 ± 13.7 *versus* 72 ± 11.8	1000 mg/day	21 days
Yamada and Natori, (44)	Randomized clinical trial	Japan	Control (n=82) *versus* TXA (n=72) *versus* Goreisan (n=78)†	57 (62.5%) *versus* 43 (59.7%) *versus* 50 (64.1%)	78.8 ± 10.8 *versus* 78.2 ± 9.8 *versus* 79.2 ± 8.7	750 mg/day	90 days
Yang et al., (45)	Retrospective cohort	South Korea	TXA (n=41) *versus* non-TXA (n=114) *versus* AT (n=85)#	33 (80.4%) *versus* 87 (76.3%) *versus* 65 (76.4%)	72 (65-83) *versus* 71.5 (60-79) *versus* 77 (68-82)¨	750 mg/day	14-141 days

*‡ Mean [95% confidence interval]. ◊ All patients underwent drainage of the cSDH through burr-hole trepanation. ¥ Minimum-maximum age. ※ After evacuation of the cSDH at the bedside using a twist-drill and placement of a SEPS drain. ¶ Or until resolution of the cSDH on the follow-up CT scan. * The standard neurosurgical procedure consisted of evacuation of the cSDH through burr-hole trepanation or mini-craniotomy, with or without drainage. † All patients underwent burr-hole drainage and were randomly allocated into the three described groups (surgery, surgery + TXA, and surgery + Goreisan). The sample size described refers to the quantity of chronic subdural hematomas assessed. # All patients underwent single burr-hole drainage with subdural drain insertion. The antithrombotics (AT) group consisted of patients with a history of cerebrovascular or cardiovascular disease, on antiplatelet or anticoagulant therapy. Results are expressed as median (interquartile range).*

Regarding the Need for Surgical Procedure

Lodewijk et al. investigated the effect of off-label first-line treatment with TXA in seven patients diagnosed with cSDH (24). Treatment discontinuation was guided by the resolution of neurological symptoms, combined with a significant reduction or complete disappearance of the hematoma on follow-up CT scans. The primary outcome assessed was the surgical need for cSDH evacuation within the first 12 weeks of TXA treatment. Of the seven patients, five (71.2%) experienced complete resolution of neurological symptoms. One patient required burr-hole trepanation 5 days after initiating treatment due to worsening clinical condition.

Regarding Recurrence Prevention

In 2019, Yamada and Natori published a randomized clinical trial involving 193 patients (232 cSDHs) to assess the effect of TXA on recurrence prevention (44). Following burr-hole trepanation for hematoma drainage, patients were randomly assigned to three groups: surgery alone, TXA, and Goreisan—a Japanese traditional medicine composed of five herbal ingredients. The instituted treatment lasted for a total of 3 months post-surgery, after which the difference in recurrence rates (including reoperation) among the groups was evaluated. Regarding the primary outcome, the authors determined that there was no statistically significant difference in recurrence rates.

Wan et al. obtained similar results in their randomized clinical trial published in 2020 (41). Ninety symptomatic cSDH patients were recruited and randomly allocated to receive standard neurosurgical treatment—burr-hole evacuation or mini-craniotomy—or adjuvant TXA with surgical intervention. The primary outcome assessed was the reduction in symptomatic cSDH recurrence post-surgery, necessitating reoperation within 6 months. There were five recurrences (10.2%) in the first group and two (4.8%) in the second group, with no statistically significant difference in the recurrence rate (odds ratio [OR] 0.51, p=0.4).

In a more recent study from 2022, Yang et al. retrospectively analyzed 240 symptomatic patients undergoing cSDH evacuation with single burr-hole trepanation and subdural drain insertion to determine the efficacy of TXA as an adjuvant in recurrence prevention and hematoma resolution (45). The study population was divided into the following groups: TXA, non-TXA (observation), and antithrombotics (AT), the latter encompassing patients with a history of cardiac or cerebrovascular disease on antiplatelet or anticoagulant therapy. The primary outcome evaluated was cSDH recurrence, defined as hematoma reappearance requiring neurosurgical intervention.

The authors identified 16 recurrence cases (6.7%): one in the TXA group, eight in the non-TXA group, and seven in the AT group. Although the recurrence rate was lower in patients treated with TXA (2.4%), there was no statistically significant difference due to the small number of events. The authors concluded that TXA could be a viable therapeutic option for reducing recurrence in selected patients.

