Pharmacology of Acetaminophen, Nonsteroidal Antiinflammatory Drugs, and Steroid Medications: Implications for Anesthesia or Unique Associated Risks

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Providing analgesia is fundamental for health care providers when treating patients undergoing different surgical procedures. Preventing pain, instead of treating the pain once it has started, is a challenging goal in everyday anesthesiology practice. Whether providing analgesia before (preemptive analgesia\textsuperscript{1}), during, or after surgery,

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it is particularly important to know which drug to choose, considering not only its indication and effectiveness, but also the pharmacologic profile, dosing, route, and potential side effects, as well as patients’ comorbidities.

Acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, and opioids are 4 major types of nonopioid drugs considered in perioperative pain management. Intraoperatively, nonopioid analgesics have been used to decrease anesthetic and opioid requirements and to reduce the hemodynamic changes related to painful stimuli.

We conducted a literature review regarding the main nonopioid analgesics used in anesthesiology practice beginning with a review of their pharmacologic characteristics. We are reporting their efficacy in the perioperative setting, essentially based on published systematic reviews and metaanalyses.

The use of analgesics has historically proven to decrease the risks related to severe pain, such as myocardial ischemia, thrombosis, and thromboembolisms associated with immobilization, atelectasis, and pulmonary complications correlated with decreased tidal volume and shallow breathing, impaired wound healing and rehabilitation. However, opioids have been linked to numerous adverse effects, especially when used alone. These effects include nausea, vomiting, pruritus, urinary retention, constipation, and respiratory depression. The risks of adverse effects can be lowered by the use of multimodal analgesia. Multimodal analgesia involves the use of different medications and techniques to produce analgesia through different mechanisms. It has been proposed since the 1990s, so that the dose of opioids can be restricted or even avoided. Nevertheless, multimodal pain management also includes approaches to regional anesthesia, peripheral nerve blocks and local infiltration techniques, and neuraxial analgesia, discussions of which are outside of the scope of this review.

ACETAMINOPHEN

Acetaminophen (also known as paracetamol) has been clinically used since 1887 and was not marketed worldwide until the 1950s owing to concerns regarding toxicity. Acetaminophen is the active metabolite of phenacetin. It has analgesic and antipyretic effects similar to those of aspirin. However, its antiinflammatory properties are weak, presumably owing to poor effectiveness when the concentration of peroxides is high (at the inflammatory site). The analgesia provided by acetaminophen is induced by an inhibition of the cyclooxygenase (COX) pathway, decreasing the production of prostaglandins. Other recently described possible mechanisms of action include an endocannabinoid effect and a modulatory effect on the descending serotonergic inhibitory pathways.

Acetaminophen can be administered orally or per rectum and, since 2010, an intravenous form was approved in the United States. Oral and rectal administrations have excellent bioavailability but undergo first-pass hepatic metabolism. Oral plasma peak concentration is noticed within 1 hour, and in approximately 30 minutes with the intravenous formulation. The therapeutic dose in adults is up to 1000 mg every 6 hours, with a maximum of 4 g/d. Conjugation with glucuronic and sulfuric acid are the principal pathways of its metabolism. However, a small proportion of acetaminophen is metabolized to NADPI, a product related to the toxic effect of overdose. This byproduct is highly reactive and hepatotoxic, and can lead to a potentially fatal hepatic failure, renal tubular acidosis, and hypoglycemia with very high doses of acetaminophen. It can be detoxified with the use of N-acetylcysteine therapy. The elimination half-life of acetaminophen is 2 to 3 hours and the analgesic effect is 4 to 6 hours.
A summary of the included most relevant studies regarding the perioperative use of acetaminophen is depicted in Table 1.

The effects of acetaminophen, COX 2 selective inhibitors (coxibs) and dexamethasone on postoperative pain, has been studied by Tiippana and colleagues randomizing a total of 160 postcholecystectomy patients in several groups, and then evaluating postoperative pain. The results showed that dexamethasone reduced the need for opioids in phase 2 post anesthetic care unit (decreasing by an average of 2 mg the need of oxycodone [7.0 mg vs 9.1 mg; \( P < 0.001 \]); patients in the groups receiving coxibs needed more rescue opioid medications compared with those receiving acetaminophen (\( P < 0.001 \)). The authors concluded that acetaminophen could be recommended for the treatment of pain after laparoscopic cholecystectomy over NSAIDs, owing to the superior safety profile of acetaminophen.

