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REVIEW ARTICLE - NEUROSURGERY GENERAL

Systematic review of current randomised control trials in chronic subdural haematoma and proposal for an international collaborative approach

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Abstract

Background Chronic subdural haematoma (CSDH) is a pathology that is frequently encountered by neurosurgeons. Nevertheless, there is a lack of guidelines based on solid evidence. There has been a recent and considerable increase in the interest on management and outcomes for CSDH. Therefore, we systematically reviewed all currently running randomised controlled trials (RCTs) in chronic subdural haematoma to understand the areas under investigation and plan future collaborative trials.

Methods Clinical trials databases (Cochrane Controlled Register of Trials, WHO ICTRP and clinical trials.gov) were searched for trials relevant to chronic subdural haematoma. It was then established which trials were currently running and fulfilled robust research methodology for a RCT.

Results There are 26 currently running RCTs in CSDH, with the most common topics covering application of steroids (7), surgical techniques (5) and tranexamic acid (5). Further to this, there are trials running on other pharmacological agents (4), middle meningeal artery (MMA) embolisation (2) and peri-operative management (3).

Conclusions Pharmacological agents are a particular focus of CSDH management currently, and a wealth of studies on steroids will hopefully lead to more harmonised, evidence-based practice regarding this in the near future. Surgical techniques and new

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procedures such as MMA embolisation are also important focuses for improving patient outcomes. There is an on-going need for future RCTs and evidence-based guidelines in CSDH, particularly including low- and middle-income countries, and it is hoped that the establishment of the iCORIC (International COllaborative Research Initiative on Chronic Subdural Haematoma) will help address this.

Keywords Chronic subdural haematoma · Head injury · Elderly · Collaboration · Trials

Abbreviations

CODE	Core outcomes and common data elements
CSDH	Chronic subdural haematoma
CT	Computed tomography
iCORIC	International COllaborative Research Initiative on CSDH
Dex/DXM	Dexamethasone
EANS	European Association of Neurological Societies
LMIC	Low- and middle-income countries
MMA	Middle meningeal artery
RCT	Randomised controlled trial
TDC	Twist drill craniostomy
TXA	Tranexamic acid

Introduction

Despite the fact that chronic subdural haematoma (CSDH) is a frequently occurring pathology in daily neurosurgical practice, with increasing frequency as the population ages, there is still a relative lack of good-quality evidence regarding optimal management [51]. This contradiction is increasingly recognised in the neurosurgical research community, which has resulted in a considerable increase in the interest on management and outcomes in CSDH and hence an associated growth in the number of CSDH-related publications (Fig. 1).

Whilst the number of publications has been increasing, it is also important that studies are robust and provide high-level evidence to instigate changes in practice. Thus, we sought to undertake a systematic review of current randomised controlled trials (RCTs) in CSDH.

It is anticipated that shifting perspectives on CSDH pathophysiology will influence the focus of trials. Despite the earliest reports of CSDH reporting it as a form of inflammatory "pachymeningitis", many subsequently believed that CSDH occurred purely as a result of traumatic haemorrhage and thus required surgical treatment only [53, 59]. However, whilst trauma may or may not be a necessary pre-requisite for CSDH formation, the subsequent process of subdural fluid and blood accumulation appears to be driven by a localised inflammatory response and formation of new membranes and leaky vessels [35, 42]. This explains a renewed and growing interest in pharmacological agents discussed in the current literature, primarily targeting anti-inflammatory or anti-angiogenic processes.

One of the most practice-changing surgical RCTs in the last decade evidenced that perioperative subdural drains were successful in reducing CSDH recurrence and improved patient outcome [61]. It is now common practice to use a post-operative drain, and it is conceivable that the mechanism of action is by continual drainage reducing post-operative residual fluid and inflammatory markers, thus removing the stimulus for further CSDH re-accumulation. Thus, optimising surgical techniques, in addition to investigating new pharmacological agents, is critical for continued improvement in CSDH management and outcomes.

The aim of this review was to formulate a list of current on-going trials in CSDH, excluding those where final trial results have already been published and are available in the literature. This review is intended to only include trials, which have been

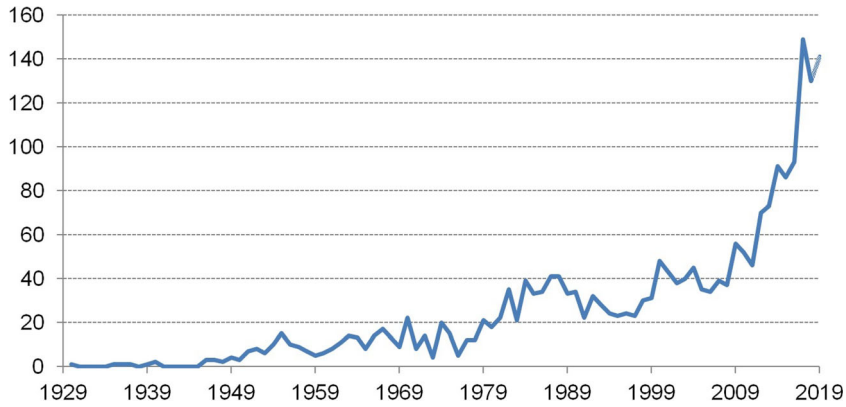

Fig. 1 Evolution of the number of publications per year on chronic subdural haematoma over 90 years from 1929 to 2019 using search terms in title only (chronic) AND (subdural) AND (hematomas OR haematomas OR hemorrhages OR haemorrhages OR hematoma OR haematoma OR hemorrhage OR bleeding)

