Aspin: Neurosurgical Aspirin Intervention Prognostic Study; perioperative continuation versus discontinuation of aspirin in spinal surgery, a randomized controlled, noninferiority trial.

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Co-primary objectives:Hemorrhagic complicationsPerioperative blood lossPerioperative blood loss is determined by measuring blood recovered in the suction device during surgery and weighting of blood saturated gauzes used during surgery. In case a...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON54741

Source
ToetsingOnline

Brief title
Aspin: Neurosurgical Aspirin Intervention Prognostic Study

Condition

- Cardiac disorders, signs and symptoms NEC
- Spinal cord and nerve root disorders
- Embolism and thrombosis

Synonym
Bleeding, stroke

Research involving

Human

Sponsors and support

Primary sponsor: Haaglanden Medisch Centrum
Source(s) of monetary or material Support: HMC Wetenschapsfonds

Intervention

Keyword: Aspin, Aspirin discontinuation, Spinal surgery, trial

Outcome measures

Primary outcome

See study objectives.

Secondary outcome

See study objectives.

Study description

Background summary

Current guidelines regarding the safety of the perioperative (dis)continuation of aspirin for surgical procedures fail to provide clear recommendations regarding patients undergoing cranial and spinal surgery. Currently, aspirin is discontinued in cranial and spinal surgery because of a potential increased risk of hemorrhagic complications. However, this policy might delay surgical procedures and carries the risk of resulting in an increase of cardiac and neurologic thrombotic perioperative events. It is unclear if the possibility for an increase of hemorrhage related complications outweighs the risk of an increase of cardiac and neurologic thrombotic perioperative events. Therefore, a randomized controlled trial is required.

Cardio vascular diseases (CVDs) are the primary cause of death in developed countries, and are expected to be the leading cause of death worldwide.(1) Cardio vascular diseases are a group of illnesses including myocardial infarction, coronary heart disease, stroke and venous thromboembolism. In the primary and secondary prevention of CVDs anticoagulant drugs play a key role, with aspirin being the most commonly used.(1-3) Specifically for the Netherlands, aspirin is prescribed for circa 230.000 patients annually.(4) With the increasing incidence of CVDs, the usage of anticoagulant drugs will

increase forming a problem during surgical intervention.

Currently, there is no consensus whether aspirin should be discontinued before neurosurgical intervention. One of the arguments leading the discussion is the POISE-2 trial by Devereaux et al., in which the conclusion was that procedural continuation of aspirin did not reduce the rates of all-cause mortality of non-fatal myocardial infarction. But it does come together with increased risks of major bleedings.(5)

These results are supported by two reviews that included mostly non-RCT studies. A review and meta-analysis by Burger et al. in non-cardiac surgery showed a significant increase of procedural bleeding complications, without a significant reduction nor increase of death or nonfatal myocardial infarctions. A low dose of aspirin did not significantly differ in bleeding risk or complications or mortality related to it.(6) The same was concluded in the review of Kiberd and Hall.(7)

Another interesting pharmacological phenomenon is the aspirin withdrawal rebound effect, hyperactivity of platelets after interruption aspirin.(8) Even though there is limited knowledge supporting this effect, it leads to clinical caution to discontinue aspirin. Multiple cases in different surgical fields describe fatal thrombo-embolic complication after discontinuing aspirin perioperatively. Limited knowledge is available about the pharmacokinetic availability of aspirin after interruption and the regaining of platelet function thereafter. A small study of Alcock et al. showed, in healthy participants, no evidence for a rebound phenomenon which leaves this argument open for discussion. (9)

These results are contrasted by the study of Oscarsson et al..(10) This randomized, double-blinded, placebo-controlled trial studied the effects of discontinuing aspirin on the occurrence of major adverse cardiac events together with hemorrhagic complications in a diversity of surgical intervention. This study showed a significant reduction in cardiac events perioperatively, a risk reduction of 7.2% and no difference in hemorrhagic complications were found. Note bene, this difference is statistically not significant because of an early termination of inclusion. Additionally, this difference is based on mainly patients undergoing abdominal, urologic, orhopaedic and gynaecologic surgery that are known as immobile patients post-operatively leading to a higher thrombo-embolic risk and are not completely comparable to neurosurgical patients undergoing spinal surgery which is often improving mobility by pain reduction and motor control. Additional to these results, the CLASP-study, a gynecological randomized trial studying the effects of low-dose aspirin in the prevention and treatment of pre-eclampsia in pregnant women, did not observe an increase in uterine, placental of fetal hemorrhagic complications in the study group. Unfortunately, these studies did not include any neurosurgical cases. This restricts the little evidence for continuing aspirin in neurosurgical cases and leads to more interest and

concern in this matter.

A systematic review and meta-analysis regarding the safety of aspirin continuation in spinal surgery was conducted by our research group.(11) Only three non-randomized studies, including 370 patients undergoing cervical, thoracic and lumbar spine surgery were identified. No significant differences in mean perioperative blood loss were seen between the aspirin-continuing group and the aspirin-discontinuing group. Similar non-significant differences between the two groups were found for cardiac events, stroke, and surgical site infections.(12-14)

In addition to spinal surgery, the evidence in cranial surgery is even more limited. A comparative study by Rahman et al. in 83 patients undergoing craniotomy for brain tumor demonstrated no increased risk of perioperative hemorrhage related complications amongst patients continuing aspirin.(15) Additionally, a observational study by Palmer at all, found no association between aspirin and postoperative hemorrhage.(16) In case of cerebral aneurysmatic pathology, aspirin is recommended for unruptured aneurysm and prevents ruptures by its anti-inflammatory effects.(17) In ruptured aneurysm with subarachnoidal hematomas continuation versus discontinuation of aspirin did not lead to significant differences in bleeding risk, bleeding related complications or prevention of secondary ischemia due to vasospasms.(18, 19)

In conclusion, there is a paucity of studies regarding the safety of continuation of aspirin during cranial and spinal procedures, and the available evidence is of low methodologic quality. The hypothesis is that potential bleeding complications in cranial and spinal surgery might exceed the risks reported in other surgical literature. Especially in cranial surgery, a postoperative bleeding may be catastrophic due to the confined space and vulnerability of the surrounding structures, but no studies exist to support this hypothesis. The current clinical practice in patients on aspirin and due to undergo a cranial of spinal is to discontinue aspirin 5-7 days prior to surgery. There is no clinical evidence to support this policy. Therefore, we propose a randomized controlled, non-inferiority study comparing the perioperative (dis)continuation of aspirin in spinal surgery.

