BMJ Open

Continuation versus discontinuation of aspirin-based antiplatelet therapy for perioperative bleeding and ischaemic events in adults undergoing neurosurgery: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Antiplatelet therapy is commonly used in primary or secondary prevention of atherosclerotic and thrombotic diseases, such as coronary artery disease, transient ischaemic attack or stroke. Recent studies noted that antiplatelet therapy should be continued perioperatively in patients at high risk of thrombosis and low bleeding risk in orthopaedic, spinal or urological surgery. However, evidence in neurosurgery is lacking. Thus, we aim to conduct a systematic review and meta-analysis to assess whether the continuous use of antiplatelet drugs in neurosurgery increases the risk of perioperative bleeding.

Methods and analysis We will search PubMed, Cochrane Central Register of Controlled Trials and Embase using a strategy that combines the terms aspirin, bleeding/ischaemic and neurosurgery. Two reviewers will independently screen all identified abstracts for eligibility and evaluate the risk of bias of the included studies using the Cochrane risk of bias tool for randomised controlled studies and the Newcastle-Ottawa Scale for observational studies (including cohort studies, case–control studies, case series). Discrepancies will be resolved by consultation with a third researcher. We will conduct a systematic review and meta-analysis. If evidence suggests moderate statistical or clinical heterogeneity, we plan to investigate this heterogeneity by performing subgroup analyses and sensitivity analysis.

Ethics and dissemination No ethics approval will be sought as no original data will be collected for this review. Findings will be disseminated through peer-reviewed publication and conference presentations.

PROSPERO registration number CRD42020202590.

Strengths and limitations of this study

► The 'grey areas' of neurosurgery perioperative anticoagulant drug management are a focus of this study.
► Unpublished ongoing clinical studies are searched using the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov.
► Standardised and universal evaluation criteria, Cochrane risk of bias tool and Newcastle-Ottawa Scale are used for risk of bias assessment.
► Grading of recommendations assessment, development and evaluation is used to grade the evidence of all the outcomes.
► No language restrictions will be applied.

BACKGROUND

Antiplatelet therapy plays an important role in primary or secondary prevention of atherosclerotic and thrombotic diseases, such as coronary artery disease, transient ischaemic attack or stroke, coronary or carotid artery stent implantation.[1 2] There are three main types of antiplatelet drugs: cyclooxygenase-1 inhibitors (aspirin), oral P2Y12 inhibitor (thienopyridines include the ticlopidine, clopidogrel and prasugrel), protease-activated receptor inhibitors (vorapaxar). Many people are prescribed with single drug (aspirin or P2Y12 inhibitor) or dual antiplatelet drugs (aspirin +clopidogrel/ticagrelor).[3–6]

WHO estimated that 312.9 million surgeries occurred in 2012, representing an increase of 226.4 million surgeries from 2004. This number may increase drastically by 2020.[7 8] In addition, the world elderly population reached 9% in 2019, and it has 'aged' by 2.11% in only 19 years. With more surgeries and more elderly people, the population undergoing surgery and administered antiplatelet drugs may continue to increase. This population will face an increasing risk of adverse outcomes, such as both myocardial infarction or stroke, and significant bleeding events are more likely. Whether antiplatelet

drugs need to be stopped prior to elective surgery has become a controversial issue.

The most recent meta-analysis indicated that continuation or discontinuation of antiplatelet therapy before non-cardiac surgery has minimal or no effect on mortality, bleeding requiring surgical intervention or ischaemic events (low-certainty evidence), and there is minimal or no difference in bleeding requiring transfusion (moderate-certainty evidence, this result was limited to few studies, participants and events).[9 10] A systematic review of spinal draws revealed no strong evidence for a difference in intraoperative blood loss, operation time and postoperative complications irrespective of aspirin discontinuation.[11]

The existing systematic review and meta-analysis have methodological shortcomings: (1) Excluded studies in neurosurgery, an extremely difficult and precise surgical operation focusing on the most sophisticated central nervous system of human beings, which has very strict perioperative management procedures and (2) Less high-quality randomised controlled trial (RCT) studies were included. The consequences of perioperative bleeding in neurosurgery are unpredictable, and the occurrence of various embolisms is serious in high-risk patients who have stopped antiplatelet drugs. Routine continuation of antiplatelet therapy prior to neurosurgery is not recommended because it is not associated with benefit and results in an increased risk of bleeding. Low-dose aspirin may be appropriate for a subset of patients when ischaemic risks outweigh bleeding risks, that is, patients with carotid and coronary artery stents. Thus, the risks and benefits for these specific populations should be balanced.

