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The use of NSAIDs in the postoperative period: advantage and disadvantages

Summary

NSAIDs are commonly used as single analgesics in minor surgery or as component of multimodal analgesia associated with opioids or locoregional techniques in the postoperative period to assure a better analgesia and reduce the dose of opioids. The analgesic potency evaluated as number needed to treat (NNT) is not very different between the traditional non selective NSAIDs and the selective cyclo-oxygenase-2-inhibitors (Coxibs). The effectiveness as analgesics is unquestionable also if these drugs are not devoid of risks. There is debate in literature about the possible side effects when administered in the perioperative period: anastomotic leakage, reduced ossification, bleeding and acute renal failure. Recent data underline as the Coxibs but also traditional NSAIDs can induce cardiac toxicity even if they are utilized for few days. The aim of this review is to provide an overview of the effectiveness and side effects of selective and non-selective NSAIDs in the perioperative period.

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Abbreviations: NNT, number needed to treat; NSAIDs, non-steroidal anti-inflammatory drugs; CKD, chronic kidney disease; GFR, glomerular filtration rate; ESRD, end-stage renal disease

Introduction

Analgesia is a cornerstone of postoperative therapy not only for ethical reasons but also in order to reduce postoperative complications and hospital stay. Despite all of the progresses in pharmacology therapy, postoperative pain remains an unresolved problem. Perioperative pain is a complex and multi factorial phenomenon that needs to be effectively controlled often with combination of several drugs with different mechanisms of action in order to ameliorate the analgesic effects with the synergism and additive effect of each drug and thereby reducing analgesic related side effects. A multimodal and multidrug approach is the best choice for treatment of postoperative pain. Different techniques and drugs are utilized: central and peripheral nerve block, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, local anaesthetics, glucocorticoids and gabapentinoids.[1-3] A single class of analgesic is seldom adequate. The association is often utilized because some drugs have some limitations such as ceiling effect, contraindication at high dosage, respiratory insufficiency, liver damage, risk of upper gastrointestinal complications or renal insufficiency.[4,5] The concept of multimodal contest-sensible analgesia is now well accepted for the treatment of postoperative pain. It has been demonstrated that different classes of analgesics are more effective than a single drug because of different mechanisms of action, and they can be used at low doses reducing the incidence of side effects and increasing the quality of perceived analgesia[6] Therefore, many pharmacological trademarks have introduced associations of analgesic drugs as paracetamol plus tramadol, or codeine plus paracetamol and NSAIDs at fixed dose whose association increases the analgesic effect for the postulated different mechanism of analgesia. An adequate pain control must be pursued for several reasons: it is not only a human right but it has been demonstrated fundamental for prevention of chronic postoperative pain, whose incidence is not negligible and is more frequent in some types of surgery as inguinal hernia, cholecystectomy, caesarean section and thoracotomy. Regarding this aspect, the timing of administration of drugs is fundamental. Many reports, although not confirmed, have shown a reduction of postoperative pain when analgesics are administered preoperatively, the so calledpreemptive analgesia.[7,8]

Between all the most widely used drugs in the world, non-steroidal anti-inflammatory drugs are the cornerstone therapy of chronic and acute pain. In mild or moderate postoperative pain NSAIDs are often utilized alone, but in severe pain they are associated with opioids, local analgesics and or adjuvants.[5-9] Currently the guidelines of American Society of Anaesthesiologists, Task Force on acute Pain Management and Italian Group of Analgesia, advocate that NSAIDs have a significant role in postoperative pain control.[10,11] The use of NSAIDs is particularly interesting if the physiopathology of postoperative nociceptive inflammatory pain is considered: nociceptors are nerve endings of primary sensory neurons Aδ and C fibers that are stimulated directly or sensitized by substances released by traumatized inflamed tissues. The set of inflammatory mediators in the tissue after injury such as prostaglandins, bradykikin, leukotrienes, serotonin, substance P, thromboxane, platelet activating factor, etc., actives nociceptors and induces primary and secondary hyperalgesia. The inflammation increases the excitability of neurons with reduction of the threshold, potential duration and intensity of activation of these nerve endings causing an expansion of the receptive field to the tissue closest not damaged, the peripheral hyperalgesia. Synaptic plasticity in the dorsal horn due to peripheral overstimulation is responsible for thecentral sensitizationwhich producesa change of nociceptive neurons in wide dynamic neurons that are activated also byinnocuous stimuli and induces a progressive increase in the responses to harmless stimuli and an increase of input.[12-15]

The utility of non-opioid analgesics resides on the possibility to be useful as single analgesic after minor surgical procedures especially in ambulatory surgery where NSAIDs and paracetamol have a huge application.[16-18] The aim of this review is to evaluate the effectiveness and the use of NSAIDs in the treatment of postoperative pain and to focus on mechanism of action of NSAID and on side effects, especially cardiovascular and renal function during postoperative acute administration.