recently registered, started recruitment or those where recruitment is complete, but the results are not yet available. It is anticipated that the results from this review will help inform on specific areas of interest of current RCTs in CSDH, and their potential completion dates. This will highlight areas where there is cross-over between studies and gaps in the field to guide timing for planning international CSDH management recommendations (pending critical trial outcomes) and future collaborative trial design in CSDH. To enable understanding of the trials reviewed a summary of key patient eligibility criteria, the interventions and comparisons received and primary outcome of each study will be summarised.

Methods

Three clinical trials databases were searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines on 31 May 2019: Cochrane Controlled Register of Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and clinical trials.gov. To identify trials relating to chronic subdural haematoma, the search terms in Table 1 were used and no date exclusions were applied.

All identified trial titles and abstracts were reviewed by two authors (EE, DH) to exclude duplications, studies not concerning CSDH and any without a summary available in the English language. The remaining abstracts were then carefully screened to exclude studies that were not RCTs, with randomisation needing to be specifically referred to in the abstract or protocol. Finally, all the trials which had been completed and the published results already available for review were excluded. This was double checked by searching all the titles in PubMed and Google for publications relating to the registered trials, which may not be reported on the databases.

The final list of trials was closely reviewed, including electronic searching of the research group and study title/details and email contact to all registered principal investigators (PI), to assess whether they were still running. Any that had been registered over 5 years ago but had no updates or evidence of recruitment and no response from the PI were excluded, as were those reported as abandoned. Further to this, trial methodology was assessed by both reviewers to ensure it was sufficiently robust to fulfil RCT criteria, as specified in the Consolidation Standards of Reporting Trials (CONSORT) statement [55]. Trials which did not report sufficient information to assess methodology or where it was felt the methodology was lacking in relation to being able to achieve the primary outcome were excluded. Both authors conducted a review of articles separately and discussed any disagreements until resolved. All trial principal investigators were contacted via email to assess study progress and estimated completion dates.

Table 1 Search terms for trials databases

Cochrane CENTRAL	WHO ICTRP	Clinical trials.gov
Chronic* NEAR/3 ((subdural*) NEAR/3 (hematom* OR haematom* OR hemorrhag* OR haemorrhag* OR bleeding*))	subdural AND hematoma OR subdural AND haematoma OR subdural AND hemorrhage OR subdural AND haemorrhage OR subdural AND bleeding	((subdural) AND (hematoma OR haematoma OR hemorrhage OR haemorrhage OR bleeding))

Results

A total of 170 registered clinical trials were identified with the original search criteria, after removal of duplicates. Following initial screening, a further 126 trials were removed for not being in English ($n = 4$), subject not concerning CSDH ($n = 48$), not being an RCT ($n = 35$) or for already having published results ($n = 39$). A further 18 trials were removed after close scrutiny due to insufficient reporting of or poor trial methodology, leaving 26 currently running RCTs in CSDH (Fig. 2).

The trial topics were divided into trials on steroids ($n = 7$), tranexamic acid ($n = 5$), other pharmacological agents ($n = 4$), surgical techniques ($n = 5$), middle meningeal artery embolisation ($n = 2$) and peri-operative care ($n = 3$) (Table 2).

Steroid trials

There are seven on-going trials assessing the efficacy of corticosteroids [2, 17, 20, 21, 37–39], most commonly dexamethasone, as treatment for CSDH. This is based on a background of observational studies suggesting that steroids can be useful both as primary conservative therapy and as an adjunct to surgery to reduce CSDH recurrence [4, 6, 33, 34, 40, 56, 58, 60, 64, 65]. Due to the paucity of level one evidence, several randomised trials were initiated in the last few years. The variation in hypotheses and methodology between the steroid trials is valuable, as different questions will be answered in relation to the role of this drug in CSDH management. Studies such as the Dex-CSDH and DRESH trials randomise patients to placebo or dexamethasone in *addition* to surgery, answering whether dexamethasone can be used as an adjunct to surgery to reduce recurrence and improve patient outcome [36, 52]. These studies have different inclusion criteria, medication regimes and outcomes, both providing valuable data. Conversely, studies such as DECSA [54] and DECS randomise patients to surgery *or* dexamethasone, thus answering whether conservative therapy with dexamethasone is as

