Aspirin and spinal haematoma after neuraxial anaesthesia: Myth or reality?

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Abstract

The safety of aspirin therapy in neuraxial anaesthesia has been historically questioned, and the current recommendations are still heterogeneous. A comprehensive review of clinical evidence and a comparative analysis of European and American guidelines were performed. Low-dose aspirin produces a selective, complete and irreversible cyclooxygenase-1 blockade, and higher doses do not increase the antiplatelet effect. Additional cyclooxygenase-2 blockade by high-dose aspirin might decrease the antithrombotic efficacy by inhibiting endothelial prostacyclin synthesis. Different doses of aspirin have been shown to be safe in a broad population subjected to neuraxial anaesthesia or analgesia. In the few case reports of spinal haematoma involving aspirin therapy, additional complicating factors were present. Considering the available evidence, the majority of national scientific societies agree that the isolated use of aspirin does not increase the risk of spinal haematoma and does not represent a contraindication to neuraxial blocks. The precautions regarding higher doses do not seem to be justified. Although aspirin alone is considered to be safe in neuraxial anaesthesia, the concurrent administration of other antithrombotic drugs significantly increases the risk of spinal haematoma and the recommended safety times for each of these other drugs must be strictly followed. An individualized assessment of the risks and benefits should be performed, before performing a neuraxial technique or catheter removal in a patient receiving aspirin.

Key words: anesthesia, epidural; anesthesia, spinal; aspirin; spinal haematoma; platelet aggregation inhibitors

Editor’s key-points

• In this review article, the authors explore the evidence base supporting our clinical practice in neuraxial anaesthetic techniques in patients taking aspirin.
• They explore the pharmacology of aspirin, and describe its impact on the risk of neuraxial bleeding.

Spinal haematoma is an infrequent but potentially catastrophic complication of neuraxial anaesthesia. The incidence was previously estimated at about 1/150000 in epidural anaesthesia and 1/220000 in spinal anaesthesia.11-12 However, more recent data suggest that the frequency is increasing.6-12

Aspirin is the most recommended antiplatelet therapy in primary or secondary prevention of atherothrombotic vascular disease.13-17 Likewise, it is the most widely used antiplatelet drug in perioperative period. In non-cardiac surgery, approximately 18% of patients receive antiplatelet drugs, of which, 82% have treatment with aspirin.18 In a population with a greater risk of perioperative cardiovascular complications, the use of aspirin reaches 36-44%.19-20

Aspirin therapy has been associated with haemorrhagic complications into the spinal canal after neuraxial anaesthesia, resulting in the development of some precautions related to their use.21-23 Although recently there has been a substantial change in the safety criteria regarding aspirin use, the recommendations of the national scientific societies are still heterogeneous.24-32 Aspirin is an important component of many patients’ treatment and their withdrawal can increase the risk of perioperative...
vascular events. On the other hand, neuraxial anaesthesia is a widely used technique, with some advantages related to general anaesthesia. Proper knowledge can reduce the risk of unnecessary suspension of aspirin or avoid the rejection of a potentially beneficial anaesthetic technique.

For clarifying the safety of aspirin in neuraxial anaesthesia, we performed an exhaustive review of the published literature through PubMed and Medline, from 1995 until October 2014, with the key words: aspirin, antiplatelet, antithrombotic, regional anaesthesia, spinal anaesthesia, epidural anaesthesia, neuraxial blocks, spinal haematoma, and epidural haematoma. A comparative analysis of European and American scientific societies’ guidelines was also performed. Additional literature was obtained from the references in the selected articles.