In a metaanalysis, Doleman and colleagues included 7 articles containing a total of 544 patients older than 16 years, aiming to determine the effect of prophylactic intravenous (IV) acetaminophen use on postoperative pain, opioid consumption, and vomiting. The results were cautiously analyzed owing to potential bias and heterogeneity (\( I^2 = 33\%–82\% \)). It was found that there was a statistically significant lower 24-hour opioid consumption (standardized mean difference [SMD], -0.52 [95% confidence interval [CI], -0.98 to -0.06]), delayed time of first analgesic request (mean difference [MD], -0.34 [95% CI, -0.67 to -0.01]) and decreased incidence of postoperative vomiting (risk ratio, 0.50 [95% CI, 0.31–0.83]); the incidence of nausea was not affected.

De Oliveira and colleagues similarly analyzed 11 prospective randomized clinical trials evaluating 740 patients who received a single 1000 mg dose of IV acetaminophen before or during surgery compared with patients who did not receive this drug. Results showed decreased pain at rest (weighted mean difference [WMD], -1.1 [95% CI, -2.0 to -0.2]), decreased pain at movement during the first 4 hours after surgery (WMD, -1.9 [95% CI, -2.8 to -1.0]) and decreased opioid consumption in the first 24 hours (WMD, -9.7 [95% CI, -13 to -6.4]). Both authors showed a correlation between the use of acetaminophen and decreased opioid use and postoperative pain, but the effect on PONV was not clear. This metaanalysis analyzed studies with different types of anesthesia, surgical procedures, postoperative analgesia, and timing for the dose of acetaminophen given, supposing a high level of heterogeneity (\( I^2 > 50\%)\), potential for bias, for which the data have to be cautiously interpreted.

In a systematic review with 1909 analyzed patients from 21 different studies, Ong and colleagues primarily compared pain scores and the need for analgesic supplementation between patients receiving a combination of an NSAID and acetaminophen and patients receiving only 1 of these 2 drugs. Results, as expected, showed that the combination was more effective: 17 of 20 studies (85%) comparing acetaminophen alone versus the combination found a reduction of pain intensity standard deviation (SD) of 35% (vs 10%) and a decreased need for analgesic supplementation of SD = 38.8% (vs 13%). Nine out of 14 studies (64%) comparing the combination versus the use of NSAID alone, indicated a reduction in pain intensity (38% vs 26%) and analgesic supplementation (31% vs 13%).

Even when acetaminophen is compared with weak opioids like tramadol, which has a potency of approximately 10% that of morphine, as studied in several randomized clinical trials, measuring postoperative pain relief and PONV; acetaminophen use showed less PONV with similar analgesia based on the visual analog scale (\( P < 0.001 \)).

Regarding the effect on PONV, Apfel and associates conducted a metaanalysis based on 30 studies and 2364 patients to determine what the relationship was.
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>Main Subject of Research</th>
<th>Statistically Relevant Reported Outcomes of Interest to the Metaanalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doleman et al, 2015</td>
<td>7</td>
<td>544</td>
<td>Effect of the use of preventive IV acetaminophen after surgery</td>
<td>Preventive acetaminophen decreased: overall opioid consumption, pain during the 2 firsts postoperative hours, incidence of PONV</td>
</tr>
<tr>
<td>De Oliveira et al, 2015</td>
<td>11</td>
<td>740</td>
<td>Effect of systemic acetaminophen to prevent postoperative pain</td>
<td>Decreased pain at rest during the first 4 h postoperative, Decreased pain at movement during the first 4 h postoperative, Decreased postoperative opioid consumption</td>
</tr>
<tr>
<td>Apfel et al, 2013</td>
<td>30</td>
<td>2364</td>
<td>Relationship between use of acetaminophen and incidence of PONV</td>
<td>Use of prophylactic acetaminophen reduced the incidence of PONV, Decreased incidence of PONV was more significant when acetaminophen was given preoperatively or intraoperatively, Reduction of PONV with prophylactic IV acetaminophen was not related with opioid consumption</td>
</tr>
<tr>
<td>Ong et al, 2010</td>
<td>21</td>
<td>1909</td>
<td>Efficacy of acetaminophen plus NSAIDs in the treatment of postoperative pain vs either drug alone</td>
<td>85% of the compared studies (17/20) showed that the coadministration was more effective than receiving only acetaminophen, 64% of the compared studies (9/14) showed that the coadministration was more effective than receiving NSAIDs alone</td>
</tr>
<tr>
<td>Remy et al, 2005</td>
<td>7</td>
<td>490</td>
<td>Effect of acetaminophen on PCA morphine consumption and side effects</td>
<td>Use of acetaminophen did not show reduction in PCA morphine side effects, Use of acetaminophen reduced the consumption of 20% PCA morphine</td>
</tr>
</tbody>
</table>

