Intravenous Non-steroidal Anti-inflammatory Agents

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Abstract

A summary of intravenous Non-Steroidal Anti-inflammatory Agents (NSAIDs) is presented with mode of action, potential complications, and therapeutic indications reviewed. Their role in a multimodal analgesic regimen for ambulatory surgery is also discussed.

Keywords: NSAIDs, Ambulatory Surgery, Intravenous.

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Intravenous Ibuprofen

NSAIDs are very effective in reduction of pain and inflammation and are among the most popular used medicines worldwide. Together with paracetamol NSAIDs are invaluable in a multimodal analgesia protocol for ambulatory surgery. Ambulatory surgery is continuously increasing with a high number of extensive and painful procedures. Adequate pain relief by simple methods, readily available at home is crucial for the well-being and quick recovery of the ambulatory surgery patient. Quality of recovery after day surgery still is poor for some patients and is heavily impacted due to postoperative pain and nausea and vomiting. Wherever possible opioids should be avoided as first line pain treatment in ambulatory surgery. Discharge opioid prescriptions have been identified as a risk factor for persistent opioid use leading to opioid use disorder.

Postoperative pain after day surgery is the most common reason for delayed discharge and unanticipated hospital admission. Furthermore, the incidence of unscheduled contact with healthcare workers is high during the first days to weeks after surgery (>20%). Most often the general practitioner is contacted by the patient for further information and guidance, with inadequate pain management as the main reason (1).

NSAIDs block the cyclooxygenase, inhibiting the transformation of arachidonic acid to prostaglandins, prostacyclin and thromboxane A2. The degree of COX-inhibition varies among different NSAIDs. Two isoforms of COX enzyme are described; COX1 and COX2. COX1 is present in most human tissues and regulates normal physiology; gastric protection, vascular homeostasis, platelet aggregation and kidney function. COX2 is undetectable in normal conditions but its expression is increased during states of inflammation, such as after surgery. COX2 stimulates the production of prostaglandins E2 and I2 resulting in inflammation and pain. COX2 increases prostacyclin production, promoting vasodilation and inhibiting platelet aggregation.

Selectively blocking COX1 leads to gastrointestinal side effects, bleeding and kidney injury. Blocking COX2 could induce coronary thrombosis and cardiovascular adverse events (2).

NSAIDs induced gastropathy manifest as gastroduodenal erosions and ulceration, ultimately leading to perforation and potentially life threatening hemorrhage. Risk factors for serious gastrointestinal complications increases in patients over the age of 70, patients with a history of previous peptic ulcer disease, patients on corticosteroids, anticoagulants and aspirin. The NSAIDs subclass and duration of treatment are significant risk factors for gastropathy. Indomethacin (subclass of indolic derivates) has a higher risk of GI complications than for non-users with a relative risk (RR) of 2.25 with a maximum relative risk at 14 days. Naproxen has a RR of 1.83, diclofenac a RR of 1.73 while ibuprofen has a RR of 1.19(3). These latter NSAIDs have a maximum risk after 50 days. The RR for upper gastrointestinal complications of ketorolac compared with ibuprofen was 11.7.(4) However NSAID use after ambulatory surgery typically is of shorter duration. Alternatively, an H2-receptor blocking drug (ranitidine) or a proton pump inhibitor can be associated to protect gastroduodenal mucosa in patients at risk (omeprazole, pantoprazole 20mg) (Table 1) (near here).

COX2 blockers and more COX2 selective NSAIDs could lead to cardiovascular side effects. In patients with prior myocardial infarction diclofenac has the highest risk of death and recurrent myocardial infarction at day 1 to 7 of treatment (Hazard ratio 3.26). The risk of death caused by diclofenac was even higher than after rofecoxib as an example of a selective COX2 inhibitor. Naproxen is the NSAID with the lowest cardiovascular risk but a high gastrointestinal risk especially dangerous in patients with prior myocardial infarction. Ibuprofen has the lowest cardiovascular risk during the first days of treatment, however, the risk increases after one week of use.

