

Atorvastatin combined with dexamethasone in chronic subdural haematoma (ATOCH II): study protocol for a randomised controlled trial

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Study protocol

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Abstract

Background

Chronic subdural haematoma (CSDH) is a common condition in the elderly that often requires neurosurgical management. For small CSDH, evidence has emerged that statins may reduce haematoma volume and improve outcomes, presumably by reducing local inflammation and promoting vascular repair. We wish to extend this evidence in a study that aims to determine the efficacy and safety of atorvastatin combined with low-dose dexamethasone in patients with CSDH.

Methods

The second ATorvastatin On Chronic subdural Hematoma (ATOCH-II) study is a multi-center, randomized, placebo-controlled, double blind trial which aims to enroll 240 adult patients with a conservative therapeutic indication for CSDH, randomly allocated to standard treatment with atorvastatin 20 mg combined with low-dose dexamethasone (or matching placebos) daily for 28 days, and with 152 days of follow-up. The primary outcome is a composite good outcome defined by any reduction from baseline in haematoma volume and survival free of surgery at 28 days. Secondary outcomes include functional outcome on the modified Rankin scale (mRS) and modified Barthel Index at 28 days, surgical transition, and reduction in haematoma volumes at 14, 28 and 90 days.

Discussion

This multi-centre clinical trial aims to provide high-quality evidence on the efficacy and safety of the combined treatment of atorvastatin and low-dose dexamethasone to reduce inflammation and enhance angiogenesis in CSDH.

Trial registration:

ChiCTR, ChiCTR1900021659. Registered 3 March 2019, <http://www.chictr.org.cn/showproj.aspx?proj=36157>

Background

Chronic subdural hematoma (CSDH) represents one of the most common forms of intracranial haemorrhage, causing a variety of diagnostic and therapeutic challenges as rates increase in ageing populations and increased use of antithrombotic agents.^{1,2} Evacuation of CSDH through twist-drill or bur-hole craniotomy remains the main form of treatment for symptomatic patients,³ but surgery is associated with high risks of operative complications and recurrence.⁴ Non-surgical options include the use of

mannitol, glucocorticoids, angiotensin converting enzyme inhibitors, tranexamic acid, and platelet activating factor receptor inhibitor, but none have been shown to be clearly effective.⁵⁻⁸

Impaired angiogenesis and inflammation of the surrounding neomembrane may be important in the pathophysiology of CSDH, promoting the slow expansion of blood from immature 'leaky' vessels after trauma.^{7,9} The pleiotropic effects of statins on inflammation and endothelial progenitor cell activity,¹⁰⁻¹⁴ which may promote haematoma reabsorption, was recently tested in the ATorvastatin On Chronic subdural Hematoma (ATOCH) study, a multicenter double-blind placebo-controlled randomised trial in China.¹⁵ The positive results of atorvastatin 20 mg daily significantly reduced haematoma volume and improving clinical outcomes¹⁵ has had a major impact on clinical practice in China, with this medical treatment being widely adopted for both primary conservative and adjunctive post-surgical management of CSDH.^{16,17} However, additional strategies are warranted, as response to atorvastatin is slow in many patients and ineffective over several weeks of treatment in 10% patients.¹⁵ Moreover, any benefits of atorvastatin at high dose may be offset by adverse effects, such as intracranial haemorrhage,¹⁸ and may not any greater efficacy than at low-dose.¹³ Dexamethasone had shown some effect on CSDH, but it is also complicated by adverse effects, particularly at high dose.¹⁹⁻²² We therefore initiated the second Atorvastatin combined with dexamethasone in Chronic subdural Haematoma (ATOCH-II) trial to determine the efficacy and safety of dexamethasone combined with low-dose atorvastatin in patients with CSDH.

Research question

The primary aim of ATOCH-II is to determine whether the combination of low-dose atorvastatin and low-dose dexamethasone is superior to low-dose atorvastatin alone on the composite outcome of haematoma volume, transition to surgery, and death at 28 days in patients with CSDH.

