Risk of Bleeding with Non-Aspirin Non-Steroidal Anti-Inflammatory Drugs Before Spine Procedures

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Myth: All oral non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs) are associated with the same risk of a bleeding complication when taken before spinal injection procedures.

Fact: Non-selective NANSAIDs (diclofenac, ibuprofen, indomethacin, and naproxen) are associated with greater inhibition of cyclooxygenase-1 (COX-1) and platelet function compared to COX-2-selective NANSAIDs (celecoxib, etodolac, meloxicam, and nabumetone). For some but not all non-spinal surgical procedures, preoperative NANSAID use is associated with increased intra-operative blood-loss. Celecoxib is the only COX-2-selective NANSAID for which multiple clinical studies confirm no additional procedural bleeding risk compared to control or placebo. These findings must be applied cautiously to spinal injections as no study to date has defined relative risk of bleeding with various NANSAIDs when used prior to these procedures. Given the elective nature of spinal injections, clinicians must carefully weigh the risks and benefits of potentially allowing continuation of an NANSAID.

Background

Various guidelines detail the bleeding risk associated with continuation of anti-coagulant and anti-platelet agents prior to spinal injection procedures [1-5]. Discussion has primarily focused on medications used for therapeutic prophylaxis, such as warfarin for stroke prophylaxis. The use of NANSAIDs prior to spinal intervention procedures is also addressed. However, less detail is provided, and there is a lack of consensus on best practices.

The American Society of Regional Anesthesia (ASRA) recommends that for high risk procedures (spinal cord stimulation trial and implantation, intrathecal catheter and pump implantation, vertebral augmentation, epiduroscopy and epidural decompression), and for certain intermediate risk procedures (interlaminar cervical epidural steroid injection and stellate ganglion block), discontinuation of NANSAIDs should be considered [1]. ASRA guidelines recommended that discontinuation occur for a duration of time equal to at least five half-lives of the particular NANSAID, except for Cyclo-oxygenase-2 (COX-2)-selective NANSAIDs, which can be continued [1]. While Scandinavian guidelines also call for discontinuation based on the half-live of each particular NANSAID [2], other guidelines recommend discontinuation the night before a block [3], or alternatively, continuation of NANSAIDs prior to spinal procedures when performed in accordance with society guidelines [4].

This incongruence is likely the result of inadequate literature that is specific to NANSAIDs from which to provide evidence-based recommendations. Indeed, only two published case reports describe an epidural hematoma following spinal injection associated with oral NANSAID use: diclofenac [6] and indomethacin [7] prior to interlaminar epidural steroid injection (IESI). A prospective cohort study that included 249 patients taking NANSAIDs prior to IESI demonstrated no major bleeding complications defined as spinal hematoma; the rate of minor bleeding was no different between patients taking NANSAIDs versus those who were not [8]. However, the 1.5% upper-limit of the 95% confidence interval of this zero prevalence figure indicates that a much larger study would be needed to provide a meaningful estimate of zero or low risk. Furthermore, no study specific to spinal injection procedures has compared the bleeding risk of various NANSAIDs. Such study would require a very large sample size given the rare incidence of spinal epidural hematoma. Thus, in order to make the most evidence-based decision, an understanding of the basic science and non-spinal procedural literature must be sought to determine if different NANSAIDs are associated with variable risk of bleeding prior to spinal injection procedures.

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Variable Effect of Different NANSAIDs on COX-1

The cyclooxygenase-1 enzyme (COX-1) synthesizes thromboxane A2, which mediates the platelet-thrombosis pathway. Alternatively, the cyclooxygenase-2 enzyme (COX-2) synthesizes prostaglandins, which mediate of inflammatory pain pathways. NANSAIDs competitively and reversibly inhibit tCOX-1 and COX-2. It follows that the degree to which a specific NANSAID attenuates platelet-mediated thrombosis is related, in part, to its relative affinity for COX-1 versus COX-2, as well as its duration of action.