In this study, we will investigate whether the continuous use of antiplatelet drugs in neurosurgery increases the risk of perioperative bleeding.

METHODS AND ANALYSES

To fill the gaps in the knowledge presented above, we aim to conduct a systematic review on continuation versus discontinuation of aspirin-based antiplatelet therapy for perioperative bleeding and ischaemic events in adults undergoing neurosurgery. We will also conduct subgroup analyses to identify the influences of single antiplatelet therapy or combination therapy, intracranial surgeries or extracranial surgeries, time to stop antiplatelet drugs and RCTs or observational studies. We hope this study has guiding significance for the use of perioperative drugs in neurosurgery and gives patients the best prognostic results.

The review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocol guidelines.[12] The PRISMA flow diagram will be used to record every step of the review process (figure 1). We are planning to start the review in July 2021 and to complete it in December 2021 at the latest.
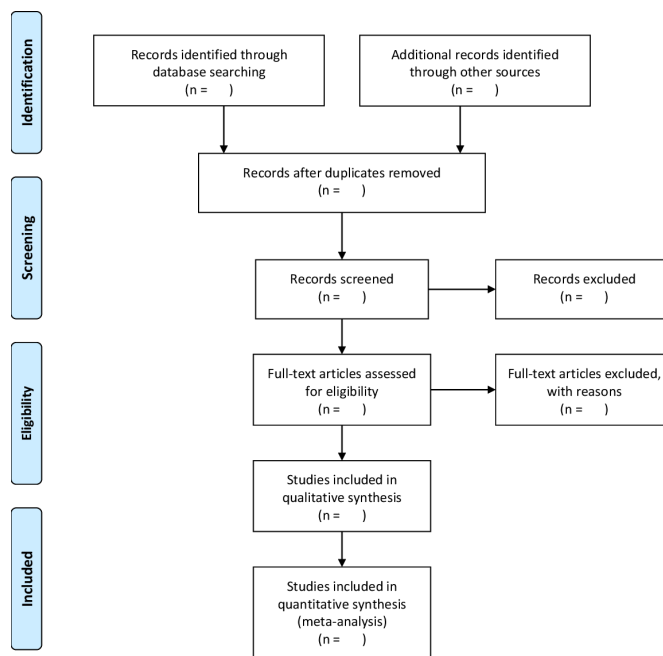

Figure 1 Flow chart diagram presents the selection of articles for systemic review and meta-analysis of continuation versus discontinuation of aspirin-based antiplatelet therapy for perioperative bleeding and ischaemic events in adults undergoing neurosurgery.

Sources of evidence and search strategy

We will include studies published in English in this protocol. The published studies are searched in PubMed, Cochrane Central Register of Controlled Trials and Embase (from the inception dates to 27 August 2021) (tables 1–3). Unpublished ongoing clinical studies are searched from the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov (until 27 August 2021). We conduct backward and forward citation searches of relevant articles (until 27 August 2021).We will continue to update and include the latest articles that meet the search criteria until the deadline The two researchers (XinyW and XinxW) will search separately according to the search strategy described in the tables (tables 1–3).

Inclusion and exclusion criteria

To be included in this systematic review, studies must fulfil each of the criteria outlined below.

Research type (S)

RCT, non-RCT study, observational study (cohort study, case–control study and case series)

Participant (P)

Inclusion criteria: Adults (18 years old or older) taking antiplatelet drugs for at least 2 weeks; scheduled for elective or emergency neurosurgery under general anaesthesia (craniotomy, spinal cord surgery, neurointervention procedure); aspirin-based antiplatelet therapy was prescribed, such as aspirin, clopidogrel, prasugrel, ticlopidine or ticagrelor; at least one risk factor for heart