Conversely, de Paula et al. presented a different suggestion in their randomized controlled clinical trial, published in 2023 (9). Fifty unilateral or bilateral cSDH patients undergoing surgical burr-hole trepanation were randomized to receive postoperative TXA or not. The recurrence rate was determined based on symptom recurrence or the need for new surgical intervention.

Clinical and radiological recurrence occurred in two out of 24 patients in the TXA group (8.3%) and in one out of 26 cases in the control group (3.8%), with no statistically significant difference (p=0.5). Consequently, the authors suggested that TXA should not be used as a therapeutic measure to prevent CSDH recurrence.

Albalkhi et al. evaluated the role of TXA as an adjuvant treatment in preventing cSDH recurrence in a systematic review with meta-analysis (1). Six studies (four randomized clinical trials and two cohorts) were included, comprising 1,403 cSDH-diagnosed patients who underwent surgical intervention. Of these, 654 patients received adjuvant TXA therapy, while 749 received standard surgical treatment (control). The recurrence rate was estimated at 5.8% in the TXA group and 13.6% in the control group. The overall relative risk (RR) revealed a significant reduction in recurrence in the TXA group compared to controls (RR 0.41 [95% CI 0.29-0.59]). Based on these findings, Albalkhi et al. (1) suggested that adjuvant TXA may reduce cSDH recurrence in elderly patients who have undergone surgical procedures.

Regarding Volumetric Changes in cSDH

In their case series, Lodewijk et al. (24) demonstrated the volumetric reduction of cSDH in all patients during follow-up, with a median of 15 weeks. The total volume, initially 83 ml, decreased by 72% to a residual of 33 ml.

Kageyama et al. analyzed 21 patients diagnosed with cSDH by CT or magnetic resonance imaging (MRI) (22). Regardless of the choice of surgical approach or symptomatology, all participants received 750 mg of TXA per day until complete resolution or sufficient reduction of the hematoma, based on imaging evolution. TXA was used as the main treatment in 18 patients (86%) and as an adjuvant to surgery in three (14%). The median volume of cSDH showed a reduction from 58.5 ml initially to 3.7 ml after therapy. There were no records of recurrence or progression of hematomas.

As a secondary outcome, Yamada and Natori's clinical trial also recorded the residual volume of cSDH 1, 2, and 3 months after treatment (44). At baseline, there was no difference in preoperative hematoma volume. At all follow-up periods, the measured volume was significantly lower in the TXA group compared to patients treated only surgically or with adjuvant Goreisan.

Kutty et al., in turn, recruited 27 patients diagnosed with cSDH for TXA treatment, which was maintained until hematoma resolution (23). Twenty cases consisted of primary cSDH, and seven of these were recurrent cSDH after surgical treatment (trepanation with twist-drill). The mean thickness of cSDH was determined as 14.31 mm. The mean volume of the hematoma

initially measured 147.05 ml in the group primarily treated with TXA and 152.14 ml in the recurrent group. The authors considered that there was satisfactory resolution of cSDH in subsequent control CT scans.

Tanweer et al. evaluated the effect of TXA on the treatment of residual subdural hematoma after a surgical procedure (39). They retrospectively analyzed 14 patients undergoing drainage of moderate to large cSDH with twist-drill, followed by placement of a subdural evacuation port system (SEPS) drain. After SEPS removal, they opted for daily administration of 650 mg of TXA on an outpatient basis for 6 months or until cSDH resolution on CT follow-up.

In the study published in 2016, the mean initial volume was 145.96 ml, with a midline shift of 9.44 mm. After surgical evacuation, the cSDH volume decreased by 40.74% ($p<0.0001$) to a mean of 80 ml, and the midline shift reduced to 4.44 ml ($p=0.0046$). At the last follow-up, the mean cSDH volume was recorded as 7.41 ml, representing an additional reduction of 91.3% after TXA treatment was instituted ($p<0.0001$). The percentage volumetric reduction was significantly higher after TXA compared to SEPS (91.3% versus 40.74%).

Although they did not prove the effect of TXA in preventing recurrence, Wan et al. demonstrated that the "surgery + TXA" group showed greater volumetric reduction of cSDH between postoperative and 6-week follow-up compared to the "surgery" group (41). However, this effect did not persist at 12 and 24 weeks of follow-up, and the maximum hematoma volume did not show a statistically significant difference between the two study arms.