The concept of preemptive analgesia relies on analgesic interventions given before any noxious stimulus. The use of NSAIDs before operation should, theoretically, be more effective than postoperative administration, and has successfully controlled postoperative pain in ambulatory surgery patients(5). Oral premedication with NSAIDs before surgery may not consistently achieve peak plasma concentrations at the time of operation. Intravenous administration at the time of induction guarantees maximal plasma levels at the time of incision

Diclofenac is a traditional component of analgesic regimens in ambulatory patients. When given intravenously it must be diluted with 100 to 500 ml of sodium chloride (0.9%) or glucose (5%) and should be buffered with sodium bicarbonate solution (0.5 ml 8.4% or 1 ml 4.2%). Diclofenac should not be given as an intravenous bolus injection as this can result in venous thrombosis and pain(6).

Pharmacokinetic modelling has shown that after an intravenous dose of ibuprofen as a 5-7 minute infusion the maximum peak plasma concentration (Cmax) is higher and comes faster than when the same dose is given as a 30 or 60 minute infusion. (120 µg/ml for a 5-7 minute infusion, 84 µg/ml and 73 µg/ml after a 30 and 60 minutes infusion respectively with tmax of 6.5 min vs 32 min vs 1 hour respectively). So Cmax increases as infusion times decreases and tmax decreases with decreased infusion duration. An oral dose of ibuprofen is not able to achieve these concentrations despite its bioavailability of near 100%(7). A rapid intravenous infusion of ibuprofen is well tolerated, although a mild discomfort is sometimes

Table 1. Suggested use of NSAIDS for Ambulatory Surgery.

NSAIDS PERIOPERATIVELY

LOW RISK
GASTROINTESTINAL COMPLICATIONS

- Age < 70
- No comorbidities
- No history of NSAIDs induced morbidities
- History of gastro-intestinal surgery
- Diaphragmatic herna

MODERATE RISK
GASTROINTESTINAL COMPLICATIONS

- Age < 70
- History of uncomplicated gastric ulcer
- Intake of aspirine (incl low dose)
  - Cortico-steroids (daily)
  - Anticoagulants

HIGH RISK
GASTROINTESTINAL COMPLICATIONS

- History of complicated gastric ulcer (recently)
- Multiple risk factors (>2)

START SURGERY

– Paracetamol 1gr IV	– Paracetamol 1gr IV	– Paracetamol 1gr IV
– Ibuprofen 600mg IV	– Ibuprofen 600mg IV	– Consider Parecoxib 40mg IV
	– Pantoprazole 20mg IV	– Consider Metamizole 100mg IV

AFTER SURGERY

– Paracetamol 1gr oral
  – max 4gr daily
	– Paracetamol 1gr oral
	  – max 4gr daily
		– Paracetamol 1gr oral
		  – max 4gr daily

– Ibuprofen 600mg oral
  – max 3 x 600mg
	– Ibuprofen 600mg oral
	  – max 3 x 600mg
		– Cox II

	– Pantoprazole 20mg oral	– Metamizole 100mg oral – max 4 x 100mg daily

reported at the site of infusion. So the place for intravenous ibuprofen seems valuable in a preemptive multimodal analgesia regimens. A network meta-analysis including 188 studies (13769 patients) on preemptive analgesia showed a reduced opioid consumption for ibuprofen and less postoperative nausea and vomiting(5).

A single dose of IV ibuprofen resulted in lower pain scores and reduced opioid use compared with paracetamol in patients undergoing laparoscopic cholecystectomy.(8, 9)

Intraoperative ibuprofen infusion can significantly reduce the incidence of emergence agitation following general anesthesia with propofol and remifentanil in children with less need for rescue fentanyl doses and positive effects on early postoperative pain after tonsillectomy(10). IV ibuprofen significantly reduced the number of postoperative doses and the amount of fentanyl administered after tonsillectomy. Ibuprofen did not increase the incidence of serious adverse events, surgical blood loss, postoperative bleeding, or the need for surgical re-exploration(11). NSAIDs are recommended in modern multimodal pain regimens after tonsillectomy(12).

Paracetamol should be first-line treatment in postoperative pain and should be associated to a traditional NSAIDs in otherwise healthy patients. Ibuprofen has a longstanding safety profile, can be administered intraoperatively as an intravenous infusion before any noxious stimulus has occurred and be continued postoperatively in different galenic forms. Patients at risk for gastrointestinal adverse events should be provided with gastroprotective drugs.

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