NSAIDs

NSAIDs are a class of heterogeneous drugs with analgesic, anti-inflammatory and antipyretic effect utilized for acute and chronic pain and available in parenteral, topical, intramuscular and rectal form. They are often chemically unrelated and have common side effects but with different expression and intensity especially for the subclass of selective cyclo-oxygenase-2-inhibitors (Coxibs) introduced for their reduced gastrointestinal toxicity. However, despite these chemical differences, the NSAIDs present some common characteristics:

1. NSAIDs show ceiling effect for which an increase of dose increases only side effects but not analgesia.
2. NSAIDs don't induce respiratory depression and physical or psychological dependence as opioids.
3. NSAIDs have antipyretic and anti-inflammatory effects.[19-22]

Mechanism of action - Inhibition of prostaglandin synthesis

Following tissue damage, hormones, peptides, cytokines and other substances activate phospholipases that release arachidonic acid from membrane phospholipids. An enzyme prostaglandin endoperoxide synthase (or cicloxigenase, COX) forms the unstable PGG2 that is further converted to more stable PGH2 from which several types of prostaglandins and tromboxanes are formed by tissue specific isomerases that are expressed in different tissues and induce specific prostaglandins that have specific biologic activity: gastric mucosal protection, renal function, bronchodilation and vasodilation preventing platelet aggregation. The enzyme prostaglandin endoperoxide synthase presents two active sites: the cyclooxygenase site (COX site) and hydroperoxide site (HOX site). The first catalytic site induces the extraction of one hydrogen atom from one atom of carbon of arachidonic acid by tyrosin radical in the COX site to form an arachidonic radical that takes two molecules of oxygen to form PGG2. The catalytic site (POX site) induces a reduction of PGG2 to equivalent alcohol PGH2. This reaction generates an oxidized radical heme that can induce an electron intermolecular transfer with regeneration of tyrosine radical of COX site. In this way NSAIDs block the access of substrate to the COX site of the enzyme.

In vivo the COX induces production of prostaglandins in response to inflammation, sensitizes nociceptors and nociceptive fibersto mediators of inflammations and modifies gene expression in peripheral and central nervous systems causing peripheral and central sensitization, allodynia and hyperalgesia.[23-26] Two forms of cyclooxygenase have been isolated. The two isolated form, COX-1 and COX-2, have a homogeneity of amino acid of 75%. The first COX 1 is constitutive and present in the majority of cells and tissues and it is responsible of regulation of physiological processes of the organs while COX-2 is inducible peripherally as expression of an injury and it is built only in special cells.[27,28] Because the principal role of COX products are swelling and pain, the anti-inflammatory and analgesic effects of the NSAIDs are due to the inhibition of cyclooxygenases that are present centrally and peripherally and in particular to COX-2 inhibition while many side effects associated with NSAIDs are due to inhibition of COX-1. Under this aspect classic NSAIDs block both COX1 and COX2 without selectivity while selective COX-2 inhibitors seem to present similar analgesic efficacy inducing a lower gastrointestinal toxicity.[29,30]

NSAIDs, Coxib in acute postoperative pain

Pain control is one of the most important role of anaesthesiologists in the perioperative period. Although the best therapeutically analgesic approach is not known, it is well demonstrated that the multimodal approach is preferable by combining peripheral and central acting drugs or by associating central or nerve blocks. Although locoregional analgesia could be the best therapy especially in major orthopaedic, abdominal and thoracic surgery, intravenous analgesia is still utilized in majority of surgical procedures. The NSAIDs, non-opioid analgesic, can be utilized alone in minor surgical procedures and in outpatients but often they are part of multimodal analgesia in association with opioids in severe postoperative pain for their incomplete effectiveness, for their ceiling effect and adverse events when utilized at high dosage or for longer periods.[31,32] NSAIDs have reported more efficacious for pain in movement respect to opioids but don't seem reduce the side effect of these drugs as nausea, vomiting and respiratory insufficiency and recently it has been shown they reduce stress response during general anaesthesia.[33]

The questions that must to be resolved are:

1. Are cyclooxygenase inhibitors 1 and 2 effective in postoperative pain control and which?
2. Are there some differences in toxicity and effectiveness between different drugs?
3. What is the best dosage of NSAIDs and which are the side effects after relative brief duration of administration during postoperative period?[34-38]