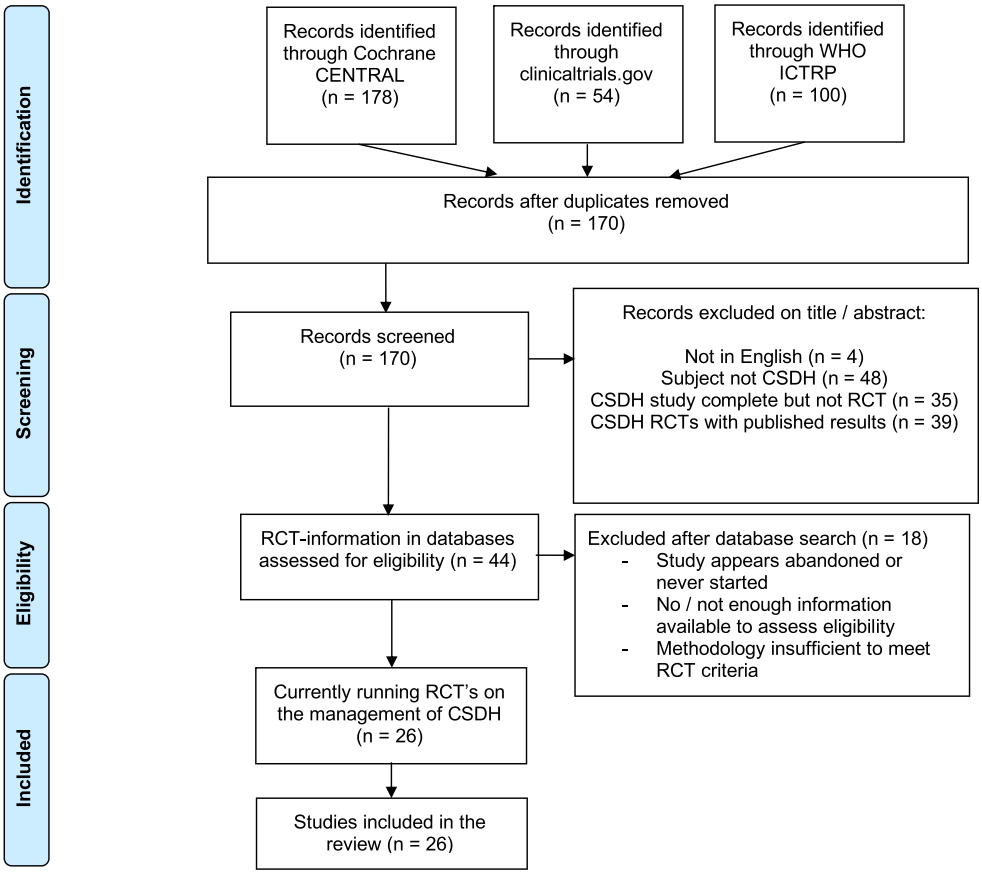

Fig. 2 Identification, screening, eligibility and inclusion of RCTs in review. As per : Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

efficacious as surgery for CSDH treatment. Many of these studies are nearing completion and, if successful, will likely alter practice in this domain significantly. This is important, as currently practice varies greatly throughout Europe, and the world. In countries such as The Netherlands, routine prescribing of steroids at diagnosis of CSDH occurs, whereas in the UK, traditional treatment has always been surgery or observation. Regional variation also occurs within countries such that care appears to be determined by physician opinion rather than robust evidence. It is essential that sufficient data is available on the risks and benefit of such treatments so that they can be applied appropriately, and these current RCTs should provide this.

Tranexamic acid trials

Five RCTs are assessing the role of tranexamic acid (TXA) [18, 19, 23, 25, 26], a drug which has been shown, in an observational study, to significantly reduce CSDH volume when used as a conservative treatment [46]. This is theorised to occur through its anti-fibrinolytic and anti-inflammatory properties. As with steroids, current trials are assessing the role of TXA as both a conservative treatment and an adjunct to surgery. To date, the data available on its efficacy in CSDH is more limited than that for steroids, and therefore, its use has been more restricted. Significant benefits will need to be proven in these trials to change practice globally.

Other pharmacological trials

Atorvastatin is another less well-researched pharmacological candidate for CSDH treatment and was the subject of a recent phase two RCT [45]. However, although this study on the effect of atorvastatin on CSDH volume found a significant difference compared with placebo, in real terms, there was only a difference of 12 mL in the volume of CSDH at 8 weeks. Further to this, only 23% of the placebo group ever required a surgical intervention, suggesting the CSDHs included were small with a high spontaneous resolution rate. This is not widely applicable to neurosurgically treated CSDH which has a natural history of continuing to grow unless treated and highlights the importance of appropriate inclusion criteria when designing such RCTs. There are two further on-going trials in atorvastatin [11, 29], although one is combining atorvastatin with and without dexamethasone with no placebo group (ATOCH2), therefore providing limited data on the efficacy of atorvastatin itself. Again, significant benefits will need to be demonstrated in trials for widespread adoption of this drug in CSDH, as currently we are unaware of any specialists using it routinely.