**Pharmacological considerations**

Aspirin inhibits platelet aggregation by irreversible acetylation of platelet cyclooxygenase-1 (COX-1), thus blocking the formation of thromboxane A2, a potent platelet aggregation agonist. Because the platelets are enucleates and cannot synthesize cyclooxygenase-1 de novo, this effect persists until the affected platelets are replaced, a process that takes approximately seven to 10 days. Although megakaryocytes are also affected by aspirin, these can regenerate cyclooxygenase-1 within 12 h. Aspirin is rapidly absorbed in the upper gastrointestinal tract, reaching peak plasma concentrations 30–40 min after ingestion, with a half-life of 15–30 min. However, three to four hours are necessary to reach peak plasma concentrations when using enteric-coated tablets. A dose as low as 30 mg per day is sufficient to completely suppress thromboxane A2 production in five to seven days, and a dose of 100 mg achieved an almost complete suppression of cyclooxygenase-1 activity at 24 h. The increasing doses only reduce the time to maximum inhibition.

Given that platelet replacement is relatively constant, 10–12% of circulating platelets are replaced every day. However, the recovery of thromboxane A2 biosynthesis is faster than expected by the rate of platelet turnover, with a non-linear relationship between inhibition of platelet COX-1 activity and inhibition of thromboxane A2 biosynthesis. In vivo, only 20–30% of platelets with normal COX-1 activity are necessary to retrieve the haemostatic function. Thus, 48–72 h after a last dose of aspirin, the clinical effect on the haemostasis practically disappears.

Depending on the dose administered, aspirin can produce opposing effects on the haemostatic mechanisms. This phenomenon is related to dose-dependent selectivity of aspirin for inhibition of the two cyclooxygenase isoforms: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Human platelets mainly produce thromboxane A2, a product derived from COX-1, and the vascular endothelium cells mainly produce prostacyclin (PGI2), derived mainly from COX-2. Thromboxane A2 induces platelet aggregation and vasoconstriction, whereas prostacyclin inhibits platelet aggregation and causes vasodilation. Low-dose aspirin preferentially inhibits platelet COX-1, preventing thromboxane A2 production. On the other hand, high-dose aspirin can also inhibit COX-2, decreasing the synthesis of prostacyclin of the vascular endothelium, possibly resulting in a paradoxical thrombogenic effect.

When the thrombogenic stimulus is weak, platelet aggregation is dependent on thromboxane A2 production, and aspirin can interfere with primary haemostasis. However, when the thrombogenic stimulus is powerful, and is accompanied by thrombin generation and/or collagen exposure, it can produce activation and platelet aggregation without thromboxane A2 formation.

Currently, there is no recommended test of platelet function for assessing the antiplatelet effect of aspirin in individual patients.
‘Low-dose’ or ‘high-dose’ aspirin - defining the limits and risks

The definitions of ‘high-dose’ and ‘low-dose’ aspirin have not been clearly established in the literature, resulting in confusion when interpreting recommendations on neuraxial anaesthesia and aspirin therapy.

Low-dose aspirin is used in primary or secondary prevention of atherothrombotic vascular disease in order to selectively obtain the antiplatelet effect of aspirin. Although the most recent and relevant studies used doses of 75–325 mg day$^{-1}$, there is a wide variation among the publications, with doses ranging from 50–650 mg day$^{-1}$, up to 100–325 mg every two days.\textsuperscript{45, 46, 61} In vivo, the functional defect in primary haemostasis is of a similar magnitude with a single oral dose of 75–81 mg or 300–325 mg day$^{-1}$.\textsuperscript{1, 40, 61} To achieve maximum efficiency with minimum toxicity, the current recommendations in long-term cardiovascular prevention suggest using doses of 75–100 mg day$^{-1}$, reserving doses of 160–325 mg for acute vascular events, when a faster antithrombotic effect is required.\textsuperscript{4, 12–17}

Low-dose aspirin is used to achieve the anti-inflammatory effect of aspirin, related to the inhibition of induced COX-2 activity in inflammatory cells. This effect requires larger doses of aspirin (greater than 500 mg) and much shorter dosing intervals to achieve a sustained effect, because nucleated cells rapidly resynthesize the enzyme (3000–5000 mg day$^{-1}$).\textsuperscript{40, 67}