The possibility to use these drugs preoperatively is of great theoretical interest in order to prevent or reduce the changes induced by pain in dorsal horn, the so called pre-emptive analgesia and reduce stress response during anaesthesia. However, the results are inconclusive: in two meta-analysis few studies have demonstrated only a partially effectiveness with no or little difference in postoperative pain.[39,40] Some authors have reported a reduction of postoperative pain when analgesics are administered before surgery. Reuben et al.[41] reported that the preoperative administration of acetaminophen or celecoxib in subjects undergoing to anterior cruciate ligament repair reduced pain scores and the incidence of nausea and vomiting.[41] Gutta et al.[42] examined the effect of preoperative administration of ketorolac in patients undergoing to extraction of third molar demonstrating that the better analgesic effect is maintained only for the first 4 hours but there is no difference in postoperative opioid consumption.[42] In another study, preoperative administration of celecoxib and acetaminophen have confirmed their effectiveness on postoperative pain only in first postoperative hour. Celecoxib has better efficacy compared with acetaminophen as pre-emptive analgesic in the four postoperative hours but after 12 hours no VAS difference exists, not only between the two groups but also in placebo group.[42,43] An unusual but useful route of administration of anti-inflammatory drugs has been experienced: continuous intra-wound infusion of diclofenac as postoperative analgesia after caesarean section compared with continuous ropivacaine infusion or administration of intravenous diclofenac every 12 h.[44]

The NSAIDs are anti-inflammatory, analgesic and antipyretic and can be classified according to the capability to inhibit COX isoenzyme (Table 1) or chemically. Acetaminophen is not inserted in table 1 because is not an anti-inflammatory substance although have analgesic effect and have some effects on COX inhibition. All non-steroidal analgesics are effective as opioid sparing and appear to reduce side effects of opioids.[5,45,46] In a systematic review that compared paracetamol, NSAIDs or COX-2 inhibitors to each other or placebo, in adults receiving patient-controlled analgesia (PCA) with morphine following major surgery, a reduction of opioids consumption of about 6 mg in acetaminophen group, and 10 mg in

the NSAIDs and Coxib group has been reported with a decrease of incidence of nausea and PONV [47]. In a meta-analysis Marretet al.[37] have reported a decrease in the incidence of nausea and vomiting of 30%, and sedation of 29%.[37] However, the authors do not think that reduction is clinically significant. Conversely, in a systematic review Elia N et al.[5] have shown that acetaminophen and NSAIDs reduce significantly opioid consumption in the first 24h and nausea, vomiting and sedation.[5,48]

Table 1 Classification of NSAIDs

Class 1	Inhibition of COX 1 and 2	Aspirin, Ibuprofen, diclofenac, indomethacin, naproxen, piroxicam
Class 2	Selectivity versus COX2 5-50 times	Celecoxib, etodolac, nimesulide
Class 3	Selectivity versus COX2 higher than 50 times	Rofecoxib,
Class 4	Low inhibition of COX 1-2	Sodium salicylate, sulfasalazine

Chemically non selective NSAIDs are a group of heterogeneous compounds with different pharmacokinetics and pharmacodynamic proprieties that have been rarely compared especially in relation with their analgesic potency.[49] Table 2 reports the chemical structure of different classes of NSAIDs remembering that all drugs can be used at equianalgesic doses, but only few drugs are commonly used in postoperative period. Some NSAIDs have been utilized only rarely as nambutone. Several drugs can be administered only orally for theirs high solubility therefore they can be beneficial in ambulatory or minor surgery but there are problems in hospitalized patients who cannot eat.[50]

The difference of anti-inflammatory and analgesic activity between NSAIDs and Coxibs are minimal. Only a study reported superiority of a Coxib, celecoxib compared with a traditional NSAIDs, ibuprofen at low doses in patients undergoing minor oral surgery: the pain relief is better and more prolonged.[51] However, the inter individual and intra individual response at the single NSAIDs may be quite different. The number of patients needed to obtain a reduction of 50% of pain, the so called number needed to treat (NNT), has been introduced to compare the effects of NSAIDs. Numbersneeded to treat are calculated for the proportion of patients with atleast 50% painrelief over 4-6 hours compared with placebo. A comparison of the efficacy of different anti-inflammatory drugs is reported in Oxford league table evaluating the number of patients to treat to obtain a 50% of pain relief over 4-6 hours.[52] As example the NNT for diclofenac 100mg is 2.6, for ibuprofen 400mg and for ketorolac 10mg is 2.6, for codeine 60mg is 16.7.