Methods

Design

ATOCH-II is a multicentre, prospective, double-blind, placebo-controlled, randomised trial involving 240 patients with CSDH to be recruited from 14 neurosurgery centres in China who are collaborative partners in the Oriental Neurosurgical Evidence-based Study Team (ONET).²³ ONET is the first neurosurgical professional organization devoted to evidence-based medicine in China (Chair, Department of Neurosurgery, Tianjin Medical University General Hospital) with the mission to establish clinical research thinking, train clinical researchers, conduct randomised trials, and promote the development of evidence-based medicine in neurosurgery.

Patient inclusion and exclusion criteria

The study population will be drawn from consecutive patients with CSDH admitted to ONET neurosurgical centres. Patients are eligible who meet all of the following inclusion criteria: age ≥ 18 and ≤ 90 years; diagnosis of supratentorial (unilateral or bilateral) CSDH confirmed on CT imaging within 72 hours after admission; a single unilateral hematoma ≥ 10 mL; pre-morbid functional independence, estimated according to scores 1 (no symptoms), 2 (symptoms), or 3 (some disability but independent in function) on the modified Rankin scale (mRS); the attending physician's judgment that cerebral herniation and/or surgical evacuation are unlikely to occur; and the provision of informed consent, or by an appropriate proxy according to local requirements.

Exclusion criteria include: known allergy to a statin (<4 weeks), glucocorticoid or their ingredients; considered to have a high likelihood of cerebral trauma or cerebral herniation and/or requirement surgical evacuation or decompression; structural lesions including tumor, haematologic diseases, tuberculous, arachnoid cyst, vascular malformation, ventricular peritoneal shunt or other severe co-morbidity; abnormal liver function, hepatitis or uncontrolled liver disease, as well as other disease that has an influence of prognosis or the ability to assess the study outcomes; uncontrolled diabetes mellitus, with blood glucose levels consistently >10 mmol/L; history of femoral head necrosis; recent (<4 weeks) corticosteroid or anticoagulation use, or abnormal coagulation function (<4 weeks); likelihood of pregnancy or breastfeeding during the course of the study; participation in another clinical trial (<4 weeks); high likelihood of poor adherence to the treatment or follow-up schedule; and any other reason according to the opinion of the attending clinician researcher.

Randomisation and blinding

Eligible patients are centrally randomised in a 1:1 allocation ratio to intervention (atorvastatin combined with low-dose dexamethasone) and control (atorvastatin combined with matching placebo) groups using a blocked randomization method via a data acquisition system for electronic data capture (DAS for EDC, Version 5.0) developed by Stemexcel Technology Co. Ltd., Beijing. DAS for Interactive Web Response System (IWRS) is used to assign the randomization number to the treatment allocation and drug distribution, and each center will compete to recruit subjects.

Study intervention

All patients are to take oral 20 mg atorvastatin (one tablet) daily for 4 weeks as a standard of care. Those patients allocated to the intervention group will receive extra dexamethasone with the dose of 0.75mg per once for three times daily during the first 14 days, and thereafter the dose will be reduced to twice daily for 7 days, and then once a day for another 7 days. Thus, a total of 560 mg atorvastatin and 47.25mg dexamethasone will be taken 28 days. Patients assigned to the control group will receive the same open atorvastatin regimen but also placebo dexamethasone in the same schedule over 28 days.

Study medication is provided free of charge to participants: atorvastatin by Pfizer Inc. and dexamethasone by Tianjin Pacific Pharmaceutical Co. Ltd. (Tianjin, China). The placebo dexamethasone, which is composed of dextrin and with the same weight and appearance as dexamethasone, is made by

Tianjin Pacific Pharmaceutical Co. Ltd. (Tianjin, China), which has a certification of good manufacturing practice for pharmaceutical products (GMP) issued by the State Food and Drug Administration of China. Study medication is packed identically and labeled 'for clinical study use only' with a packaging number, verification code, dosage, specifications, storage, batch number, duration of usage, and manufacturer.

A statistician and staff independent of the study research team oversee packaging of the study medication, with use of a package number and drug verification code on the tag. Each participant is allocated a unique number to be applied to a drug package number for dispensing and consistency in the database.

Study procedures

Baseline demographic and clinical features, including medical history, severity and type of neurological deficit, and physical and biochemical results, are collected at the time of enrollment in the study. Treatment should be initiated immediately after randomisation (Table). All background care should follow standard guideline recommendations for the management of CSDH in China which includes the withholding of anticoagulation and use of antiplatelet agents; and prescribing prophylactic antiepileptic drugs and regular use analgesics. The Study Flow chart illustrates key steps in the trial (Figure).