Study objective

Co-primary objectives:
Hemorrhagic complications
Perioperative blood loss
Perioperative blood loss is determined by measuring blood recovered in the suction device during surgery and weighting of blood saturated gauzes used during surgery. In case a vacuum drainage system is applied to the surgical wound the amount of blood loss is recorded at the time of removal. Blood loss is registered in the hospital information system and recorded with a case record form that is to be filled out at time of discharge from the hospital.

Hemorrhage related complications
Hemorrhage related complications include surgical site hemorrhages and postoperative subcutaneous, epidural or subdural hematomas. Hemorrhage related complications resulting in an increased length of hospital stay or that require either invasive or non-invasive treatment are recorded in the hospital information system and are recorded with a case record form that is to be filled out at time of discharge from the hospital and during postoperative outpatient clinic visits. Potentially, some complications of cranial and spinal surgery can also be indirectly attributed to hemorrhage related complications. For instance, surgical site hematomas are associated with an increased incidence of postoperative infections. Therefore, the overall 30-day complication rate is recorded and compared among both treatment groups.

Need for reoperation
The incidence of 30-day postoperative reoperation incidence is recorded in the hospital information system and recorded with a case record form at discharge from the hospital and during postoperative outpatient clinic visits. Of particular interest are directly hemorrhage related reoperations. The afore mentioned surgical site hemorrhages and postoperative subcutaneous, epidural or subdural hematomas are infrequent complications spinal surgery. In case these hemorrhages excerpt pressure on the surrounding neurologic structures (e.g. spinal cord, cauda equine, nerve roots or peripheral nerves) a rapid evacuation of the hematoma is required. Furthermore, perioperative hemorrhage related complications can also result in an indirect need for reoperation. For instance, suboptimal nervous tissue decompression or tumor removal due to excessive bleeding during surgery might result in a need for reoperation. Therefore, the overall 30-day reoperation rate is recorded and compared among both treatment groups.

Autologous and allogeneic transfusion requirement
Excessive perioperative blood loss can require postoperative allogenic blood transfusions. The postoperative need for allogenic blood transfusions is registered in the hospital information system and is recorded with a case record form at discharge from the hospital.
The use of autologous blood transfusion is restricted to patients undergoing extensive surgical procedures with high expected blood loss. At the discretion of the surgeon or the anesthesiologist a cell-saver autologous blood recovery system can be used during surgery. Blood recovered by this system is considered perioperative blood loss. In case a significant amount of blood is recovered and the patient is likely to benefit from an autologous transfusion, autologous blood will be transfused back to the patient.

Occurrence of cardio-vascular and cerebro-vascular thrombo-embolic events
All 30-day complications perioperatively after spinal surgery are recorded. During hospital stay and at regular postoperative outpatient clinical appointment within 6-12 weeks after surgery all perioperative complications are

recorded and evaluated in a standardized manner using a case record form. Complications are classified according to a hospital database thesaurus and the severity of the complication is graded (see table 1). The occurrence of postoperative myocardial infarction or cerebrovascular ischemia within 30 days after surgery are of utmost relevance.

Table 1. Grading of complications according to Clavien-Dindo
Grade Description
1A Recovery after non-invasive treatment (e.g. medication, physical therapy)
1B Recovery after invasive treatment (except for operation in an OR) or admission to intensive care
2 Recovery after (re-)operation in an OR
3A Complication still persists or treated at time of registration
3B Complication resulting in to permanent loss of function or disability
4 Death

Study design

The study is a randomized controlled, non-inferiority trial with two parallel groups. Patients are randomly allocated to either perioperative continuation of aspirin or discontinuation group prior to spinal surgery. Thrombotic cardiac and neurologic events, perioperative blood loss, hemorrhage related complications and need for reoperation events within 30 days after surgery are evaluated in both treatment groups.

All patients referred to the outpatient clinic of the department of neurosurgery that are scheduled for spinal surgery are eligible for inclusion. The hospitals participating in this study are:
• Haaglanden Medical Center
• HAGA teaching hospital Den Haag
• Spaarne Gasthuis Haarlem
• Alrijne hospital Leiderdorp

Intervention

The intervention group will be continuing asprin peri-operatively.

Study burden and risks

See study objectives.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Elective spinal surgery
Pre-operative use of aniplatelet drugs
Pre-operative use of aspirin

Exclusion criteria

Spinal oncology
Staged surgeries lasting more than one day
Patients with a pre-existing coagulopathy
Patients using antithrombotic drugs or other platelet aggregation inhibitors than aspirin
Patients with absolute contraindication for discontinuing aspirin (e.g. coronary stenting within 1 year)
Patients aged under 18
Emergency surgical procedures

Incompetence to decide, i.e. in case of severe cognitive impairment or psychiatric illness.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-01-2022
Enrollment:	554
Type:	Actual

Ethics review

Approved WMO

Date:	05-03-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	22-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	26-01-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	04-07-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20747
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL71200.058.20
OMON	NL-OMON20747