Similarly, Yang et al. analyzed as a secondary outcome the resolution of cSDH, defined as complete reabsorption (thickness < 5 mm) or near-total reabsorption (hematoma stability), associated with recovery of neurological deficits (45). Clinical and radiological resolution of cSDH was achieved in 85.8% of patients, with no disparities between groups. However, the median time to resolution was significantly faster ($p<0.001$) in the TXA group (51 days) than in the non-TXA group (109 days) and AT group (88 days). In multivariate analysis, the administration of TXA adjuvant to surgical treatment was considered a positive factor for the reabsorption of residual bleeding.

Regarding Symptomatology

In the case series by Kageyama et al., all participants showed significant improvement in symptoms (22). In Tanweer et al.'s analysis, all 14 patients, except one with pre-existing dementia, showed symptomatic improvement in the follow-up, with the majority (71%) experiencing complete resolution (39).

With regard to clinical presentation, Puente Tinoco et al. evaluated 22 patients undergoing cSDH drainage, with half of them undergoing placement of a Jackson–Pratt external drainage system postoperatively (Group A), and the other half receiving TXA postoperatively (Group B) (29). Upon admission, the most reported symptom was hemiparesis (68.2% of cases). In both groups, most patients showed immediate improvement and normalization of the Glasgow Coma Scale (GCS) at 15 – 63.6% in Group A and 54.5% in Group B. Regarding hospitalization time, the authors identified an average stay of 8 days in Group A, versus 6 days in Group B, determining that the adjuvant use of TXA significantly reduced the number of hospitalization days compared to the use of the Jackson–Pratt drain ($p=0.004$).

Regarding the Incidence of Adverse Events

In Wan et al.'s analysis, there were four reported cases of serious adverse events in the "surgery + TXA" group, of which one—asymptomatic thalamic infarction—could potentially be related to the treatment, although the patient had a history of multiple small strokes on MRI (41). Kutty et al. did not record mortality, complications, or hematoma enlargement due to TXA treatment (23). Yang et al., in their 2022 article, also did not identify adverse effects related to the use of TXA (45).

As a secondary outcome, de Paula et al. assessed potential clinical and/or surgical complications related to TXA use (9). Two cases of postoperative complications were reported (pulmonary embolism, potentially associated with treatment, and surgical wound infection), both in the TXA group. There was no statistically significant difference between the groups regarding the incidence of adverse events ($p=0.5$).

In their 2023 meta-analysis, Albalkhi et al. identified only two studies that reported thrombosis occurrence (1). No statistically significant association was demonstrated between TXA treatment and the risk of thrombosis (RR 0.88 [95% CI 0.64-1.19]).

Bias Risk

Among the articles assessed by the NOS tool (43), the quality of evidence was classified as "good" in four cohorts (22,29,39,45). The analysis of one non-randomized clinical trial (25), and one prospective study were categorized as "fair" (24). Albalkhi et al.'s meta-analysis (1), which had a high level of confidence, did not present any critical flaws in the assessment by the AMSTAR 2 tool (33). Regarding the randomized clinical trials, the risk of bias established through ROB 2 (36) was low for the studies by Yamada et al. (44), and Wan et al. (41), and showed "some concerns" regarding the article published by de Paula et al. (9). The results of this analysis are compiled in Figure 2.

DISCUSSION

Currently, it is understood that the formation of cSDH is initiated by the rupture of the dural border, possibly due to a mild traumatic event (15). Consequently, there is extravasation of cerebrospinal fluid (CSF) and blood into the subdural space, initiating a cascade of inflammatory, angiogenic, and fibrinolytic processes. Local inflammation in response to bleeding is suggested by the elevation of pro-inflammatory cytokines, such as IL-6 and IL-8, in the CSF compared to serum levels (37). These inflammatory mediators, in turn, contribute to the development of cSDH through two central processes: increased vascular permeability and release of t-PA, resulting in plasmin formation.

Plasmin, in turn, leads to the activation of the kallikrein–kinin system (KKS), from which bradykinin is derived, responsible

