Nonsteroidal anti-inflammatory drug

Definition

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are a class of medications used to treat pain, fever, and inflammation. In the postoperative setting, NSAIDs are commonly employed as part of **multimodal analgesia** to reduce reliance on opioids and enhance recovery.

⚙ Mechanism of Action

NSAIDs inhibit the activity of **cyclooxygenase (COX) enzymes**, primarily:

- **COX-1**: Involved in platelet aggregation and gastric mucosal protection
- **COX-2**: Induced during inflammation and responsible for pain signaling

By inhibiting these enzymes, NSAIDs reduce **prostaglandin synthesis**, leading to:

- Decreased inflammation
- Decreased nociceptor sensitization
- Reduced pain perception

Members

The term nonsteroidal distinguishes these drugs from steroids, which, among a broad range of other effects, have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic and thus are used as a non-addictive alternative to narcotics.

The most prominent members of this group of drugs, Aspirin, ibuprofen and naproxen, are all available over the counter in most countries.

Paracetamol (acetaminophen) is generally not considered an NSAID because it has only little anti-inflammatory activity. It treats pain mainly by blocking COX-2 mostly in the central nervous system, but not much in the rest of the body.

The anti-inflammatory properties of NSAIDs are primarily due to inhibition of the enzyme cyclooxygenase (COX) which participates in the synthesis of prostaglandins and thromboxanes [1)]

It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1, particularly aspirin, may cause gastrointestinal bleeding and ulcers.

There is high-quality evidence that Nonsteroidal anti-inflammatory drugs reduces pain up to 24 hours postoperatively. The evidence for reductions in pain with dexmedetomidine, pregabalin or

gabapentin, scalp blocks, and scalp infiltration is less certain and of very low to moderate quality. There is low-quality evidence that scalp blocks and dexmedetomidine may reduce additional analgesics requirements. There is low-quality evidence that gabapentin or pregabalin may decrease nausea and vomiting, with the caveat that the total number of events for this comparison was low [2].

Six of the 13 included randomized controlled trials (RCTs) showed that NSAIDs are more effective than placebo regarding pain intensity. NSAIDs are slightly more effective than placebo regarding disability. However, the magnitude of the effects is small, and the level of evidence was low. When we only included RCTs at low risk of bias, differences in effect between NSAIDs and placebo were reduced. We identified no difference in efficacy between different NSAID types, including selective versus non-selective NSAIDs. Due to inclusion of RCTs only, the relatively small sample sizes and relatively short follow-up in most included trials, we cannot make firm statements about the occurrence of adverse events or whether NSAIDs are safe for long-term use [3].

Complications

The risk of hemorrhagic stroke in patients taking these medications is unclear. In a study, Islam et al. from Taipei, Taiwan, systematically reviewed, synthesized, and criticized the epidemiological studies that evaluate the association between NSAIDs and hemorrhagic stroke risk. They, therefore, assessed the current state of knowledge, filling the gaps in our existing concern, and make a recommendation for future research.

They searched for articles in PubMed, EMBASE, Scopus, and Web of Science between January 1, 1990, and July 30, 2017, which reported on the association between the use of NSAIDs and hemorrhagic stroke. The search was limited to studies published in English. The quality of the included studies was assessed in accordance with the Cochrane guidelines and the Newcastle-Ottawa criteria. Summary risk ratios (RRs) with 95% CI were pooled using a random-effects model. Subgroup and sensitivity analyses were also conducted.

They selected 15 out of the 785 unique abstracts for full-text review using our selection criteria, and 13 out of these 15 studies met all of our inclusion criteria. The overall pooled RR of hemorrhagic stroke was 1.332 (95% CI 1.105-1.605, p = 0.003) for the random effect model. In the subgroup analysis, a significant risk was observed among meloxicam, diclofenac, and indomethacin users (RR 1.48; 95% CI 1.149-1.912, RR 1.392; 95% CI 1.107-1.751, and RR 1.363; 95% CI 1.088-1.706). In addition, a greater risk was found in studies from Asia (RR 1.490, 95% CI 1.226-1.811) followed by Europe (RR 1.393, 95% CI 1.104-1.757) and Australia (RR 1.361, 95% CI 0.755-2.452).

The results indicated that the use of NSAIDs is significantly associated with a higher risk of developing hemorrhagic stroke. These results should be interpreted with caution because they may be confounded owing to the observational design of the individual studies. Nevertheless, we recommend that NSAIDs should be used judiciously, and their efficacy and safety should be monitored proactively [4].

Systematic Reviews and Meta-Analysis

Concerns remain about their safety, particularly regarding the risk of postoperative bleeding because of cyclooxygenase inhibition. A Systematic Review and Meta-Analysis aimed to evaluate whether NSAIDs increase the risk of hemorrhagic complications after craniotomy for brain surgery when compared with non-NSAID approaches or placebo.

A systematic search was conducted in PubMed, Scopus, Web of Science, and Cochrane databases to identify studies comparing NSAIDs with non-NSAID drugs for postoperative analgesia after craniotomy for brain surgery. End points were (1) all bleeding complications and (2) bleeding complications requiring surgical intervention. Subanalyses focused on randomized controlled trials (RCTs) and patients undergoing tumor resection. Risk ratios (RR) and risk difference (RD) with 95% CI were pooled using a random-effects model, and heterogeneity was assessed with the I2 statistic.

Seven studies (5 RCTs), including 2251 patients (1119 males; median ages ranging from 11 to 55 years), of whom 583 (25.9%) received NSAIDs, met the inclusion criteria. Surgical indications included tumor resection, aneurysm clipping, and microsurgery for brain arteriovenous malformations. No significant differences were observed between NSAID and non-NSAID groups for overall bleeding complications (RR: 1.05; 95% CI: 0.58, 1.93; I2 = 0%; RD: 0.31%; 95% CI: -1.46%, 0.84%) or bleeding complications requiring surgical intervention (RR: 1.27; 95% CI: 0.51, 3.16; I2 = 0%; RD: 0.03%; 95% CI: -0.90%, 0.97%). Similar results were found in the RCT-only and tumor resection subanalyses.

The findings suggest that NSAIDs are a safe option for postoperative analgesia in patients undergoing craniotomy for brain surgery, because they do not significantly increase the risk of bleeding complications, including those requiring surgical intervention, compared with non-NSAID analgesics [5].

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2)
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