Table 1 Search strategy for PubMed

ID	Query
#1	Aspirin [MeSH Terms]
#2	Acetylsalicylic Acid [Title/Abstract])) OR (2-(Acetyloxy)benzoic Acid [Title/Abstract])) OR (Acylpyrin [Title/Abstract]
#3	#1or #2
#4	Neurosurgery [MeSH Terms]) OR (Neurosurgical Procedures [MeSH Terms])
#5	(Procedure, Neurosurgical[Title/Abstract])) OR (Procedure, Neurosurgical[Title/Abstract])) OR (Neurologic Surgical Procedure[Title/Abstract])) OR (Procedure, Neurologic Surgical[Title/Abstract])) OR (((intracranial hematoma, traumatic[MeSH Terms]) OR (traumatic brain injuries[MeSH Terms]))
#6	(surgery or (operative and procedure*) or (operative and surgical and procedure*) or (surgical and procedure*)).mp
#7	#4 or #5 or #6
#8	(Hemorrhage [MeSH Terms]) OR (Bleeding [MeSH Terms])
#9	((Ischemia [MeSH Terms]) OR (ischemi*[Title/Abstract])) OR (ischaemic*[Title/Abstract])
#10	#8 or #9
#11	(("Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Non-Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh]) OR ("Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh])) OR ("Observational Study" [Publication Type] OR "Observational Studies as Topic"[Mesh])OR "Cohort Studies"[Mesh]
#12	#3 and #7 and #10 and #11

and cerebrovascular event (such as atrial fibrillation, coronary stent implantation, carotid stent implantation, secondary prevention of stroke, vascular stent implantation in other parts).

Table 2 Search strategy for Cochrane central register of controlled trials

ID	Search
#1	MeSH descriptor: [Aspirin] explode all trees
#2	MeSH descriptor: [Neurosurgery] explode all trees
#3	("Traumatic Brain Injury "or "Brain Injury, Traumatic"): ti, ab, kw (Word variations have been searched)
#4	(intracranial hematoma): ti, ab, kw (Word variations have been searched)
#5	surgery or (operative and procedure*) or (operative and surgical and procedure*) or (surgical and procedure*)
#6	#2 or #3 or #4 or #5
#7	MeSH descriptor: [Haemorrhage] explode all trees
#8	(bleeding): ti, ab, kw (Word variations have been searched)
#9	(ischemi* or ischaemic*): ti, ab, kw (Word variations have been searched)
#10	#7 or #8 or #9
#11	MeSH descriptor: [Randomised Controlled Trial] explode all trees
#12	MeSH descriptor:(Non-Randomized Controlled Trials as Topic)explode all trees
#13	MeSH descriptor: [Clinical Trial] explode all trees
#14	MeSH descriptor: [Observational Study] explode all trees
#15	MeSH descriptor: [Cohort Studies] explode all trees
#16	#11 or #12 or #13 or #14 or #15
#17	#1 and #6 and #10 and #16

Exclusion criteria: Studies that do not meet the inclusion criteria, such as studies that include patients administered platelet drugs for less than 2 weeks or studies with information that is not clearly stated; minor surgeries (such as scalp tumour, scalp trauma); surgeries under local anaesthesia and sedation; single or combined antiplatelet therapy does not include aspirin; outcomes do not include the main outcome of this protocol (perioperative bleeding events: using composite indicators, consisting of intraoperative blood loss, intraoperative blood transfusion and secondary operations due to intraoperative bleeding); cross-sectional studies, experimental studies, .

Intervention and control

Included studies: Continuation of antiplatelet drugs during the perioperative period (aspirin or dual

Table 3 Search strategy for Embase

ID	Query
#1	'acetylsalicylic acid'/exp
#2	'neurosurgery'/exp
#3	'brain hematoma'/exp OR 'traumatic brain injury'/exp
#4	surgery OR (operative AND procedure*) OR (operative AND surgical AND procedure*) OR (surgical AND procedure*)
#5	#2 OR #3 OR #4
#6	'bleeding'/exp OR 'ischemia'/exp
#7	'randomized controlled trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'observational study'/exp OR 'cohort analysis'/exp OR 'clinical trial'/exp
#8	#1 AND #5 AND #6 AND #7

anticoagulant therapy was not stopped before surgery) compared with the group that stopped using all anti-platelet drugs for ≥5 days before surgery.[9] A placebo or no antiplatelet drugs can be used during the withdrawal period.

Exclusion of trial intervention: Studies with dual anti-platelet therapy that just stop one antiplatelet drug during the perioperative period or studies that chose other types of drugs to replace antiplatelet therapy.

Outcomes
The primary outcome is a composite indicator, namely, the incidence of perioperative bleeding events, including intraoperative blood loss, intraoperative blood trans-fusion, and secondary operations due to intraoperative bleeding. Secondary outcomes: (1) Incidence of systemic haemorrhage, including gastrointestinal haemorrhage, cerebral haemorrhage (intracranial haemorrhage, subarachnoid haemorrhage or spinal/epidural haema-roma), and bleeding during tracheal intubation; (2) The incidence of peripheral thrombosis, cerebral infarction and myocardial infarction within 30 days and (3) All-cause mortality (30 days follow-up and 6 months follow-up). We will collect the number of people and incidence related to the outcomes and use relative risks as effect measures.