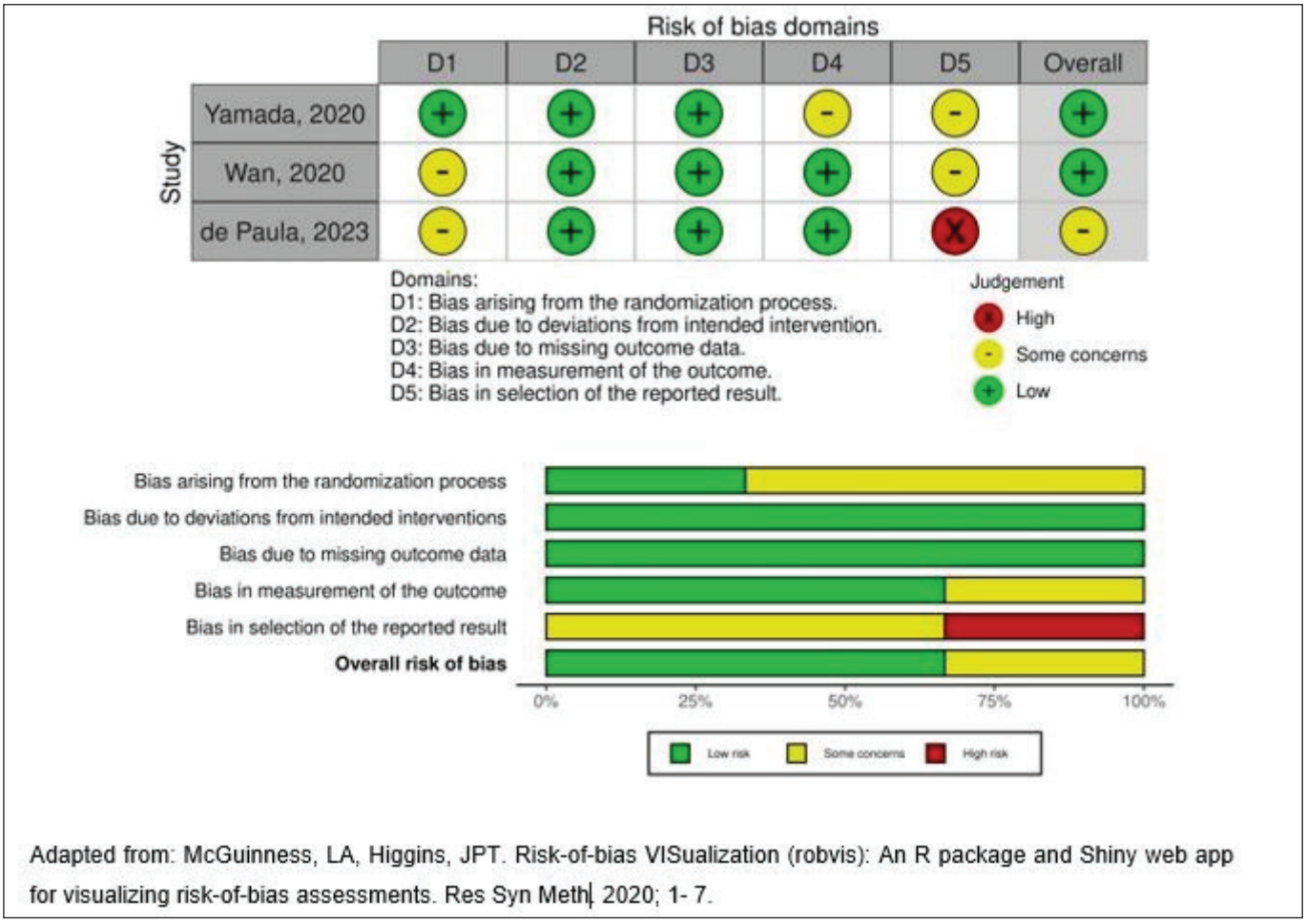

Figure 2: Risk of bias.

for increasing vascular permeability (12). Fujisawa et al. experimentally determined an elevation in bradykinin concentration in cSDH (13), suggesting a reciprocal stimulation between the KKS and coagulation and fibrinolysis pathways. The result involves angiogenesis, plasma exudation, and hyperfibrinolysis, critical events for hematoma progression.

Advancements in understanding the pathophysiology of cSDH have been accompanied by changes in the therapeutic paradigm. However, surgical evacuation of the hematoma remains the first-line treatment until now (21). Surgical treatment is generally accepted in patients with neurological symptoms and considerable radiological findings; conversely, asymptomatic cases without obvious mass effect are often clinically monitored (35). Amidst these two scenarios with more easily perceivable approaches, there are several controversies: when to indicate surgical management? What is the best surgical method? Is pharmacological treatment possible?

Although surgical intervention is considered effective, with a high cure rate (generally above 70%), the procedure's mortality is not negligible (approximately 2 to 4%) (42). Recurrence is also a relevant factor to be evaluated. Santarius et al. estimated recurrence at 9.3% in patients with postoperative drainage and 24% in cases where drainage placement was omitted (31). In their analysis of more than 60,000 patients, Toi et al. estimated the recurrence rate at 13.1% (40). Functional outcomes were considered poor in 28.4% (modified Rankin Scale 3-6), especially in elderly patients. Approximately 30% of patients experienced some degree of morbidity, requiring assistance after discharge. These outcomes raised questions about the previously perceived "benign" prognosis of cSDH.