Table 2 Currently running randomised controlled trials (RCTs) in chronic subdural haematoma included in review

Trial name; title *Registered number*	Primary objective	Trial design	Estimated completion	Sample size	PICO				Country
					Patients	Intervention	Comparison	Outcome (primary)	
STEROID (dexamethasone = DXM) TRIALS = 7									
Management of CSDH using DXM *NCT02938468* [21]	Efficacy and safety of DXM in management of chronic subdural haematoma	Single centre RCT	Recruitment complete Sept 2018	326	Patients ≥ 18 years with symptomatic CSDH, sub-acute or chronic on imaging	DXM for 21 days	Any surgical procedure for CSDH treatment	Surgical intervention in the DXM group or re-operation in the surgical group at 3 months	Canada
DEX-CSDH; DXM in CSDH *EUCTR201400494835* [38]	To assess the clinical outcomes of a 2-week course of DXM versus placebo for CSDH	Multicentre, double-blind, placebo--controlled RCT	2020	750	Patients ≥ 18 years with symptomatic CSDH, predominantly iso- or hypo-dense on imaging	DXM for 14-day tapering course; starting with 16 mg/day for 3 days, reducing every 3 days	Placebo as per DXM regimen	Modified Rankin Scale (mRS) at 6 months	UK
SUCRE; Treatment of CSDH by corticosteroids *NCT02650609* [20]	To evaluate the efficacy of corticosteroids in CSDH patients without clinical or radiological signs of severity	Double-blind, placebo--controlled RCT	June 2020	202	Patients ≥ 18 years with primary CSDH without clinical/-radiological signs of severity	Methylprednisolone for 21 days: < 60 kg = 48 mg/day (3 tablets) 60–80 kg = 64 mg/day (4 tablets) > 80 kg = 80 mg/day (5 tablets)	Placebo as per methylpredniso-lone regimen	Delay of CSDH surgical treatment measured at 1 month	France
Hemacort; interest of oral corticosteroids in treatment of CSDH *NCT01380028* [17]	To compare the recurrence rate at 6 months in patients receiving post-operative prednisolone or placebo	Double-blind, placebo--controlled RCT	Dec 2019	340	Patients ≥ 18 years with primary symptomatic CSDH treated with surgery. Hypo- or iso-dense on imaging	Prednisone within 72 h of surgery, 1 mg/kg/day for 1 week. Decreasing by 10 mg/week until 5 mg/day for last week (average 2 months)	Placebo as per prednisone regimen	Clinical and radiological recurrence rate 6 months after surgery	France
DECSA; DXM therapy in patients with CSDH *EUCTR201500156339* [39]	Non-inferiority of primary DXM therapy versus BHC on functional outcome	Multi-centre, 2-arm, RCT	October 2021	420	Patients ≥ 18 years with CSD with Markwalder Grading Scale 1–3	DXM for 20-day tapering course; starting with 16 mg/day for 4 days, reducing every 3 days	Burr hole craniostomy	Modified Rankin Scale (mRS) at 3 months and cost-effectiveness at 12 months	The Netherla-nds
DRESH; DXM in reduction of re-operation rate for CSDH *EUCTR201100354442* [37]	To test the efficacy of 6 days postoperative DXM on reduction in the reoperation rate of CSDH	Multi-centre, double-blind placebo--controlled RCT	Unknown	820	Patients ≥ 25 years requiring surgical treatment of CSDH due to symptoms or radiological findings	DXM for 6 days, started within 48 h of surgery (16-16-12-12-8-4 mg/-day)	Placebo as per DXM regimen	Reoperation rate within 12 weeks of primary surgery	Austria
CSDH-surgery with and without corticosteroids	To compare recurrence rates in CSDH-surgery	double-blind placebo--controlled RCT	Unknown, recruited 47 patients	100	Patients ≥ 18 years with symptomatic	Surgery + DXM for up to 2 weeks 16 mg/day for 3 days then wean to	Surgery + placebo as per DXM regimen	Recurrence rate within 6 months of surgery	Australia

Table 2 (continued)