Low-dose aspirin achieves a selective, complete and irreversible blockade of platelet COX-1, and higher doses do not increase the antiaggregation effect. Instead, by blocking endothelial COX-2 and inhibiting prostacyclin synthesis, it is possible that higher doses of aspirin could have a paradoxical effect on haemostasis.\textsuperscript{27, 29, 40, 44, 54} Although it is not established that more profound suppression of PGI2 by higher doses of aspirin is sufficient to predispose the subject to thrombosis, three lines of evidence suggest that COX-2 inhibiting could be related to a diminished antithrombotic effect. The first is the observed increase in thrombotic vascular events associated with selective COX-2 inhibitors and a high dose of traditional nonsteroidal anti-inflammatory drugs (NSAIDs).\textsuperscript{68, 69} The second is the increase in platelet activation and thrombosis susceptibility observed in mice lacking the PGI2 receptor.\textsuperscript{70, 71} The third is the indirect data observed in a small number of randomized trials comparing clinical effects of different doses of aspirin and the meta-analysis of the Antiplatelet Trialists’ Collaboration.\textsuperscript{66, 72–74} The ACE Trial reported that the risk of stroke, myocardial infarction, or death within three months of carotid endarterectomy is significantly lower for patients taking 81 or 325 mg day$^{-1}$ aspirin than for those taking 650 or 1,300 mg (6.2 vs 8.4%; P= 0.03). The risk is increased mainly by a higher frequency of thrombotic vascular events (myocardial infarction and ischaemic stroke) in the group taking high doses of aspirin.\textsuperscript{74} According to the meta-analysis of the Antiplatelet Trialists’ Collaboration, aspirin showed a 32% reduction in ischaemic events at doses of 75–150 mg day$^{-1}$, 26% at doses of 160–325 mg day$^{-1}$ and 19% at doses of 500–1500 mg day$^{-1}$.\textsuperscript{40, 65} Thus, both this limited set of randomized comparisons and the indirect comparisons reported in the overview of the Antithrombotic Trialists’ Collaboration, are compatible with blunting of the antithrombotic effect at higher doses of aspirin, consistent with dose-dependent inhibition of PGI2.\textsuperscript{65} (Fig. 1)

These results should not be interpreted as higher doses of aspirin have a protective effect against bleeding. As compared with placebo, aspirin therapy is associated with an increased risk of major bleeding, mainly with gastrointestinal (GI) bleeding and, to a lesser extent, with haemorrhagic stroke.\textsuperscript{52, 75} Aspirin-induced GI toxicity (including GI bleeding) appears to be a dose-related effect.\textsuperscript{76} However, such a relationship is thought to reflect at least two different components: dose-dependent inhibition of COX-1 in the GI mucosa and dose-independent inhibition of COX-1 in platelets.\textsuperscript{40, 61} The clinical effects of different doses of aspirin have been compared directly in a relatively small number of randomized trials. Excluding GI toxicity, bleeding complications were unrelated to aspirin dose.\textsuperscript{72–74, 77–79} Similarly, no differences in bleeding rate between doses from 75–160 or 160–325 mg day$^{-1}$ were described in an extensive systematic review.\textsuperscript{74} A dose-dependent increase in bleeding complications has been previously suggested in a retrospective analysis in 192,000 patients, stratified by aspirin daily doses into low (<100 mg), moderate (100–200 mg), and high (>200 mg) cohorts.\textsuperscript{80} However, several major aspects of this report have been questioned.\textsuperscript{81, 82}

Perioperatively, low-dose aspirin therapy has been related to a quantitative increase in surgical bleeding, without an associated increase in mortality or morbidity.\textsuperscript{20, 23} However, in high-risk bleeding procedures (intracranial and medullary canal surgery, posterior chamber of the eye surgery, tonsillectomy, and transurethral prostatectomy) even this minimally increased risk of bleeding from aspirin may be significant, showing that aspirin should be discontinued.\textsuperscript{83–85} Interestingly, some studies did not find an increase in aspirin-related perioperative bleeding complications in a heterogeneous population undergoing to non-cardiac surgery.\textsuperscript{37, 86–90} On the other hand, in cardiac surgery, a systematic review has suggested that higher doses of aspirin may be associated with an increased risk of surgical bleeding.\textsuperscript{91} However, a more recent study did not confirm these results.\textsuperscript{92} Therefore, with the exception of high-risk bleeding procedures, current recommendations include the maintenance of aspirin throughout the perioperative period for patients at high cardiovascular risk.\textsuperscript{86–89, 94–96}