Each patient receives an in-person clinical assessment at an outpatient clinic by two attending neurosurgeons who are kept blind to the treatment allocation, every two weeks during the 28-day treatment duration, and then each month thereafter until 180 days post-randomization. If a participant develops any form of neurological deterioration (e.g. altered level of consciousness) that is suggestive of expansion of the haematoma, they may be admitted to hospital for assessment and treatment until their symptoms are relieved or resolve. If surgery is undertaken for a deteriorating patient, the randomised oral study medication is to be resumed as soon as possible after the operation until the end of the planned 28-day treatment period.

Treatment compliance is monitored through pill counts and regular contact with participants, with instructions to adjust medication dosage at weekly outpatient clinic visits. The use of other medications is recorded, including their name, dose, and duration of treatment. Any change in haematological and biochemical markers, such as liver function tests, and side-effects such as myalgia, constipation, and other possible drug-related symptoms, will be recorded.

At the end of the 28-day treatment period, haematoma volume will be re-evaluated on repeat CT scans and the following treatment regimens considered: (i) if the haematoma has resolved or present in a very small amount, the investigator can stop study treatment and only conduct follow-up observations until 180 days; (ii) if the haematoma appears reduced but still present, the investigator can decide either to consider ceasing medication and observing considering early surgery; (iii) if there is no obvious change in the haematoma, two researchers can jointly determine whether to continue conservative management or undertake surgery; and (iv) if the amount of haematoma is increased, the patient may undergo surgery. All details of any treatment during the 180 days study period are recorded.

Outcomes

The primary outcome is a composite of 'good outcome', including any reduction in subdural haematoma volume from baseline and free of surgery and death within 28 days of the treatment. The haematoma volume is measured centrally using the Tada formula of maximal length (L) × maximal width (W) × maximal thickness (H), divided by 2,²⁴ on the acquired CT images by 3 independent neuroradiologists blind to treatment location. Details of the location, density, and compartment of the haematoma are also recorded.

Secondary outcomes include: functional outcome according to a 'shift' in the distribution of the full range of scores on mRS at 28 days; function on the modified Barthel Index measure of activities of daily living (ADL-BI) at 28 days; surgical intervention at 28, 90 and 180 days; and reduction in haematoma volume at 14, 28 and 90 days.

Safety

Details of all the adverse events will be recorded in hospital and via outpatient clinic follow-up visits as well as via telephone checks until 180 days. Those reporting an adverse event will have a comprehensive physical examination to document vital signs (body temperature, heart rate, respiratory rate and blood pressure) and general items for any positive signs (coverage of the skin, eye, ear, nose, throat, lung, heart, stomach, skeletal muscle, limbs and nervous system); and laboratory tests of haematology, biochemistry and renal function, lipid profile, and coagulation, and myoglobin and creatine kinases in patients with suspected rhabdomyolysis; and electrocardiography.

A serious adverse event (SAE) is defined as an event with causing or with potential to cause, significant harm or requiring medical intervention, whether or not it is considered related to the study treatment. A non-serious adverse event is defined as any undesirable medical experience occurring to a patient, including abnormal laboratory values without clinical consequences.

All SAEs are to be reported within 24 hours of the site investigator becoming aware, and a full report is to be filled to the sponsor and the state food and drug administration (SFDA). The ethics committee of pharmaceutical affairs of ONET will conduct an investigation to confirm the causes of an SAE, decide whether the participant can continue with study medication and deal with the related participants complications and adverse events. All patients are to be follow-up according to the intention-to-treat (ITT) principle.

Sample size

We estimate a sample size of 240 patients will provide 90% power to detect a treatment effect of 20% absolute improvement in the primary composite good outcome, after considering a 5% loss-to-follow-up at 4 weeks, then 240 patients in total with 120 per group is needed to be recruited for this study and good outcome in the single atorvastatin control group of 62.6% being consistent with the single atorvastatin

group of the ATOCH trial(48 of 81),¹⁵ a pilot trial showing 20 of 30 patients had a good outcome in a single atorvastatin group,²⁴ and medical record data showing 9 of 12 patients had a good outcome at a single center in 2017.¹⁷ The combined drug treatment effect was assumed to be consistent with the percentage of good outcome found in 29 of 30 patients in a pilot clinical trial²⁴ and 95 of 108 patients medical record from our single center showing with a good outcome.