Trial name; title *Registered number*	Primary objective	Trial design	Estimated completion	Sample size	PICO				Country
					Patients	Intervention	Comparison	Outcome (primary)	
ACTRN12613000175774 [2]	with and without corticosteroids				CSDH requiring surgery	6 mg/day). First dose at start of operation			
Tranexamic acid (TXA) trials = 5									
TRACE; TXA in the treatment of residual CSDH *NCT03280212* [23]	To compare haematoma volume 4–8 weeks after CSDH surgery in patients on TXA versus no treatment	Single-centre, observer-blinded RCT	2020	60	Patients with CSDH requiring surgical treatment	TXA for 4–8 weeks post-surgery: < 60 kg: 1 g/day 60–100 kg: 1.5 g/day > 100 kg: 2 g/day	Control arm receiving no medication or placebo	Change in haematoma volume in mL from immediately post-operative to repeat at 4–8 weeks	Canada
Study on the safety of TXA in CSDH *NCT02618382* [19]	To determine whether TXA reduces the rate of CSDH recurrence after surgery	Single centre, open single arm study	Recruitment complete in Nov 2018	50	Patients 18–85 years with CSDH on imaging (predominately hypo- or iso-dense) requiring surgery	TXA 1.3 g peri-operatively and then 3.9 g/day for 3 days or until discharge, whichever comes first	None	Complications at 30 days (Stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism)	USA
Tocilizumab (TMAB) and TXA as adjuncts in CSDH surgery *NCT03353259* [25]	To evaluate if adjuvant treatment with tocilizumab (TMAB) or TXA reduces recurrence in operated CSDH	3-arm open study; surgery only, surgery + TMAB, surgery + TXA	May 2020	600	Patients 55–100 years with CSDH requiring surgery	Surgery + TXA 1 g/day until haematoma disappearance Or surgery + TXA 1 g/day + tocilizumab 162 mg/week until haematoma disappearance	Surgery only (burr hole craniostomy)	Recurrence requiring re-operation within 6 months	Norway
TRACS; TXA in CSDH *NCT02568124* [18]	To investigate if TXA can be used as conservative treatment for CSDH, lower surgical procedures and decrease recurrence	Double-blinded, placebo--controlled RCT	June 2020	130	Patients ≥ 18 years with CSDH confirmed on CT containing a chronic component	TXA 750 mg/day until complete radiological resolution of CSDH or a maximum of 20 weeks	Placebo daily until complete radiological resolution of CSDH or a maximum of 20 weeks	Rate of CSDH resolution at 20 weeks without intervening unplanned surgical procedure (surgery is at discretion of treating team)	Canada
TORCH; Tranexamic acid to prevent OpeRation in CSDH *NCT03582293* [26]	To investigate the efficacy and safety of TXA as primary conservative treatment of CSDH	Double-blind, placebo--controlled, multicentre RCT	December 2021	130	Patients ≥ 50 years with CSDH on CT safe for primary conservative treatment based on symptoms and signs	TXA 1 g/day for 28 days	Placebo as per TXA regimen	Surgery for CSDH within 12 weeks of start of treatment	The Netherla-nds
Other pharmacological trials = 4									
	To evaluate the efficacy and	Double-blind,	Unknown	690	Patients ≥ 18 years with	Atorvastatin 20 mg/day for 8 weeks from day of		Favourable modified Rankin Scale	

Table 2 (continued)

Trial name; title *Registered number*	Primary objective	Trial design	Estimated completion	Sample size	PICO				Country
					Patients	Intervention	Comparison	Outcome (primary)	
REACH; Efficacy of Atorvastatin in CSDH *NCT03956368* [29]	safety of atorvastatin in patients with CSDH	placebo--controlled, multicentre RCT			symptomatic CSDH on CT	admission to neurosurgery	Placebo as per atorvastatin regimen	(mRS 0–3) at 6 months	Hong Kong SAR, China
ATOCH2; Efficacy and safety of combining atorvastatin and DXM on CSDH *ChiCTR1900021659* [11]	Atorvastatin versus atorvastatin combined with dexamethasone in CSDH	Double-blind, 2-arm RCT	2022	240	Patients 18–90 years with CSDH on imaging > 10 mL and modified Rankin Scale 1–3	4 weeks atorvastatin (20 mg/day) and DXM (2.25 mg/day for 2 weeks, 1 1.5 mg/day for 1 week, 0.75 mg/day for 1 week)	4 weeks atorvastatin (20 mg/day) and placebo (as per DXM regimen)	Completeness of haematoma resolution at 4 weeks including conversion to surgery or death	China
SECA; CSDH and aspirin *NCT03120182* [22]	Impact of continuing or discontinuing low-dose aspirin after CSDH surgery	Double-blind, placebo--controlled RCT	Dec 2022	142	Patients ≥ 18 years with CSDH already taking low-dose aspirin (100 mg/day) for secondary prevention	Acetylsalicylic acid (ASA) (100 mg/day) for 12 day then resumed normal ASA treatment	Placebo for 12 days hen resumed normal ASA treatment	Recurrence requiring re-operation within 6 months	Switzerland
Clinical study on chronic subdural hematoma by traditional Chinese medicine *jRCTs051180131* [44]	Effect of 3 months of Goreisan vs Saireito for CSDH recurrence after surgical drainage	2-arm, open RCT	Unknown, currently recruiting	300	Patients ≥ 20 years with primary CSDH requiring surgical treatment	Goreisan (6.0 g/day) for 3 months after surgery	Saireito (8.1 g/day) for 3 months after surgery	Recurrence rate of CSDH within 3 months of surgery	Japan
Surgical trials = 5									
COMPACT; optimal treatment for CSDH *NCT02655445* [13]	To evaluate the 30-day re-operation rate in CSDH for; mini--craniotomy, twist drill craniostomy and burr hole craniostomy	3-arm, open RCT	September 2019	250	Patients ≥18 years with CSDH requiring surgery	* Mini-craniotomy (bone flap >30 mm replaced and drain) * Twist drill craniostomy (twist drill burr hole < 5 mm and drain) * Burr hole craniostomy (2 burr holes 5–30 mm and drain)	None	Re-operation for recurrent or persistent CSDH within 30 days of primary surgery	Belgium
SSS; surgical techniques for CSDH study *JPRN-UMIN000031033* [66]	Comparison of drainage, irrigation or both combined on recovery and recurrence rate of CSDH	3-arm parallel open RCT (assessors are blinded)	Not stated	90	Patients ≥ 20 years with symptomatic CSDH	* Only drainage * Only irrigation * Irrigation and drainage	None	Restlessness after surgery, recurrence and modified Rankin Scale of 0 and 1 at 1 month	Japan
DECiDE: DrainagE of ChronIc SubDural HEmatoma *NCT03053895* [15]	Bedside twist drill versus operating room burr hole drainage of	2-arm, parallel open RCT	February 2020	486	Patients ≥ 18 years with symptomatic CSDH on imaging	Bedside twist drill technique	Operating room burr hole technique	Recurrence rate at 6 months	Canada