The heterogeneity of surgical approaches, coupled with the inherent risk of recurrence and complications, prompted the search for new therapies, initially focusing on oligosymptomatic patients or those with prohibitive surgical risk. In this context, the option of TXA emerged, a synthetic antifibrinolytic that competitively blocks plasminogen activation into plasmin. Additionally, it has an indirect anti-inflammatory action through the KKS (27). It has wide clinical applicability, with evidence of reducing intraoperative bleeding and postpartum hemorrhage (16). Another alternative that has been studied to reduce the risk of recurrence of cSDH is middle meningeal artery embolization (EMMA). The meta-analysis published by Dian et al. included a total of four studies (n=888 patients) and, despite limited data, concluded that the relative risk of recurrence with EMMA was significantly lower compared to

surgical drainage (RR 0.17, [CI 95% 0.05-0.67]), making it a promising option to consider (10).

The biological rationale for using TXA in cases of cSDH is based on the hypothesis that its antifibrinolytic action would inhibit the ongoing hyperfibrinolysis and increased vascular permeability processes, thereby allowing gradual hematoma absorption (22).

Regarding the prevention of postoperative recurrence of cSDH with adjuvant use of TXA, the results of this systematic review are contradictory. Some of the included studies (9,41,44,45) did not show a reduction in recurrence with the use of TXA; however, a recent meta-analysis demonstrates the effectiveness of the antifibrinolytic in reducing recurrence in elderly patients (1).

Recently, Ridwan et al. investigated predictive factors for cSDH recurrence (30). The authors concluded that the residual hematoma volume in the postoperative period, as well as the composition and morphology of cSDH, are the most relevant predictors of recurrence and cure. In this systematic review, several studies demonstrated the effect of adjuvant TXA in reducing the residual volume of cSDH, which may indirectly contribute to preventing recurrence (22-24,29). The network meta-analysis by Yu et al. reinforces this hypothesis: TXA showed definitive efficacy in reducing recurrence (OR = 0.26, [95% CI 0.07-0.41]) (47).

With regard to the safety profile, TXA exhibits mostly mild side effects, such as headache, abdominal pain, nausea, and diarrhea (4). In a recent meta-analysis, the use of TXA reduced all-cause mortality in non-surgical patients without increasing the risk of arterial or venous thrombotic complications (7). Taeuber et al. (38), in a meta-analysis of 216 studies, concluded that intravenous TXA, regardless of the dose, is not associated with an increased risk of thromboembolic events and is safe for neurological patients.

Limitations

While the results of this systematic review are optimistic regarding the role of TXA as primary or adjuvant therapy in the surgical management of cSDH, some limitations need to be addressed. Firstly, many of the studies included in the analysis had a limited sample size and retrospective design. Among the clinical trials, there is a notable risk of bias due to the possibility of unblinding. Additionally, the follow-up period was less than 12 months in the examined studies, limiting the assessment of outcomes, particularly recurrence and late adverse effects of the medication. Furthermore, a meta-analysis was not performed due to the heterogeneity of the articles considered in this review.

It is suggested that multicenter randomized clinical trials with a larger number of participants and meta-analyses be conducted to obtain a higher level of confidence regarding the use of TXA in the treatment of cSDH. Given the limitation of currently available evidence, two larger-scale clinical trials are underway. The TRACS study is a phase IIB, multicenter, double-blind, randomized, placebo-controlled study with an expected completion date of June 2025 (19). Its aim is to determine if TXA can increase the rate of cSDH resolution, obviating the need for surgical intervention. The study intends to evaluate, in addition to clinical parameters, the impact of treatment on cognitive function, functional autonomy, and quality of life. Another phase III study, called TORCH (18), with an expected completion date in 2024, seeks to analyze the efficacy of the antifibrinolytic as a primary treatment in cSDH.

CONCLUSION

In summary, this systematic review suggests that TXA can be considered a safe and effective therapeutic adjunct in the surgical management of cSDH. Evidence regarding the use of the antifibrinolytic as primary, non-operative treatment is still limited. It is suggested to continue with further studies involving larger sample sizes to establish its role in neurosurgical practice conclusively.