Recently Maund et al published in a Cochrane database systemic review an overview of 45.000 subjects utilizing different NSAIDs and other analgesic as acetaminophen and codeine. NNTs varied from 1, 5 to 20 regarding type of analgesic or surgery. The major advantage is the reduction of the relative risk of nausea and vomiting but does not seem result in reduction in other side effects as urinary retention, itch or respiratory depression.[53] Actually all NSAIDs, selective and non-selective, have the same analgesic effects and effectiveness in the postoperative period,[53-60] but difference arise by their specific side effects that are the limitation of these drugs for chronic administration but also when utilized for a brief period as in the postoperative period. Then the choice of the drug can be guided by several factors: economic, pre-existing gastrointestinal bleeding, high risk bleeding surgery, option to use the enteral route. In this context coxibs do not inhibit platelet aggregation and can be utilized in pre and postoperative period without increasing the risk of bleeding. Certainly COX-2 inhibitors reduce the gastrointestinal toxicity but can have other side effects.[61,62] The major limits of the studies on NSAIDs are that they concern to be used in minor surgery, especially dental surgery and oral prescription. Only few studies regard major surgery and overall few patients have been enrolled.

Table 2 Classification and dosage of some Non-steroidal anti-inflammatory drugs and Coxibs

Average Dose	Dose Interval	T1/2	Daily Dose	
Acetaminophen	0.2 -2	4-6 h	2-3 h	4.000mg
Salicylates	0500-1000 mg	4-6 h	0.25 h	4.000mg
NSAIDs				
Propionic Acid				
Ibuprofen	200-400 mg	8-12 h	2-2.5 h	2400mg
Naproxene	250-500 mg	6-8 h	12-15 h	1500mg
Ketoprofene	25-50 mg	6-8 h		300mg
Indolacetic Acid				
Acetic Acid				
Ketorolac	30 mg e.v. 30-60 mg i.m.	6	6 h	90-120 (Max 5 days)
Diclofenac	50 mg	8	1-1.5 h	150 mg
Piroxicam	20-40	24	50	40
COX 2-				
Celecoxib	200-400 mg	Dec-24	11	400mg
Etoricoxib	30-120 mg	24	22	120

Table 3 Adverse effects of COX-1 and COX2

Cardiovascular	**Hypertension, myocardial infarction, heart failure, stroke**
Gastrointestinal	Nausea, ulcers, anemia, perforation, gastrointestinal haemorrhage
Renal	Renal failure, analgesic nephropathy, decrease effect of diuretics
Hypersensitivityreactions	Urticaria, asthma, hypotension, shock

NSAIDs and Coxibs and adverse effects

Conventional non-selective NSAIDs are usually utilized orally, intramuscularly or intravenously. They are chemically heterogeneous compounds the effectiveness of which can result different from a patient to another. In this review only the most common drugs administered intravenously or per os will be considered and the dosage of the most common drugs used per os will be reported in Table 1. The distinction between inhibition of Cox-1 and Cox 2 can be clinically relevant for cardiovascular and gastric side effects. COX-2 selectivity is obtained measuring the potency of a drug on inhibition of COX-1 and COX-2 in isolated cells or enzymes. All NSAIDs inhibit COX-1 and COX-2 but only Coxibs inhibits at different percentage COX-2. As example lumiracoxib is the most potent and celecoxib the less.[63]

The analgesic effect is not directly correlated to enzyme inhibition: acetylsalicylic acid has a little effect on inflammatory response but has an analgesic effect as diclofenac that is a potent inhibitor of PG [64]. Acetylsalicylic acid and diflunisal are among the oldest analgesics the use of which has been almost discarded in the setting of postoperative pain and of chronic pain for theirs common adverse effects: gastric toxicity, bleeding and the association with the Reye's syndrome that prohibits the administration to children under 12 years with viral illness.[65]

Cardiovascular risk and postoperative cardiovascular effects

The major concerns of non-selective and selective NSAIDs are the possible side effects not only when they are administered chronically but also when utilized for few days in the immediate postoperative

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period. For these reasons some COX-2 have been withdrawn from the market and actually only celecoxib and etorecoxib are available in Europe, while only celecoxib is commercialized in USA. COX 1 and 2 inhibitors are equally effective as analgesic and antipyretic but COX2 have been introduced because of their reduced effect on platelet dysfunction, postoperative bleeding, and gastrointestinal toxicity. Haematological, gastrointestinal and renal effects are the most important side effects with some cyclooxygenase-1 inhibitors while cardiovascular and renal complications seemed more related to cyclooxygenase-2 inhibitors.[65,66] The selectivity for COX-2 vs COX-1 differs among the drugs and it increases respectively with celecoxib (1:30), rofecoxib (1:276) lumaricoxib (1:433).[67] However, there is no straight correlation between the entity of COX-2 inhibition and cardiovascular risk. The lumaricoxib that is the most complete inhibitor of COX-2 has the same cardiovascular toxicity of naproxen that blocks about 80% of COX-1.