Aspirin and spinal haematoma: clinical evidence in neuraxial anaesthesia

Spinal haematoma is an infrequent but potentially catastrophic complication of neuraxial anaesthesia. Although the incidence was previously estimated at about 1:150,000 in epidural anaesthesia and 1:220,000 in spinal anaesthesia, more recent data suggest that the frequency may be increasing, particularly in some patient populations.\textsuperscript{1–12} An overall incidence of spinal haematoma ranging from 1:20,000 to 1:58,000 neuraxial blockades has been described, mainly related to epidural anaesthesia rather than spinal anaesthesia.\textsuperscript{8, 10–12} A high incidence of 1:4,000 in patients with indwelling epidural catheters and 1:3,600 in elderly females undergoing orthopaedic surgery under epidural anaesthesia was also reported.\textsuperscript{6, 7, 77} Obstetric populations have a significantly lower incidence of complications (approximately 1:200,000) than their elderly counterparts.\textsuperscript{10} The presence of impaired coagulation increased the bleeding incidence to 1:40,800, 1:6,600 and 1:3,100 patients after spinal anaesthesia, single-shot epidural anaesthesia and epidural catheter techniques, respectively.\textsuperscript{5} Although the case series involved in the first calculations was conducted before implementation of routine perioperative thromboprophylaxis suggesting a causal relationship, a detailed analysis of the causes for increase in spinal haematoma incidence after neuraxial anaesthesia is beyond the scope of this review.

Spinal haematoma represents the most extreme of a continuous spectrum of haemorrhagic phenomena into spinal canal
after neuraxial anaesthesia, with the majority of these spinal haemorrhages clinically silent. Although the source of bleeding is controversial, the temporal sequence in the clinical manifestation of spinal haematomata suggests a venous origin rather than arterial bleeding. The majority of spinal haematomata occur in the epidural space because of a rich epidural network of longitudinally oriented veins, called Batson’s venous plexus. It is thought that after a disruption of spinal vessels during neuraxial blockade, aspirin could interfere with haemostasis, favouring the development of spinal haematomata. However, a traumatic vascular injury is a potent thrombogenic stimulus, with platelet activation and aggregation that are non-dependent on thromboxane A2 formation.

Although aspirin and other non-steroidal anti-inflammatory drugs have been associated with spinal haematoma after neuraxial techniques in published case reports, a careful assessment of the same must be done. In an extensive retrospective review (1906–1994), out of 61 published cases of spinal haematoma after neuraxial anaesthesia, only one identified the isolated use of aspirin as a probable risk factor. However, in this case, in addition to the use of aspirin (650 mg every 12 h starting four h after surgery), a repetitive and traumatic epidural technique, with unintentional dural puncture and spinal catheter placement was described. In a similar retrospective review of 30 patients reported in China (1954–2008), only one identified the continued use of aspirin in the preoperative period, although this study did not include individualized data with regard to the technical difficulty, the dose of aspirin, the timing of administration or the concomitant use of heparin. In another patient, the spinal haematoma was located in a region away from the puncture site, indicating a non-causal relationship between the neuraxial technique and the use of aspirin. Other conditions, such as the concomitant use of multiple antiplatelet drugs or vascular angiomas in the epidural space, have been identified in patients with spinal haematoma associated with peri-procedural aspirin therapy.