Data management and quality control

Data management will be performed by the Stemexcel Technology company, Beijing, China²³ using specially designed case report forms (CRF) on a DAS for EDC system. All CRFs are first examined and verified by 2 investigators at each study site, before a data manager undertakes further central checks and confirmation or correction of any errors or inconsistencies via a clinical monitor before finalization of the data. The CRF will be inspected by an assigned person at regular intervals throughout the trial in order to verify adherence to the protocol. Data lock occurs when all subjects have completed their follow-up and there are no outstanding data queries.

Statistical analysis

The primary analysis will be performed according to the modified ITT principle, comprising all randomized participants. A per-protocol analysis will also be undertaken for all participants who have taken at least one dose of the trial medication and complete at least one follow-up assessment. The description of indicators will be by number of cases (and percentages) for categorical variables, and mean (standard deviation) or median (interquartile range) for continuous variables. The Chi-square test and logistic regression with adjustment for site, age, sex, and baseline haematoma volume will be adopted for the comparison of the primary outcome between treatment groups. For secondary outcomes, the Student's t-test or non-parametric Wilcoxon tests will be performed for continuous outcomes and the Chi-square test for dichotomous outcomes, respectively. Ordinal logistic regression will be used for analysis of the shift in the full range of scores on the mRS. All statistical tests are two-sided, with a p-value <0.05 indicating statistical significance. All analysis will be conducted using SAS 9.4 (SAS Institute Inc. US).

Ethics and dissemination

All ethical and legal requirements are required to be met before any subject is enrolled in the trial. The study protocol, participant information sheet and consent form are to be approved according to local and national regulations, centrally by the ethics committee of Tianjin Medical University General Hospital and at ethics committees of each participating site. Participants are to be made aware of the investigational nature of the study. The study will be conducted according to the Declaration of Helsinki (2008) and the results reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Discussion

Although there is natural re-absorption of the haematoma of CSDH,^{25, 26} most neurosurgeons recommend surgical evacuation in symptomatic patients despite limited randomised evidence.²⁷ However, the ATOCH trial has attracted considerable attention in suggesting an effective medical therapy with low-dose atorvastatin in those with mild and stable CSDH.^{6, 16, 17} In China, an expert consensus statement now advocates for atorvastatin being standard treatment for CSDH, offering reduced overall healthcare costs and avoidance of surgery. Yet, the treatment has only a modest effect over several weeks duration, and some 10% of patients failure to respond.¹⁵ A short course of combined low-dose atorvastatin and low-dose dexamethasone may enhance the anti-inflammatory effect of either treatment alone.²⁴

ATOCH-II aims to extend the results of ATOCH in determining the combined effects of low-doses of atorvastatin and dexamethasone over 28 days on reduction in haematoma volume and survival free of surgery. We chose not to use change in the neurological impairment as an outcome because most patients have some change in neurological status at the time of diagnosis of CSDH, and for which any temporal change can be difficult to objectively measure in a short-term open study. Conversely, the use of the mRS and ADL-BI as secondary outcomes reflects their wide use as standard measures of functional status and which reflect neurological status.

We recognize several potential concerns or limitations in this surgical trial, in particular of selection bias introduced because of the judgment of doctors in their interpretation of the recruitment criteria in the decision to avoid early surgery. Surgery is likely to be preferentially chosen in those considered at high risk of cerebral herniation, according to contemporary practice, while patients with mild-moderate sized haematomas and mild symptoms only represent a subgroup of all CSDH. Finally, as this trial will be conducted exclusively among Chinese patients in China, there may be concerns over the generalizability of the findings to other races/ethnicities and health care systems.

Trial status

All ethics committee approvals were granted for the study to commence across all participating hospitals in China. The study is registered on March 3, 2019 (ChiCTR1900021659). Patient enrolment commenced March 15, 2019, with version 2.0 of the protocol. As of 10th Aug 2020, 70 patients have been enrolled. The expected date for completion of recruitment is July 30, 2021.