Several explanations of cardiovascular toxicity have been proposed. The more considered likely theory is that the inhibition of COX-1 and COX-2 induces an unbalance between thromboxane production not reduced and the PGI2 reduced. So the production of thromboxane from platelets is not inhibited if there is not a complete platelet COX-1 activity block while the production of endothelial PGI2 is suppressed by COX-2 inhibition. It should be stressed that PGI2 is a powerful inhibitor of platelets aggregation and a potent vasodilator while thromboxane is a potent vasoconstrictor and induce platelet aggregation. Under this point of view rocefoxib and celecoxib reduce the PGI2 formation of 70%, but not the platelet activation by thromboxane.[68,69] These modifications can explain the cardiovascular risk of myocardial infarction and stroke.

The side effects have been reported after a long period of drug consumptionof COX-2 inhibitors, but it is not clear if the administration during few days can be harmful for NSAIDs and Coxibs (Table 3). The administration of rofecoxib (vioxx) 50 mg, (withdrawn from the market due to toxicity), in a randomized controlled trial comparing rofecoxib with naproxen has shown a five-fold risk of myocardial infarct with a reduction of gastrointestinal toxicity (VIGOR study). The trial was stopped early for increase of cardiovascular events, myocardial infarction, stroke and the increase of cardiovascular risk has been confirmed by several authors.[70-72] In another study to verify the effectiveness by rofecoxib 25mg in prevention of adenomatous polyps, a two-three fold increased risk of cardiovascular events has been reported.[73] The relative cardiovascular risk by 2.24-2.3 for rofecoxibis confirmed in a meta-analysis.[74] For anaesthesiologist the most important question is: can selective and non-selective NSAIDs be utilized in the perioperative period? What are the risks? It is clear that no drug is risk free, but the NSAIDs are taken under any circumstances for which a little increase of perioperative risk can induce an enormous number of complications due to huge number of surgery.

Cox- 2 has been involved in an increased cardiovascular risk that has been reported also in the immediate postoperative period in patients treated with valdecoxib. In an editorial Furberg et al.[75] evaluated in two combined studies the incidence of cerebrovascular accidents in patients undergoing coronary artery bypass graft (CABG) and showed a three-fold higher risk of cardiovascular events compared with placebo.[76] These data have not been confirmed in a recent study of 1.065 patients undergoing thoracic and cardiovascular surgery and treated with different non selective NSAIDs, particularly diclofenac, ketorolac and indomethacin. Moreover, a significant difference in consumption of morphine has been reported: a media of 5mg - 7.6mg reduction of narcotic has been found respectively in patients with and without regional block and a greater reduction in use of morphine in the group of thoracic surgery compared to cardiac surgery. No difference in side effects were found between the groups treated with NSAIDs and the control group.[75] As underlined by authors, the short duration of drug administration and low risk patients could have influenced the lack of cardiovascular and renal side effects. However, in a recent cohort study that has enrolled 83.6777 patients the use of NSAIDs in patients with prior myocardial infarct resulted in an increased risk of death and recurrent myocardial infarction also if the drugs are utilized for short time. The cardiac complications seem not correlated to duration of treatment and the risk appears more pronounced from the first week with diclofenac and in the next weeks utilizing ibuprofen and celecoxib.[77] Moreover, also celecoxib at lower dose, 200mg/ day, has shown an increased risk of composite cardiovascular events. However actually data do not encourage the use of NSAIDsin patient with cardiovascular diseases or other risks.[78] The current idea that there is a great difference in cardiovascular risk between NSAIDs a COX-2 selective drugs should be revisited. Non selective NSAIDs inhibit both COX-1 and COX-2 enzymes while selective COX-2 inhibitors produce lower effect on COX-1. For this reason, difference in cardiovascular risk between the two drugs is more hypothetical than real. Indeed NSAIDs block completely the COX-2 and because the cardiovascular risk is linked to this inhibition it is obvious that the NSAIDs do not present a reduction of cardiovascular risk.

Since the cardiovascular adverse profile is related with the degree of thromboxane (TX) synthesis in platelets and reduction of endothelial PGI production, an inhibition of platelet thromboxane greater than 95% produces cardiovascular protection as low dose of aspirin. The incomplete block of thromboxane with coxib and many non-selective NSAIDs does not reduce thromboxane production in significant percentage predisposing to cardiovascular complications.[79] On the topic of this article, it is more interesting evaluates the effect of NSAIDs and Coxib in the acute phase, for short time, the immediate postoperative period. However, the study is inconclusive. However, it seems confirmed that administration of Coxib, paracoxib and valdecoxib, in the immediate postoperative period after coronary surgery increased the risk of cardiovascular events (risk ratio 3.7).[80] However, anon-selective NSAIDs, ketorolac, administered in postoperative period of cardiac surgery has not showed an increase of cardiovascular risk.[81] On 10.873 patients undergoing total join replacement it has shown no increase in incidence of postoperative myocardial infarction: 0.8% for patients that received meloxicam or ketorolac, 1.3 % for patients that received celecoxib, 1.8% in subjects who does not receive NSAIDs.[82] From the data of literature the European Medicine Agency Committee for Medicinal Products for Human Use decided that coxibs but not non-selective inhibitors should be contraindicated in patients with cardiovascular disease.[83] The possible increase of cardiovascular adverse events has been receipted by the Food and Drug Administration that stated that in the characteristics of the drugs a boxed warning about the risk of cardiovascular disease is reported.