On the other hand, the relative safety of aspirin in neuraxial anaesthesia, without an increase in the risk of spinal haematoma has been described in a broad and heterogeneous population. No patients with spinal haematoma were found in a retrospective study of 1013 neuraxial techniques (39% spinal, 61% epidural) although 39% of patients were treated with antiplatelet agents, more than half were taking aspirin in high doses (average: 1889 mg day−1). However, patients receiving antiplatelet medications had an increased incidence of ‘minor’ haemorrhagic events such as blood-tinged cerebrospinal fluid or blood aspirated during needle or catheter placement. Later, a prospective study of 1000 orthopaedic procedures performed with anaesthesia neuraxial showed that even the rate of minor haemorrhagic complications (blood or blood-stained fluid during needle or catheter placement) related to neuraxial anaesthesia was not increased, in spite of the use of aspirin and other non-steroidal anti-inflammatory drugs in 39% of the patients. In half of them, patients took aspirin at doses of 60–4800 mg day−1. There were no documented patients with spinal haematoma. In a multicentre study with patients taking 160 mg day−1 of aspirin or placebo, there were no patients with spinal haematoma among 4603 patients with hip fracture receiving neuraxial anaesthesia. In a pain clinic population, there were no reported major haemorrhagic complications in the spinal canal in a prospective study of 1214 patients using epidural steroids, although 32% were receiving some type of non-steroidal anti-inflammatory, of whom 41% were taking aspirin up to doses of 50–4000 mg per day. In the obstetric population, two extensive studies supported the safe use of low-dose aspirin in neuraxial anaesthesia. In a study for the prevention of preeclampsia, 9634 pregnant women were assigned to 60 mg day−1 of aspirin or placebo. 53% of patients received the study medication within 24 h before delivery. There were 1422 epidural techniques in the group receiving aspirin. There were no patients with spinal haematoma and only three patients with minor bleeding (blood-stained fluid into the catheter) were reported. In a similar study, 3135 nulliparous women were assigned to 60 mg day−1 of aspirin or placebo until delivery. There were 891 epidural techniques, 451 under treatment with aspirin. There were no reported incidences of bleeding related to neuraxial anaesthesia, despite the fact that 13 patients had a bleeding time greater than 10 min.

Although the risk factors for spinal haematoma after neuraxial anaesthesia are not fully known, coagulopathy (existing or acquired) or traumatic neuraxial puncture are now recognized as major risk factors. In conjunction with the use of anticoagulant therapy (particularly heparin), aspirin significantly increases the risk of spinal haematoma after neuraxial anaesthesia. Thromboprophylaxis with heparin can produce a seven-fold increase in risk of spinal haematoma in patients on chronic aspirin therapy. A traumatic neuraxial puncture can increase the risk of spinal haematoma from 11-fold without concomitant heparin therapy, up to 35-fold if heparin is used.

Current guidelines and recommendations in neuraxial anaesthesia

USA

The American Society of Regional Anesthesia (ASRA), in a consensus document published in 2003, established that nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are considered safe in neuraxial blockades, both with single shot and with catheter techniques. Based on available clinical evidence, these recommendations were reaffirmed in a recent update, without identifying specific concerns regarding the dosing or timing of aspirin administration.

European Union

The 2010 European Society of Anaesthesiology (ESA) guidelines, based on three studies previously commented on, clearly established that NSAIDs, including aspirin, do not increase the risk of spinal haematoma and are not a contraindication to neuraxial blocks or catheter procedures, without precise regard to doses. In two of the mentioned studies, high doses of aspirin were also used. Despite these recent changes in the safety criteria regarding aspirin use in neuraxial anaesthesia, the European national scientific societies’ recommendations are still heterogeneous and, in some cases, apparently contradictory.