Table 2 (continued)

Trial name; title *Registered number*	Primary objective	Trial design	Estimated completion	Sample size	PICO				Country
					Patients	Intervention	Comparison	Outcome (primary)	
	CSDH on recurrence rate								
SIC!; Irrigation fluid temperature in the evacuation of CSDH *NCT02757235* [14]	To investigate the effect of irrigation fluid temperature on CSDH recurrence rate	Multi-centre, 2-arm, RCT	Dec 2019	600	Patients ≥ 18 years with CSDH requiring burr hole evacuation	Burr hole evacuation of CSDH with irrigation fluid at room temperature (± 22 °C)	Burr hole evacuation of CSDH with irrigation fluid at body temperature (± 37 °C)	Recurrence requiring re-operation within 6 months	Sweden
CORRECT-SCAR; Covers to improve aesthetic outcome after surgery in CSDH *NCT03755349* [27]	To evaluate if burr hole covers improve patient satisfaction of the scar in CSDH surgery	2-arm, single-blinded (patient not surgeon) RCT	January 2021	80	Patients ≥18 years with primary CSDH (hypo-, iso-, hyper- or mixed-density on CT) requiring burr hole surgery	Any burr hole on intervention side is covered by a burr hole cover	None of the burr holes on the intervention side are covered by a burr hole cover	Patient satisfaction (using patient reported outcome and scale 1–10) with the aesthetic result of the scar at 90 days	Switzerland
Middle meningeal artery (MMA) trials = 2									
MMA Embolization in the Treatment of Chronic Subdural Hematoma *ChiCTR1800018714* [10]	To evaluate the efficacy of MMA embolisation compared with traditional surgery for CSDH	3-arm, parallel RCT	December 2020	60	Patients ≥ 18 years with symptomatic CSDH without significant mass effect or requiring urgent surgery	Traditional surgery + MMA embolisation or MMA embolisation only	Traditional surgery	Recurrence rate, re-operation rate and improvement of clinical symptoms (time not specified)	China
MMA Embolization for Treatment of CSDH *NCT03307395* [24]	To evaluate the safety and efficacy of MMA embolisation for symptomatic CSDH	Single arm, open label	December 2020	50	Patients ≥18 years with symptomatic CSDH, classified on imaging as chronic or acute-on-chronic, without significant shift	MMA embolisation	None	Changes in neurological status and size of the CSDH within 6 weeks of procedure	USA
Peri-operative trials = 3									
NEURANESTH; General anaesthesia versus locoregional anaesthesia for CSDH *NCT03666949* [16]	Effect of local versus general anaesthetic during CSDH surgery on length of stay and functional outcome	2-arm parallel RCT	January 2020	60	Patients ≥ 18 years with CSDH requiring surgery	General anaesthesia with propofol (2.5 mg/kg), remifentanil (1 yg/kg), atracurium (0.5 mg/kg) and orotracheal intubation with mechanical ventilation	Locoregional anaesthesia with xylocaine 1% for a scalp nerve block	Length of post-operative hospitalisation required until fit for following completion of medical checklist	France
GAS-CDE; General anaesthesia versus local anaesthesia *CTRI/2019/04/018544* [12]	Effect of local versus general anaesthetic during CSDH surgery on	2-arm parallel RCT	July 2020	250	Patients 65–90 years with primary CSDH requiring evacuation and a Glasgow Coma	General anaesthesia with IV induction agent (propofol, thiopentone or etomidate), fentanyl and muscle relaxant and maintained on inhalation	Scalp block with lignocaine, adrenaline and bupivacaine plus supplemental sedation if require	Change in cognitive function as measured by a neuropsychologist from pre-operatively to	India

Table 2 (continued)