Declarations

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AUTHORSHIP CONTRIBUTION

Study conception and design: AFG, BRM, JPMB
Data collection: BRM, JPMB
Analysis and interpretation of results: AFG, BRM, JPMB
Draft manuscript preparation: BRM
Critical revision of the article: AFG, BRM, JPMB
Other (study supervision, fundings, materials, etc...): AFG
All authors (BRM, JPMB, AFG) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Albalkhi I, Alaswad M, Saleh T, Senjab A, Helal B, Khan JA: Adjuvant tranexamic acid for reducing postoperative recurrence of chronic subdural hematoma in the elderly: A systematic review and meta-analysis. World Neurosurg182:e829-e836, 2024. https://doi.org/10.1016/j.wneu.2023.12.054.
2. Balser D, Farooq S, Mehmood T, Reyes M, Samadani U: Actual and projected incidence rates for chronic subdural hematomas in United States Veterans Administration and civilian populations. J Neurosurg 123:1209-1215, 2015. https://doi.org/10.3171/2014.9.JNS141550.
3. Brennan PM, Kolias AG, Joannides AJ, Shapey J, Marcus HJ, Gregson BA, Grover PJ, Hutchinson PJ, Coulter IC; British Neurosurgical Trainee Research Collaborative. The management and outcome for patients with chronic subdural hematoma: A prospective, multicenter, observational cohort study in the United Kingdom. J Neurosurg 127:732-739, 2017. https://doi.org/10.3171/2016.8.JNS16134.