NSAIDs – Coxib and thoracic surgery

The locoregional techniques, epidural paravertebral and, recently, intratecal morphine are recommended as first line analgesia in post thoracotomy pain. NSAIDs and Coxib can be utilized associated to opioid analgesia when systemic analgesia is preferred or there is contraindication to neuraxial analgesia or paravertebral block. For this reason only few articles evaluated the morphine sparing effects ofparacetamol, NSAIDs, and Coxib. Manud et al have

reported in a systematic review that NSAIDs and Coxib reduce the amount of opioids in thoracotomy although the shoulder pain is only little affected by these drugs and opioids but can be reduced by suprascapularblock.[84,85] Senard et al.[86] that have enrolled few patients, suggesting that celecoxib administered before during and 48h after surgery, does not reduce the epidural consumption of ropivacaine and sufentanil administered by PCEA pump, does not reduce the recue dose of tramadol but induces a little but statistical significative reduction of pain at rest and after cough.[86]

Postoperative effects after abdominal surgery

Among abdominal surgery colonic and rectal resection are the most frequent major surgeries. Morphine delays the recovery of bowel function and slows the functional recovery. Epidural analgesia has no long recommended in laparoscopic surgery therefore in order to reduce postoperative morphine consumption the use of NSAIDs has been advocated as part of multimodal analgesia.[87,88] However, some concerns are raised because some experimental studies have stressed the risk of a higher incidence of anastomotic leakages especially ileum dehiscence, with the use of NSAIDs in postoperative period.[89] A recent survey study performed on data from Danish Colorectal Cancer Group, has pointed out that the assumption of diclofenac and ibuprofen even for just two days increased the absolute risk of anastomotic leakage of 7.8% after diclofenac and of 3.2% after ibuprofen treatment. However, after a multivariate analysis only diclofenac, definite by authors a COX2inhibitor, resulted in an increased risk of anastomotic leak, concluding that an increased risk has been shown only after COX-2 inhibitors.[90]

Although with all the limits of a non-randomized and retrospective study, Tillman et al. have observed an increase of postoperative complications in patients undergoing colorectal surgery also after etoricoxib administration.[91] On the contrary, Gorissen et al.[92] reported a higher incidence of complications with use of non-selective COX inhibitors.[92] Also other authors have evaluated a multimodal analgesia with use of NSAIDs in abdominal surgery. A systematic review of 12 randomized studies pointed out that multimodal analgesia with employment of NSAIDs and methylprednisolone can be used in order to reduce postoperative pain and in particular the comment of the authors were that this kind of multimodal analgesia could substitute neuraxialblocks burdened with high risk.[88] Saleh et al have investigated the association between ketolarac and postoperative anastomotic leakage although in a relative small number of patients they have found no significant difference in complications (3.2vs 3.4).[93] Another recent retrospective cohort study that have enrolled 13.082 patients substantially confirms the safety of NSAIDs in elective colorectal surgery but it was seen an increased risk in subjects undergoing emergency surgery.[94] A reduction of 73.8% of opioid with administration of acetaminophen and ketorolac has been reported by Zieman-Gimmel in bariatric surgery without an increase of complications.[95] Particularly important in OSAS and Obese patients is the reduction of opioids in order to reduce postoperative apnea and pulmonary complications, a problem relevant in this kind of patients. However the study are still inconclusive because a large randomized controlled study is not ethic and because many factors can be involved. For example the types of selective and non-selective NSAID's, comorbility, nutritional state, smoking, infection etc.