Spain

A consensus forum in 2001 recommended a systematic withdrawal of aspirin therapy seven days before elective surgery. In 2002, an experts’ meeting suggested that the isolated use of aspirin was safe in neuraxial anaesthesia, without clarification regarding doses. Subsequently, in a consensus document published in 2005, the safety of NSAIDs (including aspirin) in neuraxial anaesthesia was reaffirmed. A 2011 update of the Spanish guidelines regarding perioperative management of antiplatelet drugs stated that aspirin is not a contraindication to neuraxial anaesthesia, without established accuracy regarding doses. However, these recommendations are based on previous documents indicating an increased risk of spinal haematoma with a
dose higher than 300 mg of aspirin, or requiring minimum time intervals before a neuraxial blockade.28 113

Germany

The 2003 German guidelines recommended discontinuing aspirin therapy three days before a neuraxial block.22 114 A 2007 update of the German guidelines established the safety of low-dose aspirin (100 mg) without considerations of higher doses.25 Clinical evidence supporting dose restriction on the recommendations is not indicated. As with the recommendations of the ESA, the safety of aspirin is based on three studies previously discussed, in which high doses of aspirin were also used.102 105 106

Belgium

The 2005 Belgium guidelines established the safety of low doses of aspirin in neuraxial anaesthesia without specifying recommendations regarding higher doses.115 The Third edition of the Belgian Association for Regional Anaesthesia guidelines published in 2011 reaffirmed that a low-dose of aspirin (60–300) in isolation, is not associated with an increased risk of spinal haematoma in the presence of a normal platelet count.30 These conclusions are based particularly on experts’ consensus. Although current ASRA and ESA guidelines have been identified as references, the clinical evidence supporting dose restriction on the recommendations is not indicated.

Austria

A consensus document published in 2005 recommended the suspension of aspirin 48–72 h before neuraxial anaesthesia.23 Consistent with ESA guidelines, an update in 2013 rescinded this restriction, without precise regard to doses.32

Italy

The 2006 guidelines established that aspirin alone at ‘usual doses’ (unspecified) did not significantly increase the risk of bleeding after neuraxial blockades, if others risk factors could be excluded.24

United Kingdom (UK)

Based on previously published 2007 German guidelines and 2010 ASRA guidelines, no precautions regarding the use of aspirin in neuraxial techniques has been established in the 2013 UK guidelines, without precise regard to doses.31 However, as has been previously mentioned, there are no limitations regarding the doses considered safe in ASRA guidelines, and German guidelines seem to limit security to low-dose aspirin.25 27

Nordic Countries

Unlike the majority of European scientific societies, Nordic guidelines published in 2010 recommended discontinuing aspirin from 12 h up to three to seven days before neuraxial blocks, depending on the dose administered and thrombotic risk. Thus, aspirin prescribed for primary prevention can and should be discontinued for at least three days before a neuraxial blockade, and up to seven days before, if the dose is greater than 1 g d$^{-1}$. The use of desmopressin (and tranexamic acid) to reverse the antiaggregation effect of aspirin is also suggested in emergency cases that require neuraxial anaesthesia. These recommendations are mostly based on experts’ opinions and pharmacokinetic data.28

Although there are some differences, particularly regarding aspirin dose, the majority of national scientific societies, based on the available evidence, agreed to establish that aspirin is considered to be safe in neuraxial anaesthesia. Although some publications seem to suggest that the aspirin safety in neuraxial blockades is limited to the lower doses, there are no data supporting this claim.25 30 36 113 116 Current recommendations on neuraxial blockades in patients receiving aspirin therapy are summarized in Table 1.

Importantly, all published guidelines agree in indicating an increased risk of spinal haematoma when aspirin is combined with other medications, which could interfere with the coagulation mechanisms at various levels.24–32

Specific recommendations

Although aspirin alone is considered to be safe in neuraxial anaesthesia, concomitant administration with another antithrombotic drugs (particularly heparin therapy or dual antiplatelet therapy) significantly increases the risk of spinal haematoma. In elective procedures, the recommended safety times for each of these other drugs must be strictly followed, while maintaining aspirin therapy in the large majority of patients.25 26 32

In general, neuraxial techniques could be performed at least 10–12 h after thromboprophylactic dose, and 24 h after full therapeutic dose of low molecular weight heparin (LMWH).24 25 30 36 113 However, a cautionary approach (unspecified) in the presence of aspirin is also recommended in ESA and ASRA guidelines.25 26 32 113 In German guidelines, a safety time of 36–42 h between subcutaneous administration of prophylactic dose of LMWH and the neuraxial techniques is recommended in patients taking aspirin.25