Trial name; title *Registered number*	Primary objective	Trial design	Estimated completion	Sample size	PICO				Country
					Patients	Intervention	Comparison	Outcome (primary)	
	post-operative cognitive change				Scale of 15 at randomisation	agent, with intubation and ventilation	(propofol or dexmedetomidine)	24 h, 3 months and 1 year post-operatively	
GET-UP; Impact of Early Out-of-bed in Postoperative Outcomes of CSDH *NCT03788005* [28]	To compare early mobilisation and 48 h bed rest on postoperative complications	2-arm, parallel open RCT	April 2021	208	Patients ≥ 18 years with primary CSDH drained by burr hole craniostomy	Early mobilisation within 12 h post-surgery. Subdural drains are closed during mobilisation and removed 48 h post-surgery	Bed rest with head of bed at 0° for 48 h. Subdural drains will be removed > 48 h post-surgery	Medical complications until discharge: infections, venous thromboembolism, seizures	Portugal

There is a large burden of anti-thrombotic drug use in the CSDH population, with rates as high as 43% in a recent UK national audit [5, 57]. Despite this, there is limited published data on the risks and benefits of stopping these drugs, which has led to great variations in practice [47, 48, 63]. The SECA trial [22] is aimed at answering whether patients taking aspirin should have this stopped in the peri-operative period or whether it can be safely continued throughout [46]. This is an area where there appears to be room for growth in studies assessing management of anti-platelets (including other agents such as clopidogrel) and anti-coagulants in CSDH patients. This is an important issue, as unnecessary halting of such medications may increase the patients' risk of complications such as stroke, DVT and PE. We advocate wider reporting of routine practice and outcomes in this area, so that future RCTs can be appropriately designed.

Finally, one randomised study on traditional Chinese medicines is included in this analysis [44], an area of medicine that, whilst gaining some international support from the World Health Organization, is still considered contentious by many Western physicians and scientists [31]. Therefore, it is unknown how much global impact such a trial may have on the treatment of CSDH, but it is unlikely to be integrated into European practice.

Surgical trials

Current surgical RCTs in CSDH are focused on operative techniques, characteristics of intra-operative irrigation fluid and wound closure aesthetics. Different operative techniques have been used over the years, with preferences varying between surgeons. A meta-analysis in 2014 showed that bedside twist drill craniostomy (TDC) was as efficacious as burr holes and that the associated cost savings of the procedure might make it a preferable option, whereas craniotomy carried a higher morbidity but was a superior treatment for recurrent CSDH [1]. Direct comparison of these three techniques is being investigated in the COMPACT study, which may lead to a more harmonised practice if one procedure is found to be significantly superior [13]. The DECiDE study is also comparing just two of the techniques: burr holes and bedside TDC [15]. However, as CSDH is not a homogenous condition, different patterns of bleeding and/or membranes may indicate the need for different approaches, which may limit the perceived generalisability of even a randomised trial. Further to this, there are resource implications, with low- and middle-income countries (LMIC) more likely to benefit from using interventions which are less costly and can be performed outside an operating theatre.

Another refinement to surgery for CSDH, which is not currently being trialled, but may be a good candidate for the future, is minimally invasive hollow screws. This is a modification of TDC that can still be performed at the bedside with a

Fig. 3 iCORIC logo

twist drill but does not require the blind insertion of a subdural catheter through a small skull opening [9]. Such techniques must be evaluated prospectively and systematically, for example with the use of the IDEAL framework for evaluation of surgical innovation [41].

The use and temperature of intra-operative irrigation fluid are also being investigated in trials (SSS and SIC), with body temperature fluid assumed to have a positive effect on coagulation and solubility of the CSDH, improving evacuation and recurrence rate [14, 66]. However, as only 40% of neurosurgeons have reported using irrigation fluid at body temperature, a randomised trial on this matter is indicated [3].

The aesthetic outcome after burr hole craniostomy may be unsatisfactory for some patients, although there is very little discussion of this in the literature. The CORRECT-SCAR trial studies whether the application of burr hole plates improves patient satisfaction with the aesthetic result of the surgery, as was suggested in their retrospective review [27, 67]. This may be of growing importance, as the aging population is living longer, healthier lives, and issues such of cosmesis can therefore become more of a concern. However, again there is a resource implication which is likely to make such studies more relevant to resource-rich populations rather than LMICs.

Middle meningeal artery embolisation trials

There has been a recent growing interest in middle meningeal artery (MMA) embolisation as a minimally invasive technique to treat CSDH, with two on-going RCTs reported in this review [10, 24]. A recent systematic review on this technique showed that currently data only exists from case series and non-randomised studies with low numbers, and the technique has mostly been applied to recurrent CSDH [68]. Most studies report the use of polyvinvyl alcohol (PVA) particles for embolisation but coils and other substances have also been used. Overall the review suggested a low recurrence rate with this technique (3.6% across 182 patients) and no procedural complications were reported. However, larger randomised studies are required before the true long-term outcomes of this technique can be known. It has been suggested the MMA embolisation may also improve outcome in patients on antithrombotic drugs and there is a further study assessing early resumption of anticoagulants following surgery with and without MMA embolisation, which is awaited (EMMACS study) [43]. Currently this procedure is performed in very few countries, and therefore, time and larger follow-on studies will be needed for broader adoption.