In vitro studies have characterized the relative selectivity of various NANSAIDs for COX-1 compared to COX-2. Diclofenac, ibuprofen, indomethecin, naproxen, and piroxicam are non-selective inhibitors of both COX-1 and COX-2. Celecoxib, etodolac, meloxicam, and nabumetone have greater selectivity for COX-2 [9-12]. Meloxicam is more selective for COX-2 than nabumetone [13]. Celecoxib is more selective for COX-2 than meloxicam, etodolac, and nabumetone [10].

Assuming normal excretion, systemic clearance of a medication occurs after approximately five half-lives [14]. Based on this definition, the upper range of systemic clearance is 24 hours for diclofenac and ibuprofen [1], 48 hours for etodolac and indomethacin [2], and greater than 72 hours for meloxicam, nabumetone, naproxen, and piroxicam [1]. These clearance times reflect the duration of inhibition of COX-1 when serum levels of thromboxane A2 are measured as a proxy of COX-1 enzyme activity [15].

Variable Effect of Different NANSAIDs on Platelet Aggregation and Bleeding Time

In order to confirm the effect of COX-1 inhibition on platelet function, investigators have tested the effect of NANSAIDs on platelet aggregation and bleeding time.

Non-selective NANSAIDs
Diclofenac, ibuprofen, indomethacin, and naproxen all decrease platelet aggregation and increase bleeding time compared to placebo [10,16,17]. Ibuprofen and naproxen decrease platelet aggregation and increase bleeding time more than diclofenac, but not compared to each other [10]. These effects reverse by 24 hours for ibuprofen, 48 hours for diclofenac and indomethacin, and 72 hours for naproxen [11,18-20].

COX-2-selective NANSAIDs
While meloxicam and nabumetone cause measureable inhibition of COX-1, both have no effect on platelet aggregation or bleeding time compared to placebo or control [9-11,17,21], even at supratherapeutic doses (30mg daily) for meloxicam [22]; this suggests that the degree of COX-1 inhibition is not physiologically relevant. Multiple studies have demonstrated that celecoxib also has no effect on platelet function compared to placebo [11,23,24], also even at supratherapeutic doses (600mg BID) [24].

Variable Effect of Different NANSAIDs on Intra-operative Bleeding in Surgical Studies

Other investigation has suggested that platelet function studies may not reliably predict the clinically-relevant risk of bleeding [25], thus the clinical literature must be examined. Relevant studies of spinal injection procedures have not been conducted, but intra-operative bleeding associated with NANSAID use during various surgeries has been investigated.

Non-selective NANSAIDs
Some but not all studies demonstrate increased blood-loss associated with non-selective NANSAIDs. Preoperative ibuprofen use increases intraoperative blood loss during periodontal and total hip arthroplasty (THA) surgery [26-28]. However, no difference is observed for plastic surgery [29] and tonsillectomy [30]. Studies that compare non-selective to COX-2-selective NANSAIDs show increased blood-loss in the non-selective NANSAID group during THA [31,32] and gynecologic or breast surgery [33].

COX-2-selective NANSAIDs
Meta-analysis has demonstrated that COX-2-selective NANSAIDs do not increase the risk of surgical blood loss across a variety procedure types [34]. Celecoxib is associated with no more blood loss than placebo or control when administered prior to tonsillectomy [35,36], total knee arthroplasty [37,38], and thyroid surgery [39], which is also true of celecoxib and etoricoxib administration prior to laparoscopic cholecystectomy [40].

Implications

The body of literature on COX-1 inhibition, platelet function, and surgical bleeding-risk suggests that non-selective NANSAIDs are associated with greater bleeding risk than COX-2 selective NSAIDs. However, celecoxib is the only COX-2-selective NANSAID for which multiple

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clinical studies of procedural bleeding risk confirm in vitro findings. Extrapolation of this literature to spinal injections must be performed with caution, since inadequate parallel clinical study of bleeding risk has been performed for these elective procedures. It must also be emphasized that not all spinal injection procedures carry the same risk of clinically significant bleeding (i.e. spinal epidural hematoma). It is beyond the scope of this FactFinder to stratify bleeding risk for various spinal injections, but this information is available elsewhere [5]. Finally, given the elective nature of spinal injections, clinicians must carefully weigh the risks and benefits of potentially allowing continuation of an NANSAID.

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