In patients receiving full therapy with low molecular weight heparin and taking aspirin (e.g. prosthetic valve or atrial fibrillation in coronary patients), a neuraxial technique or epidural catheter for postoperative analgesia is not recommended. The increased thrombotic risk of a 24-h heparin-free interval could be considered in individual patients where the neuraxial technique is clearly beneficial.24 27

Table 1 Current guidelines and recommendations on neuraxial blocks in patients receiving aspirin. ESA: European Society of Anaesthesiology. ASRA: American Society of Regional Anaesthesia. *In patients on aspirin treatment for its analgesic or anti-inflammatory effects (>1gr day$^{-1}$). † A dose higher than 300 mg of aspirin is considered as risk factor for spinal haematoma.113

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Dual antiplatelet therapy with clopidogrel and aspirin is common in the perioperative period. Current guidelines in noncardiac surgery recommend stopping thienopyridine therapy (ADP receptor antagonist) before elective surgery. Consistent with these recommendations, a complete recovery of ADP-mediated platelet activation is also required before performing a neuraxial technique. Thus, the suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is five to seven days for clopidogrel, seven to 10 days for prasugrel and five to 10 days for ticagrelor. The majority of recommendations in noncardiac surgery agree that clopidogrel should be stopped at least five days before the procedure. However, in the large majority of guidelines regarding neuraxial blockades a stopping time of seven days for clopidogrel is required. According to the ASRA guidelines, if a neuraxial block is indicated between five and seven days of discontinuation of clopidogrel, normalisation of platelet function should be documented. Although it is possible to assess the residual clopidogrel effect using assays of platelet function (e.g. PFA II, P2Y12 assay), only a normal result would be reassuring, and the clinical applicability of these tests remains undetermined at this time.

In patients with coronary artery stents at a high risk of thrombosis (4–6 weeks for non–pharmacological stents, 6–12 months in drug-eluting stents) undergoing urgent non-cardiac surgery, because of a significantly increased spinal haematoma risk associated with thienopyridine therapy, neuraxial anaesthesia or analgesia is contraindicated. Beyond this period, consistent with current recommendations on perioperative management of antiplatelet therapy in noncardiac surgery, the suspension of the dual antiplatelet therapy can be considered, and a neuraxial blockade can be performed while maintaining the aspirin. Those with drug-eluting stents should only stop aspirin before a planned operation, when there is a life-threatening bleeding risk such as in neurosurgical procedures.

Inhibiting effects of local anaesthetics on platelet aggregation have been described. However, at clinical doses, local anaesthetic drugs used in neuraxial anaesthesia appear to be safe and do not represent an additional risk factor for spinal haematoma in patients taking aspirin. In general, there is no restriction regarding local anaesthetics, volatile agents or i.v. anaesthetic drugs in the American or European guidelines.

Although the use of herbal medications does not create a level of risk that will interfere with the performance of neuraxial blockades, there is no data evaluating the combination of herbal therapy with other antithrombotic drugs, including aspirin.

If a traumatic neuraxial technique occurs in a patient currently using aspirin (blood or blood-stained fluid during puncture or catheter placement), it is recommended that the next dose of heparin be delayed at least 24 h in the postoperative period.

In other patient-related conditions associated with an increased risk of spinal haematoma (e.g. elderly, female sex, ankylosing spondylitis or spinal stenosis, renal or hepatic failure), if a neuraxial blockade is considered beneficial, a cautionary approach should be considered to minimize the risk, such as using a single-shot spinal blockade, using a small calibre spinal needle, avoiding multiple attempts and avoiding catheter placement. According to Nordic guidelines, the number of attempts should be limited to three, and, in the case of a bloody tap, the procedure should be abandoned. Adrenaline also promotes platelet aggregation and may reduce risk of bleeding. Neuraxial anaesthesia should be avoided in patients with severe hepatic or renal failure.