Languages
English.

Time
Anticipated start date is July 2021, and anticipated completion date is December 2021.

Study records
Data management
Results of the literature search will be imported into an EndNote V.X9.3.3 database, and duplicates will be removed. We will establish several independent groups for each selecting stage in the EndNote database. Abstracts and full-text articles will be uploaded to the database. The extraction information table of final included studies has been designed and the study team will receive training (table 4).

Selection process
We (XinyW and XinxW) will search studies according to the above search formula, separately. The merged results will be imported into Endnote V.X9.3.3, and duplicate studies will be removed.

All searched articles will be selected in a two-stage process. First, the title and abstract will be assessed based on the inclusion and exclusion criteria. The study will be removed if it does not meet the criteria. Next, full texts of articles retained in the first round of screening will be retrieved and examined based on eligibility criteria to confirm their inclusion, and studies that do not fulfil the criteria will be removed.

Both steps of the assessment will be performed inde-pendently by two reviewers (XinyW and XinxW). If

Table 4	Extracted information
Characteristics of included studies	
Study ID	First author +year, for example: Zhang 2020
Study type	For example: randomised controlled trial, non-randomised controlled study, observational study (cohort study, case–control study)
Participants	► Total no of randomised participants ► Inclusion criteria ► Exclusion criteria ► Baseline characteristics Continuation group, discontinuation group (age, gender……) Overall ► Country ► Setting
Interventions	Continuation group Discontinuation group
Outcomes	
Funding	
Study dates	Start and end dates, for example: 31 July 2020

an inconsistency occurs, a third review author resolve conflicts when necessary. We will record reasons for exclu-sion at both stages of the inclusion process.

Data extraction
We (XinyW and XinxW) will independently extract study type (RCT, non-randomised controlled study, cohort study, case–control studies, case series), participants, inclusion criteria, exclusion criteria, baseline character-istics (age, gender, etc), country, setting, interventions (types of drugs, single or dual aspirin-based antiplatelet therapy, dose of drugs), all outcomes (numbers of events and measures of effect), findings and study dates from each included studies (table 4). After data extraction, we will compile the information and import it to excel spreadsheets. When an inconsistency occurs, we will recheck the original document to correct the error. When dealing with missing data, we will contact principal investigators to obtain unreported data or other detailed information.

Risk of bias assessment
We (XinyW and XinxW) will evaluate the risk of bias for each included study independently. The Cochrane risk of bias tool is used to assess randomised controlled studies.[13] The Newcastle-Ottawa Scale is used to assess observa-tional studies.[14 15] The evaluation scale is imported into the Revman software in advance, and specific reasons will be provided for each evaluation characteristic. If an inconsistency occurs, a third review author (YY or RH) will be consulted to resolve conflicts.

Data synthesis

We use Review Manager V.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to perform meta-analysis for outcomes for which we had comparable effect measures from more than one study and when measures of heterogeneity indicated that the pooling of results is appropriate. For each outcome, we calculate risk ratios using the summary data presented in each trial report. We use a Mantel-Haenszel effects model and a random-effects statistical model to account for the variation in different types of neurosurgeries in studies.

If evidence suggests moderate statistical or clinical heterogeneity, we plan to investigate this by performing subgroup and sensitivity analyses. R software is used to conduct subgroup and sensitivity analyses. We will conduct subgroup and sensitivity analyses based on the actual situation of the included studies.

Subgroup analysis will be performed for the following subgroups: (1) Single antiplatelet therapy and combination therapy; (2) Intracranial surgeries and extracranial surgeries; (3) Time to stop antiplatelet drugs during the perioperative period (more than 5 days and less than 5 days are divided into two groups)[9] and (4) RCTs or observational studies.

For sensitivity analysis, we will eliminate included studies one by one to determine the overall impact of an individual study using R software.

The funnel chart is used to express publication bias when the number of final included studies is greater than 10. GRADEpro software is used to grade the evidence of all the outcomes, and this process is completed by two individuals separately.

ETHICS AND DISSEMINATION

No ethics approval will be sought as no original data will be collected for this review. Findings will be disseminated through peer-reviewed publication and conference presentations.

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