The possible explanation of the increase of anastomotic complication especially in patients with inflammation (60%) could be due to inhibition of COX-2 production that influence healing with several mechanism on collagen, leucocyte adhesion, etc.[96] The effectiveness of Coxib in postoperative pain in different type of surgery has been evaluated in a Cochrane database Syst Review. Celecoxib administered in a single dose of 200 and 400 mg reduced postoperative pain with a NNT of 4.2 and 2.6 respectively.[97] Etoricoxib at dose of 90 and 120 mg/die h reduced the consumption of morphine and a more rapid bowel recovery.[98]

Postoperative effects in orthopaedic surgery

Among the different orthopaedic pathologies, fractures involve a great number of patients and in elderly patients the more frequent pathology is femur fractures. The process of fracture healing is complex and influenced by multiple factors. Some of them are intrinsic to patient, as age, sex, smoking, nutritional status, while other can be influenced by therapeutic regimen. It is worth recall that prostaglandins play a fundamental role in bone fracture repair stimulating both bone formation and bone reabsorption binding different receptors and that NSAIDs are routinely used as analgesic regime for pain control in postoperative periods of patients undergoing to surgical repair. NSAIDs are also therapeutically used to prevent heterotopic ossification e.g after hip arthroplasty, but the effects on bone fracture healing during administration of NSAIDs are still debated.[99,100] After the first experimental report of negative effect of NSAIDs on healing fracture, several animal studies have been published but actually the data are controversial also if the studies have utilized same animal model and same drugs.[101-103] The same controversial results are reported in humans. These conflicting results are due to different factors: different kind of surgery, e.g. hip replacement, periodontal surgery and some studies are retrospective.[104-106] Furthermore the negative effects of NSAIDs on bone healing could be due to high dose of drugs administered for a long period. More recently, beneficial effects of ketolorac in rib fractures have been reported. The drug reduces pain, decreases incidence of pneumonia and number of hours of postoperative ventilation.[107,108] The effectiveness of a selective and a non-selective NSAIDs, Etoricoxib 90-120mg and ibuprofen 1800mg compared with placebo in postoperative period after total knee replacement has been confirmed in a randomized study on 713 patients. Adverse effects due to morphine administration was more frequent in placebo group and also the incidence of bleeding was not different among the groups.[109]

From data of literature it is possible speculate that the use of selective or not selective NSAIDs for a prolonged period of time can cause disturbances to bone metabolism and inhibition of bone healing but short term use, probably not more than a week after fracture, could not influence significantly fracture healing. There is no strong evidence that NSAIDs should be contraindicated in patients suffering of fractures but should be used with caution in high-risk patients.

Postoperative renal toxicity

The NSAIDs reduce the formation of PG that regulate renal function modulating the renal flow, glomerular filtration and renal transport of liquid and electrolytes at medullar level. The NSAIDs induce different effects on the kidney but the principal side effects are the ischemic renal insufficiency and acute interstitial nephritis, the latter reported in a recent report that identified a 2.7% of acute renal failure due to NSAIDs administration in children.[110] However, other studies have demonstrated that NSAIDs does not decrease slightly renal blood flow in the setting of normal effective circulating volume. In a retrospective cohort study of more 20.000 patients ketorolac or opioids have been administered. Renal function was evaluated in the first two postoperative days measuring creatinine clearance, serum creatinine, urine volume and urinary electrolytes. A non-significant reduction of creatinine clearance and potassium output has been

shown regardless of the type of NSAIDs. Ketorolac results a risk factor of renal failure only if administered for more 5 days.[111,112] A transitory decrease of creatinine clearance and an increase excretion of urinary electrolytes and albumin during acute administration have been reported in a recent study. However no clinical adverse outcome has been reported in elderly patients undergoing orthopaedic surgery, hip replacement and femoral shaft and in women undergoing to hysterectomy after parecoxib administration.[113,114] In this setting NSAIDs have no clinical effects and can be administered with safety, however when hypovolemia is present, NSAIDs decrease renal blood flow through blockade of prostaglandin-mediated vasodilatation of the preglomerular (afferent) arteriole and this can result in unopposed preglomerular vasoconstriction via the actions of endogenous catecholamines and other vasoactive compounds. This can lead to decreased glomerular filtration rate (GFR), decreased natriuresis, and as a consequence of the combined effect of NSAIDs and reduced effective circulating volume, can ultimately result in renal ischemia and acute tubular necrosis (ATN) especially in elderly patients and in patients with risk factor as diabetes, hypertension.[115]

Analgesic therapy pones ulterior problems in patients with chronic kidney disease (CKD). The National Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board has divided the progression of CKD in five stages;

1. Stage 1 is defined as kidney damage with normal or increased glomerular filtration rate (GFR);
2. Stage 2 is defined as a mild reduction in renal function (GFR 60-89ml/min/1.73m2). However patients may be asymptomatic ad kidney disease may be diagnosed incidentally;
3. Stage 3 and 4 are associated with moderate to severe impairment of renal function and reduction in GFR;
4. Stage 5 is the end-stage renal disease (ESRD) where patients require dialysis o renal replacement therapy.