*Abbreviations: I², index of heterogeneity of the analysis; IV, intravenous; NSAIDs, nonsteroidal antiinflammatory drugs; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting.*
between the use of acetaminophen and the decrease of PONV. They found that, when acetaminophen was given prophylactically (either before surgery, intraoperatively, or immediately after surgery), there was a statistically significant reduction of PONV (RR [risk ratio] 0.63 [95% CI 0.54–0.75]) not related to the amount of postoperative opioid consumption; this reduction was more significant if the dose of acetaminophen was given preoperatively or intraoperatively rather than postoperatively. Similarly, Remy and colleagues conducted a metaanalysis, wherein morphine consumption and side effects were compared in patients either receiving only patient-controlled analgesia with morphine (226 patients), or patients receiving patient-controlled analgesia with morphine plus oral or IV acetaminophen (265 patients). An acetaminophen-related morphine-sparing effect was statistically significant (−9 mg [95% CI, -15 to -3]; \(P = .003\)). However, Remy and colleagues failed to show a decrease in morphine side effects when acetaminophen was used. It is important to mention that in the former metaanalysis, neither the route of administration nor the moment when acetaminophen was administered were standardized, leading to possible bias and elevated heterogeneity.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

NSAIDs are very versatile antiinflammatory, antipyretic, and analgesic drugs, with a wide therapeutic index, and few noteworthy adverse effects when used in appropriate dosing. However, a boxed warning was issued for all prescription NSAIDs by the US Food and Drug Administration on April 6, 2005, which indicated that NSAIDs can cause gastrointestinal (GI) side effects (obstruction, perforation, bleeding) and cardiovascular side effects (thrombosis, myocardial infarction, stroke), even in standardized doses. Furthermore, this warning is applicable to all prescription NSAIDs without regard to COX selectivity (COX 1 selective; COX 2 selective; or nonselective). They are useful in perioperative analgesia and are usually prescribed for the management of immediate postoperative pain. However, the pharmacologic profile can vary among different NSAIDs, for which a brief, evidence-based description is provided in this review.

Even though NSAIDs have been used for centuries, their mechanism of action was elucidated in 1971 and was found to include an inhibition of the synthesis of prostaglandins. NSAIDs block the action of the enzyme responsible for this effect, COX. COX has 2 main isoforms: COX-1, expressed constitutively in almost every cell, and COX-2, which is upregulated by cytokines, growth factors, and shear stress. There is evidence that whenever the cell is damaged there is release of prostaglandins, which is what triggers an inflammatory cascade response. At high doses of NSAIDs, other mechanisms have been implicated in their effects. However, the main mechanism involved seems to be the COX inhibition. Aspirin differs from NSAIDs because aspirin irreversibly acetylates the enzyme.\(^{23,24}\)

NSAIDs include a variety of drugs with interindividual and intraindividual differences in their clinical effects and pharmacokinetics. In general, they have high bioavailability, with peak concentrations occurring within the first 4 hours when administered orally. IV ibuprofen and IV ketorolac are available in the United States. Most NSAIDs are bound to plasma proteins in more than 90%, and undergo hepatic metabolism and renal excretion. Thus, this should be taken into consideration for patients with severe hepatic or renal disease.\(^{24}\)

Most NSAIDs inhibit both COX isoenzymes with little selectivity, although some (coxibs, meloxicam, nimesulide) have been shown to mainly block COX-2. A comparison of 2 of the COX-2–selective NSAIDs (meloxicam vs celecoxib) did not show...
significant differences in pain severity. A summary of the included most relevant studies regarding perioperative use of NSAIDs is provided in Table 2.