4. Chapin JC, Hajjar KA: Fibrinolysis and the control of blood coagulation. Blood Rev 29:17-24, 2015. https://doi.org/10.1016/j.blre.2014.09.003.
5. Chauncey JM, Wieters JS: Tranexamic acid. In: StatPearls [website]. Treasure Island (FL): StatPearls Publishing. Available at: https://www.ncbi.nlm.nih.gov/books/NBK532909/. Accessed March 27, 2024.
6. Chen JW, Xu JC, Malkasian D, Perez-Rosendahl MA, Tran DK: The mini-craniotomy for cSDH revisited: New perspectives. Front Neurol 12:660885, 2021. https://doi.org/10.3389/fneur.2021.660885.
7. Chornenki NLJ, Um KJ, Mendoza PA, Samienezhad A, Swarup V, Chai-Adisaksopha C, Siegal DM: Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis. Thromb Res 79:81-86, 2019. https://doi.org/10.1016/j.thromres.2019.05.003.
8. CRASH-3 trial collaborators: Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): A randomised, placebo-controlled trial. Lancet 394:1713-1723, 2019. Erratum in: Lancet 394:1712, 2019.
9. de Paula MVCT, Ribeiro BDC, Melo MM, de Freitas PVV, Pahl FH, de Oliveira MF, Rotta JM: Effect of postoperative tranexamic acid on recurrence rate and complications in chronic subdural hematomas patients: Preliminary results of a randomized controlled clinical trial. Neurosurg Rev 46:90, 2023. https://doi.org/10.1007/s10143-023-01991-9.
10. Dian J, Linton J, Shankar JJ: Risk of recurrence of subdural hematoma after EMMA vs surgical drainage - Systematic review and meta-analysis. Interv Neuroradiol 27:577-583, 2021. https://doi.org/10.1177/1591019921990962.
11. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ: Pathophysiology of chronic subdural haematoma: Inflammation, angiogenesis and implications for pharmacotherapy. J Neuroinflammation 14:108, 2017. https://doi.org/10.1186/s12974-017-0881-y.
12. Ewald GA, Eisenberg PR: Plasmin-mediated activation of contact system in response to pharmacological thrombolysis. Circulation 91:28-36, 1995. https://doi.org/10.1161/01.cir.91.1.28.
13. Fujisawa H, Ito H, Kashiwagi S, Nomura S, Toyosawa M: Kallikrein-kinin system in chronic subdural haematomas: Its roles in vascular permeability and regulation of fibrinolysis and coagulation. J Neurol Neurosurg Psychiatry 59:388-394, 1995. https://doi.org/10.1136/jnnp.59.4.388.
14. Grant FC: Chronic subdural haematoma. Ann Surg 86:485-493, 1927. https://doi.org/10.1097/00000658-192710000-00003.
15. 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 Group (DSHR): Pathophysiology and nonsurgical treatment of chronic subdural hematoma: From Past to present to future. World Neurosurg 116:402-411.e2, 2018. https://doi.org/10.1016/j.wneu.2018.05.037.
16. Hunt BJ: The current place of tranexamic acid in the management of bleeding. Anaesthesia 70 Suppl 1:50-53, e18, 2015. https://doi.org/10.1111/anae.12910.
17. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, Agyemang K, Thomson S, Anderson IA, Al-Tamimi YZ, Henderson D, Whitfield PC, Gherle M, Brennan PM, Allison A, Thelin EP, Tarantino S, Pantaleo B, Caldwell K, Davis-Wilkie C, Mee H, Warburton EA, Barton G, Chari A, Marcus HJ, King AT, Belli A, Myint PK, Wilkinson I, Santarius T, Turner C, Bond S, Kolias AG; British Neurosurgical Trainee Research Collaborative; Dex-CSDH Trial Collaborators: Trial of dexamethasone for chronic subdural hematoma. N Engl J Med 383:2616-2627, 2020. https://doi.org/10.1056/NEJMoa2020473.
18. Immenga S, Lodewijkx R, Roos YBWEM, Middeldorp S, Majoie CBLM, Willems HC, Vandertop WP, Verbaan D: Tranexamic acid to prevent operation in chronic subdural haematoma (TORCH): Study protocol for a randomised placebo-controlled clinical trial. Trials 23:56, 2022. https://doi.org/10.1186/s13063-021-05907-0.
19. Iorio-Morin C, Blanchard J, Richer M, Mathieu D: Tranexamic acid in chronic subdural hematomas (TRACS): Study protocol for a randomized controlled trial. Trials 17:235, 2016. https://doi.org/10.1186/s13063-016-1358-5.
20. Kim HC, Ko JH, Yoo DS, Lee SK: Spontaneous resolution of chronic subdural hematoma: Close observation as a treatment strategy. J Korean Neurosurg Soc 59:628-636, 2016. https://doi.org/10.3340/jkns.2016.59.6.628.
21. Kolias AG, Chari A, Santarius T, Hutchinson PJ: Chronic subdural haematoma: Modern management and emerging therapies. Nat Rev Neurol 10:570-578, 2014. https://doi.org/10.1038/nrneurol.2014.163.
22. Kageyama H, Toyooka T, Tsuzuki N, Oka K: Nonsurgical treatment of chronic subdural hematoma with tranexamic acid. J Neurosurg 119:332-337, 2013. https://doi.org/10.3171/2013.3.JNS122162.
23. Kutty RK, Leela SK, Sreemathyamma SB, Sivanandapanicker JL, Asher P, Peethambaran A, Prabhakar RB: The outcome of medical management of chronic subdural hematoma with tranexamic acid - a prospective observational study. J Stroke Cerebrovasc Dis 29:105273, 2020. dhttps://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105273.
24. Lodewijkx R, Immenga S, van den Berg R, Post R, Westerink LG, Nabuurs RJA, Can A, Vandertop WP, Verbaan D: Tranexamic acid for chronic subdural hematoma. Br J Neurosurg 35:564-569, 2021. https://doi.org/10.1080/02688697.2021.1918328.
25. Mascolo A, Scavone C, Scisciola L, Chiodini P, Capuano A, Paolisso G: SGLT-2 inhibitors reduce the risk of cerebrovascular/cardiovascular outcomes and mortality: A systematic review and meta-analysis of retrospective cohort studies. Pharmacol Res 172:105836, 2021. https://doi.org/10.1016/j.phrs.2021.105836.
26. McGuinness LA, Higgins JPT: Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods 12:55-61, 2021. https://doi.org/10.1002/jrsm.1411.