Peri-operative trials

As CSDH primarily affects the elderly population, who may suffer from multiple co-morbidities, the type of anaesthetic used may be significant, particularly as longer anaesthetic times in elderly head injury have been linked to mortality at 1 year [69]. It is well recognised that practice varies greatly between countries and even individual units; indeed, approximately 60% of the authors of this paper report using general anaesthetic in their practice, whilst the other 40% routinely use local for CSDH surgery. There are two on-going RCTs comparing the two, with one focused on length of stay and functional outcome, whilst the other is assessing the effect on cognition [12, 16]. Finally, comparisons of outcomes between bed rest and early mobilisation are being trialled, again an area of wide variations in practice between regions and countries and an important question to answer through a well-designed RCT [28].

Conclusions and the future of CSDH research

As with many neurosurgical pathologies, the relative lack of evidence base has led to varied practice in the management of CSDH. Within any single centre, individual neurosurgeons can take differing approaches, but the variation in management tends to be even wider when observing across different centres, and further across different nations. Therefore, high-quality RCTs are necessary to highlight clear treatment benefits and align practice where appropriate. Reviewing the current areas of interest and investigation in trials is helpful to understand the direction of progress, although this is limited by the rapid and dynamically changing nature of research, meaning newer studies will not be captured.

As anticipated, pharmacological agents, particularly steroids, are currently dominating the RCT field with several on-going studies. It is hoped that this provides a clear answer on the utility of such medications in the near future such that they are either adopted into routine practice more widely or only used in specific cases as indicated. Following this, there is the on-going question of the optimal surgical management of CSDH, with several different surgical techniques in practice. It may be that increased pharmacological treatments diminish the requirements for surgery, only making it necessary in more protracted or challenging cases. This raises the question for the future of CSDH management on which technique is best specifically for these difficult, recurrent cases, rather than just for "any" CSDH. This brings us to the essence of future CSDH management as a whole, which may become more "patient-centred" than it currently is. Thus, it may be that some patients are more responsive, or better treated with pharmacological treatments such as steroids, whilst those that have potential contra-indications or are resistant need focused surgical techniques. Either way, refining our understand and knowledge of each treatment modality and what it has to offer patients, and observing the changing aging population and their needs, is likely to be essential.

The challenge to all of these trials is that the heterogeneity of CSDH means that very large sample sizes are often needed to show significant differences. This offers a recruitment challenge and questions the viability of multiple trials answering the same or similar questions. It is evident that a more collaborative approach in the future may help solve this issue and negate the possibility of duplication of studies. A mini-symposium held at the October 2018 EANS meeting in Brussels led to the establishment of an International COllaborative Research Initiative on CSDH (iCORIC; Fig. 3), and this systematic review is the first piece of work commissioned by the collaborative in order to understand the current status of RCTs in CSDH. It is hoped that this group will support the development of future collaborative trials in this field, and potentially lead an international consensus meeting on CSDH management when many of the current RCTs provide results by 2021/2022. A collaborative approach to research is important and provides the opportunity to share ideas and data and also importantly attempt to harmonise the quality and reporting methods in this complex condition. This has been started with the CODE-CSDH project which was established in 2015 to review how data elements and outcomes are reported in the CSDH literature, and highlighted wide heterogeneity in terms, scales and time points [7, 8]. The iCORIC group plan to take this forward by publishing work on a clear definition for CSDH, including an International Classification of Diseases (ICD) code, which does not currently exist. Following this, we aim to set out clear, robust terminology and outcomes which will be recommended for all future CSDH publications so that comparison between studies and systematic review will be easier and more reliable.

Additionally, one should not forget that CSDH is not just a disease of Western societies, but it is also frequently seen in LMICs. This review highlights that nearly all the current RCTs are taking place in high-income countries, with the possible exception of China, which has a growing economy but still limited resources in large rural areas. In many LMICs, the surgical treatment of CSDH is often delayed since access to CT is difficult, and patients are usually misdiagnosed with other neurological problems [50]. The CSDH population in LMICs also tends to be younger, have less comorbidity and are less likely to be on antithrombotics, as the threshold for using these for cerebrovascular prophylaxis disease is much higher than that in Western societies. These factors may have implications with regard to the recurrence risk and therefore the necessity for interventions such as post-operative subdural drains [62]. One study from Ghana reported much lower recurrence rates compared with high-income settings, but as there is only scanty literature on surgical techniques in LMICs, it is hard to make direct comparisons [32, 51]. Due to the limited neurosurgical workforce in LMICs [30], there is also some interest in task-sharing; for example, in a recent study, general surgeons performed burr hole evacuations of CSDH in rural Kenya with good results [49]. Overall, research from LMICs is severely limited and we hope to address this to some extent with this international collaborative, targeting engagement from countries throughout the world.

Despite the breadth of RCTs identified in this review, there are still many opportunities to grow the research field in CSDH and answer important questions. There is also evidence of cross-over between trials, which could be addressed with a more collaborative approach. It is intended to expand this collaboration to further countries worldwide and network with other relevant specialities and professionals involved in CSDH research and management to support this growing field.

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