It's very important to understand the clinical staging of kidney function in CKD patients undergoing surgery in order to reduce possible adverse effects of analgesics and to understand the difficulties in managing post-operative pain. Use of NSAIDs in patients in the first stage is not a contraindication and the treatment should be no different from subjects without kidney disease. In patients in second stage of CKD attention must be put in use of NSAIDs. The vasodilatatory effects of prostaglandins on afferent arterioles is blocked by use of NSAIDs so in case of contemporary hypotension and use of ACE-inhibitor the GFR and renal function can be impaired severely. The risk of using NSAIDs in this group of patients should be balanced against the benefit. In third and fourth stage patients the clinical utility of most analgesics is altered because of altered clearance of drugs. NSAIDs may also worsen the pre-existing renal impairment.[116,117]

Postoperative bleeding

The production of Thromboxane A2 by platelet cyclo-oxygenase (COX-1) is essential for the platelet aggregation and vessel vasoconstriction. NSAIDs can interfere with haemostasis because platelets function is prevented by salycilates that acetylates irreversibly cyclooxygenase and by NSAIDs that inhibit reversibly this enzyme. COX-2 have no influence on platelets because spare the constitutive COX-1. So aspirin is routinely suspended before some types of surgery for the risk of postoperative bleeding although recently it was shown that low doses of aspirin does not increase postoperative bleeding in radical prostatectomy.[118] However aspirin should not be be administered unless there is a close indication.[119] About the other NSAIDs, their action on bleeding is unique in the various studies. In a study of patients undergoing tonsillectomy, an increase of number of reoperation but not an increase in bleeding has been observed with a number needed to treat of 60.[120] An slightly increase of reoperation has been confirmed in a recent review, while results of another recent review consider NSAIDs safe not only because does not increase bleeding and secondary haemorrhage but does not influence the need of reoperation.[121,122] Two studies evaluating perioperative blood loss during preoperative administration of diclofenac and ibuprofen after hip arthroplasty and hip replacement have been discordant because an increase of 45% and 32% of blood loss.[122,123] In contrast, a recent study of Friedman et al. have shown no increased risk of bleeding also when non-steroidal anti-inflammatory drugs or aspirin is associated to dabigratan in patients undergone to hip or total knee arthroplasty.[124] Considering other types of surgery, an increased risk of bleeding is reported in breast surgery and in gastric bypass surgery during ketorolac administration for which the Authors suggest a caution on administration of NSAIDs.[125,126] In particular a single perioperative intravenous dose of ketorolac was associated with a greater than three-fold increase in the likelihood of requirement for surgical hematoma evacuation. The authors suggest that it may be prudent to consider carefully whether the potential risks associated with the use of ketorolac outweigh the potential benefits of using ketorolac in patients undergoing breast reduction.

Conclusion

NSAIDs play a very important role in postoperative pain control in mild and moderate pain and play a fundamental role in outpatient surgery where they can be used per os after discharge. They are not suitable for major surgery and are associated with opioids, adjuvants or loco-regional technique. The type of NSAIDs or coxibs utilized in perioperative period must be related to various factors: cost effectiveness, duration and modality of administration, comorbidities, taking into account that the selective and non-selective compounds are equally effective as analgesic showing almost the same NNT and identical opioid sparing effects by about 20-50%. The correct use and choice of different analgesic depends of habit hospital, beliefs of health and the routes of administration that is preferred. The wide use of NSAIDs and Coxibs for acute and chronic pain has focused on the advantages but also the side effects often severe or life threatening. In acute setting, considering the contraindications and reducing dosage in elderly, these drugs can be utilized with efficacy in all almost types of surgery. Their role is irreplaceable. However, the acute side effects induced by a brief period of administration as in the immediate postoperative period is not well understood. Gastrointestinal and cardiovascular adverse events, renal impairment, bleeding and cardiovascular complications are rare in postoperative period. Safety profile varies for each substance, dose and duration. Different toxicity is reported in different trials and studies and the same drug have been implicated in an increase or decrease of cardiovascular toxicity related to type of trial and patients being particularly at risk are patients with cardiovascular disease. As example celecoxib is retained to produce more or less cardiovascular risk. In an experimental study the ligation of anterior descendent coronary artery produced a reduction of infarct size and apoptosis in animal pre-treated with celecoxib.[127] Despite the similar effects of non-selective COX1 and Coxib, some true or potential advantages can be attribute to these last drugs. Certainly they does not give antiplatelet aggregation and can be administered or continued in the preoperative period in subjects with empty stomach and, as underlined by some authors, ameliorate the quality of postoperative analgesia. A risk of postoperative bleeding must be in mind when they are utilized in some types of surgery and some concerts are suggested when utilized after bone fractures.

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Conflicts of Interest

The authors do not have any Conflict of interests.

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