The decision to keep aspirin therapy in the perioperative period is conditioned primarily to balance the risk of surgical bleeding and the risk of thrombotic vascular events. Once this first decision is established, in a second step, the risk of performing neuraxial anaesthesia in patients maintaining aspirin treatment should be considered. Thus, in patients at a low risk for cardiovascular events (e.g. primary prevention), preoperative interruption of aspirin to reduce the risk of surgical or neuraxial bleeding may be reasonable. In patients at moderate or high thrombotic risk (e.g. secondary prevention), with the exception of high-risk bleeding procedures, perioperative maintenance of aspirin is usually recommended. On the other hand, an inappropriate interruption of antplatelet therapy with aspirin can significantly increase the rate of perioperative cardiovascular complications.

There are no specific medications that reverse the effect of antiplatelet drugs. In patients requiring reversal of the antiplatelet effects (e.g. uncontrolled or life-threatening bleeding), platelet transfusion is the treatment of choice. Alternative options include desmopressin or recombinant factor VII, but there is not enough evidence supporting the inclusion of these medications as a standard recommendation to reduce excessive bleeding in patients receiving aspirin.

Regardless of the precautions taken before performing a neuraxial technique, all patients should be carefully monitored for signs or symptoms of a developing spinal haematoma. When there is a clinical suspicion of neuraxial haematoma, immediate steps must be taken to confirm the diagnosis and allow a prompt intervention. The diagnostic method of choice is magnetic resonance imaging, as this allows for a view of the precise location and extent of the haematoma. When it is unavailable, as an alternative, computed tomography or myelography should be requested immediately. If the diagnosis is confirmed, a decompressive laminectomy should be performed less than 8–12 h after the appearance of the first symptoms of medullary compression in order to increase the patient’s chances of making a complete neurological recovery. Any delay in effective treatment (laminectomy) may cause a permanent disability. All hospitals need an updated protocol for the diagnosis and treatment of a spinal haematoma.

**Conclusion**

Aspirin is the most commonly used antiplatelet drug in the perioperative period and its safety in patients receiving neuraxial anaesthesia has historically been questioned. Low-dose aspirin achieves a selective, complete and irreversible blockade of platelet cyclooxygenase-1 and higher doses do not increase the antiplatelet effect. Additional cyclooxygenase-2 blockade by high-dose aspirin might decrease the antithrombotic efficacy by inhibition of endothelial prostacyclin synthesis. Different doses of aspirin have been shown to be safe in a broad population subjected to neuraxial anaesthesia or analgesia. In the few case reports of spinal haematoma involving aspirin therapy, additional complicating factors were usually identified. Currently, on the basis of the available data, the majority of national scientific societies agree that the use of aspirin and other non-steroidal anti-inflammatory drugs does not increase the risk of spinal haemorrhagic complications and does not represent a contra-indication to neuraxial blocks or catheter procedures. Although some publications seem to suggest that the aspirin safety in neuraxial blockades is limited to the lower doses, there are no data supporting this claim. The concurrent administration of anticoagulation therapy and a traumatic puncture, represent the major risk factors for spinal haematoma after neuraxial...
anaesthesia. Although aspirin alone is considered to be safe in neuraxial anaesthesia, concomitant administration with other antihaemostatic drugs significantly increases the risk of spinal haematoma. Therefore, the recommended safety times for each of these other drugs must be strictly followed while maintaining aspirin therapy in the large majority of patients. The final decision to perform a neuraxial anaesthetic technique must be based on an individual assessment of the risk of haemorrhagic complications and the benefits of the neuraxial technique. It is necessary to establish uniform criteria and recommendations based on clinical evidence to define the role of aspirin in regional neuraxial anaesthesia.

**Authors’ contribution**

Project design/planning: R.S.V.V.
Data analysis: R.S.V.V.
Writing paper: R.S.V.V.
Revising paper: all authors

**Declaration of interest**

None declared.

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