Abbreviations

ATOCH: atorvastatin on chronic subdural hematoma; mRS:modified Rankin scale; CSDH:chronic subdural hematoma; ONET:Oriental Neurosurgical Evidence-based Study Team; CT:Computerized tomography; DAS:Data Acquisition System; EDC:Electronic Data Capture; IWRS:Interactive Web Response System;

GMP:pharmaceutical products; ADL-BI:Daily Life-the Barthel Index scale; SAE:serious adverse event; SFDA:state food and drug administration; CRF:Case report form.

Declarations

Ethics approval and consent to participate

The protocol has been approved by the Research and Ethics Committee of the IMSS (CNIC registry number: IRB2018-088-01). The procedures are in compliance with the SPIRIT guidelines and letter of the Declaration of Helsinki, the conditions and principles of GCP, applicable local regulatory requirements and laws. Before enrollment, patients or their family guardians, are fully informed of the trial, its potential outcomes and adverse events, and are to provide informed consent.

Consent for publication

Not applicable

Availability of data and materials

Not applicable, no datasets are included in this study protocol.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JNZ and RJ designed the study, with input from XL and CA. DW and YT conceived the study, and participated in its design and coordination, and drafting of the manuscript. SZ, RW, DK, ZZ, JJW, YH, XZ, JW, XJ, CG, HW, SZ, WQ, SY, PL and LS adapted the protocol to Chinese conditions and elected the study sites. All authors commented and approved the final manuscript.

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References

1. Miranda LB, Braxton E, Hobbs J, Quigley MR. Chronic subdural hematoma in the elderly: not a benign disease. *J Neurosurg*. 2011;114:72–6.
2. Huang J, Tian Y, Song Y, et al. Effect of Different Factors on the Short-Term Outcome of Chinese Patients With Primary Chronic Subdural Hematoma at Different Age Groups: A Two-Center Retrospective Study. *Front Aging Neurosci*. 2019;11:325.
3. Motiei-Langroudi R, Stippler M, Shi S, et al. Factors predicting reoperation of chronic subdural hematoma following primary surgical evacuation. *J Neurosurg* 2017:1–8.
4. Rovlias A, Theodoropoulos S, Papoutsakis D. Chronic subdural hematoma: Surgical management and outcome in 986 cases: A classification and regression tree approach. *Surg Neurol Int*. 2015;6:127.
5. Soleman J, Nocera F, Mariani L. The conservative and pharmacological management of chronic subdural haematoma. *Swiss Med Wkly*. 2017;147:w14398.
6. Holl DC, Volovici V, Dirven CMF, et al. Pathophysiology and Nonsurgical Treatment of Chronic Subdural Hematoma: From Past to Present to Future. *World Neurosurg* 2018.
7. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ. Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. *J Neuroinflammation*. 2017;14:108.
8. Poulsen FR, Munthe S, Soe M, Halle B. Perindopril and residual chronic subdural hematoma volumes six weeks after burr hole surgery: a randomized trial. *Clin Neurol Neurosurg*. 2014;123:4–8.
9. Osuka K, Watanabe Y, Usuda N, et al. Inhibitory Mechanism of the Outer Membrane Growth of Chronic Subdural Hematomas. *J Neurotrauma*. 2017;34:1996–2000.
10. Oikonomou E, Siasos G, Zaromitidou M, et al. Atorvastatin treatment improves endothelial function through endothelial progenitor cells mobilization in ischemic heart failure patients. *Atherosclerosis*. 2015;238:159–64.
11. Lin LY, Huang CC, Chen JS, et al. Effects of pitavastatin versus atorvastatin on the peripheral endothelial progenitor cells and vascular endothelial growth factor in high-risk patients: a pilot prospective, double-blind, randomized study. *Cardiovasc Diabetol*. 2014;13:111.
12. Araujo FA, Rocha MA, Mendes JB, Andrade SP. Atorvastatin inhibits inflammatory angiogenesis in mice through down regulation of VEGF, TNF-alpha and TGF-beta1. *Biomed Pharmacother*. 2010;64:29–34.
13. Wang D, Li T, Wei H, et al. Atorvastatin enhances angiogenesis to reduce subdural hematoma in a rat model. *J Neurol Sci*. 2016;362:91–9.
14. Li T, Wang D, Tian Y, et al. Effects of atorvastatin on the inflammation regulation and elimination of subdural hematoma in rats. *J Neurol Sci*. 2014;341:88–96.