27. Ng W, Jerath A, Wąsowicz M: Tranexamic acid: A clinical review. Anaesthesiol Intensive Ther 47:339-350, 2015. https://doi.org/10.5603/AIT.a2015.0011.
28. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372:n71, 2021. https://doi.org/10.1136/bmj.n71.
29. Puente Tinoco MR, Reyes Graterol EO, García Oduber SM: Recuperación de pacientes en postoperatorio de drenaje de hematoma subdural crónico asociado al uso de ácido tranexámico. Rev Chil Neurocirugía 42:45-51, 2016. Available at: https://www.neurocirugiachile.org/pdfrevista/v42_n1_2016/puente_p45_v42n1_2016.pdf. Accessed February 17, 2024. https://doi.org/10.36593/rev.chil.neurocir.v42i1.93
30. Ridwan S, Bohrer AM, Grote A, Simon M: Surgical treatment of chronic subdural hematoma: Predicting recurrence and cure. World Neurosurg 128:e1010-e1023, 2019. https://doi.org/10.1016/j.wneu.2019.05.063.
31. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, Richards HK, Marcus H, Parker RA, Price SJ, Kirollos RW, Pickard JD, Hutchinson PJ: Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: A randomised controlled trial. Lancet 374:1067-1073, 2009. https://doi.org/10.1016/S0140-6736(09)61115-6.
32. Santarius T, Kirkpatrick PJ, Kolias AG, Hutchinson PJ: Working toward rational and evidence-based treatment of chronic subdural hematoma. Clin Neurosurg 57:112-122, 2010.
33. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA: AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 358:j4008, 2017. https://doi.org/10.1136/bmj.j4008.
34. Soleman J, Nocera F, Mariani L: The conservative and pharmacological management of chronic subdural haematoma. Swiss Med Wkly 147:w14398, 2017. https://doi.org/10.57187/smw.2017.14398.
35. Solou M, Ydreos I, Gavra M, Papadopoulos EK, Banos S, Boviatsis EJ, Savvanis G, Stavrinou LC: Controversies in the surgical treatment of chronic subdural hematoma: A systematic scoping review. Diagnostics 12:2060, 2022. https://doi.org/10.3390/diagnostics12092060.
36. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT: RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898, 2019. https://doi.org/10.1136/bmj.l4898.
37. Suzuki M, Endo S, Inada K, Kudo A, Kitakami A, Kuroda K, Ogawa A: Inflammatory cytokines locally elevated in chronic subdural haematoma. Acta Neurochir 140:51-55, 1998. https://doi.org/10.1007/s007010050057.
38. Taeuber I, Weibel S, Herrmann E, Neef V, Schlesinger T, Kranke P, Messroghli L, Zacharowski K, Choorapoikayil S, Meybohm P: Association of intravenous tranexamic acid with thromboembolic events and mortality: A systematic review, meta-analysis, and meta-regression. JAMA Surg 156:e210884, 2021. https://doi.org/10.1001/jamasurg.2021.0884.
39. Tanweer O, Frisoli FA, Bravate C, Harrison G, Pacione D, Kondziolka D, Huang PP: Tranexamic acid for treatment of residual subdural hematoma after bedside twist-drill evacuation. World Neurosurg 91:29-33, 2016. https://doi.org/10.1016/j.wneu.2016.03.062.
40. Toi H, Kinoshita K, Hirai S, Takai H, Hara K, Matsushita N, Matsubara S, Otani M, Muramatsu K, Matsuda S, Fushimi K, Uno M: Present epidemiology of chronic subdural hematoma in Japan: Analysis of 63,358 cases recorded in a national administrative database. J Neurosurg 128:222-228, 2018. https://doi.org/10.3171/2016.9.JNS16623.
41. Wan KR, Qiu L, Saffari SE, Khong WXL, Ong JCL, See AA, Ng WH, King NKK: An open label randomized trial to assess the efficacy of tranexamic acid in reducing post-operative recurrence of chronic subdural haemorrhage. J Clin Neurosci 82:147-154, 2020. https://doi.org/10.1016/j.jocn.2020.10.053.
42. Weigel R, Schmiedek P, Krauss JK: Outcome of contemporary surgery for chronic subdural haematoma: Evidence based review. J Neurol Neurosurg Psychiatry 74:937-943, 2003. https://doi.org/10.1136/jnnp.74.7.937.
43. Wells GA, Shea B, O'Connel D, Peterson J, Welch V, Losos M, Tugwell P: The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www ohri ca/programs/clinical_epidemiology/oxford. Accessed March 10, 2024.
44. Yamada T, Natori Y: Prospective study on the efficacy of orally administered tranexamic acid and goreisan for the prevention of recurrence after chronic subdural hematoma burr hole surgery. World Neurosurg 134:e549-e553, 2020. https://doi.org/10.1016/j.wneu.2019.10.134.
45. Yang K, Kim KH, Lee HJ, Jeong EO, Kwon HJ, Kim SH: Role of adjunctive tranexamic acid in facilitating resolution of chronic subdural hematoma after surgery. J Korean Neurosurg Soc 66:446-455, 2023. https://doi.org/10.3340/jkns.2022.0200.
46. Yang W, Huang J: Chronic subdural hematoma: Epidemiology and natural history. Neurosurg Clin N Am 28:205-210, 2017. https://doi.org/10.1016/j.nec.2016.11.002.
47. Yu W, Chen W, Jiang Y, Ma M, Zhang W, Zhang X, Cheng Y: Effectiveness comparisons of drug therapy on chronic subdural hematoma recurrence: A bayesian network meta-analysis and systematic review. Front Pharmacol 13:845386, 2022. https://doi.org/10.3389/fphar.2022.845386.