15. Jiang R, Zhao S, Wang R, et al. Safety and Efficacy of Atorvastatin for Chronic Subdural Hematoma in Chinese Patients: A Randomized Clinical Trial. *JAMA Neurol.* 2018;75:1338–46.
16. Tang R, Shi J, Li X, et al. Effects of Atorvastatin on Surgical Treatments of Chronic Subdural Hematoma. *World Neurosurg.* 2018;117:e425–9.
17. Chan DY, Chan DT, Sun TF, Ng SC, Wong GK, Poon WS. The use of atorvastatin for chronic subdural haematoma: a retrospective cohort comparison study. *Br J Neurosurg.* 2017;31:72–7.
18. Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA.* 1996;275:128–33.
19. Prud'homme M, Mathieu F, Marcotte N, Cottin S. A Pilot Placebo Controlled Randomized Trial of Dexamethasone for Chronic Subdural Hematoma. *Can J Neurol Sci.* 2016;43:284–90.
20. Zhang Y, Chen S, Xiao Y, Tang W. Effects of Dexamethasone in the Treatment of Recurrent Chronic Subdural Hematoma. *World Neurosurg.* 2017;105:115–21.
21. Yao Z, Hu X, Ma L, You C. Dexamethasone for chronic subdural haematoma: a systematic review and meta-analysis. *Acta Neurochir (Wien).* 2017;159:2037–44.
22. Thotakura AK, Marabathina NR. Nonsurgical Treatment of Chronic Subdural Hematoma with Steroids. *World Neurosurg.* 2015;84:1968–72.
23. Jiang R, Wang D, Poon WS, et al. Effect of ATorvastatin On Chronic subdural Hematoma (ATOCH): a study protocol for a randomized controlled trial. *Trials.* 2015;16:528.
24. Wang D, Gao C, Xu X, et al. Treatment of chronic subdural hematoma with atorvastatin combined with low-dose dexamethasone: phase II randomized proof-of-concept clinical trial. *J Neurosurg* 2020:1–9.
25. Junior MGP, Pessoa BL, Landeiro JA, de Abreu Macedo PH, Leite MAA. Spontaneous resolution of chronic subdural hematoma: Does only the size matter? *Surg Neurol Int.* 2019;10:194.
26. Kim HC, Ko JH, Yoo DS, Lee SK. Spontaneous Resolution of Chronic Subdural Hematoma: Close Observation as a Treatment Strategy. *J Korean Neurosurg Soc.* 2016;59:628–36.
27. Huang J, Gao C, Dong J, Zhang J, Jiang R. Drug treatment of chronic subdural hematoma. *Expert Opin Pharmacother* 2020:1–10.

Tables

Table Visit and assessment schedule

ADL-BI denotes activities of daily life on the Barthel Index, mRS the modified Rankin scale

1. Accreditation of laboratory examination within 3 days, including head CT, before enrollment
2. Combined use of drugs before commencing study treatment and continue until the end of the 28-day treatment period.
3. During conservative treatment, if a participant's neurological function deteriorates associated with an increase in the size of the haematoma and risk of cerebral herniation, they must change over to

surgical treatment.

4. Remaining drugs are to be recycled.

Items	Screen	Day 1	Day 7±1	Day 14±1	Day 28±3	Day 90±7	Day 180±7
Informed consent	×						
Inclusion/exclusion ¹	×						
Filling general information	×						
Collect medical history	×						
Concomitant medications ²	×	×	×	×	×		
Physical examination	×						
Surgery		×	×	×	×	×	×
Neurological symptoms ³	×	×	×	×	×	×	×
Haematoma volume ³	×			×	×	×	
mRS ³	×				×	×	×
ADL-BI					×	×	×
Blood routine	×	×		×	×		
Biochemistry	×	×		×	×		
Coagulation	×	×		×	×		
Vital signs ³	×	×	×	×	×		
Electrocardiography	×			×	×		
Adverse events		×	×	×	×	×	×
Allocate random number	×						
Drug recycling ⁴	×	×	×	×	×		

Figures

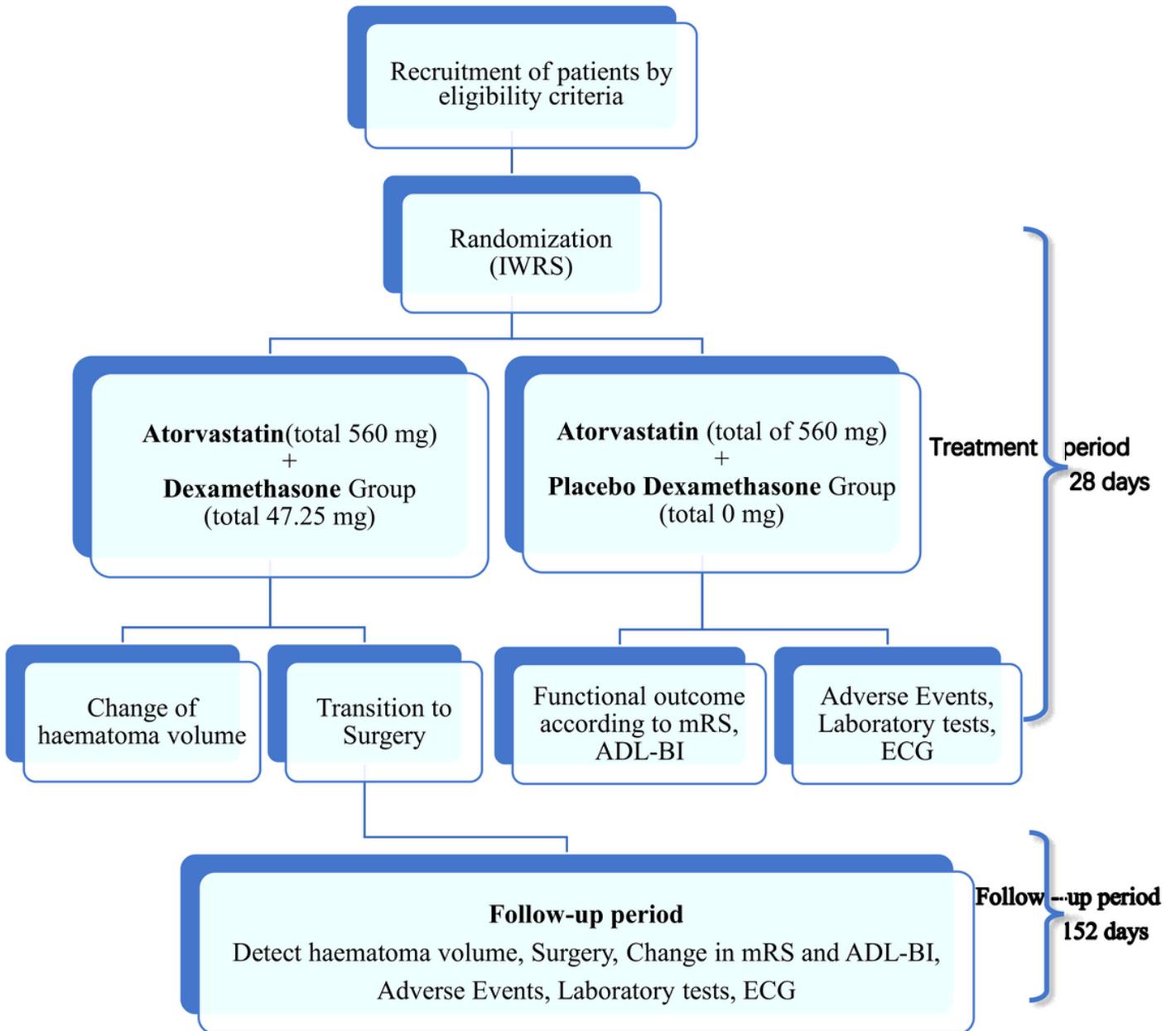


Figure 1

Flow chart to illustrate the design of the trial. Footnotes: ADL-BI denotes activities of daily life on the Barthel Index; ECG electrocardiography; IWRS Interactive Web Response System; mRS modified Rankin scale

Supplementary Files

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