A systematic review conducted by Straube and colleagues included 22 clinical trials and 2246 patients, and focused on the effect of COX-2–selective NSAIDs (coxibs) in postoperative outcomes. Unfortunately, these drugs have shown an increased number of adverse effects related to thrombosis and myocardial infarction. However, in none of the clinical trials reviewed by Straube and colleagues is there a mention of serious cardiovascular or renal impairment, or any infections. Even though this study indicates that coxibs may have a potential use as postoperative analgesia, there was not enough evidence to support the use of coxibs over nonselective NSAIDs.

Michelet and colleagues conducted a metaanalysis based on 27 articles, comparing postoperative outcomes in 567 pediatric patients who received NSAIDs (25 articles comparing nonselective NSAIDs, and 2 comparing coxibs) either before or during surgery in 418 patients who did not receive this medication. Although an increased heterogeneity ($I^2 = \text{ranging from 0\% to 90\%}$) and possible publication bias were present, the metaanalysis showed that the use of NSAIDs decreased opioid consumption in the postanesthetic care unit (SMD, $-0.66$ [95\% CI, $-0.84$ to $-0.48$]; $P<.00001$) as well as during the following 24 hours (SMD, $-0.83$ [95\% CI, $-1.11$ to $-0.55$]; $P<.00001$). There was also a statistically significant reduction in PONV in patients 24 hours after adenotonsillectomy (odds ratio, 0.75; $P = .04$). The study failed to show a difference between nonselective NSAIDs and rofecoxib on pain severity, opioid consumption and postoperative nausea and vomiting (PONV) incidence. Subsequently, Bu and colleagues confirmed these results through a metaanalysis in pediatric patients assessing the efficacy and safety of parecoxib for acute postoperative pain. The data from 12 trials (994 patients) were analyzed. The results showed an overall reduction of pain scores and lower PONV compared with placebo.

The data from 31 randomized controlled studies were analyzed by Wong and colleagues to determine the effect of acetaminophen and NSAIDs on opioid consumption in children. To further explain this effect, the studies were classified in 4 groups (A–D), based on the type of administration and the distribution of the doses. In groups A and B, an infusion of IV opioid was controlled by the patient (patient-controlled analgesia) or the nurse (nurse-controlled analgesia). When NSAIDs or NSAID plus paracetamol were administered several times perioperatively (group A), the opioid dose requirements were reduced by 31.6\% (95\% CI, 16\%–46\%). When only 1 dose of NSAIDs was given (group B), the mean reduction was 24\%. Likewise, in groups C and D (where the distribution of doses for NSAIDs and acetaminophen was similar to groups A and B), the opioids were given in bolus doses (instead of as infusions) and showed significant opioid-sparing effects with a mean reduction for the amount required for analgesia by 24\%. The use of NSAIDs alone or in combination also resulted in increased patient satisfaction, lower pain scores and a reduced incidence of PONV. No increased risk of bleeding was noted.

In adults, Bainbridge and colleagues after a metaanalysis of 20 randomized, controlled trials (RCTs), with a total of 1065 patients, showed a significant reduction in pain scores and opioid consumption with NSAID use. The studies included only postcardiothoracic surgery patients receiving NSAIDs. All-cause mortality, incidence of atrial fibrillation, bleeding, or any other major side effect did not experience a significantly different change overall.

Nevertheless, special attention must be paid to aspirin. It has long been established that it has a potent and irreversible platelet antiaggregation effect. In a metaanalysis based on 28 studies and more than 20,000 patients, the authors showed that, with
<table>
<thead>
<tr>
<th>Author and Year</th>
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<th>$I^2$ Range (%)</th>
</tr>
</thead>
</table>
| Moore et al,\[26\], 2015 [Review] | 41 | >10,000 | Oral analgesic in postoperative pain in adults (single dose) | - Efficacy of analgesic (NSAIDs, opioids and acetaminophen) varies with type, dose and combination  
- All analgesics provided and significant absolute risk reduction, with an average NNT between 2 and 3 | N/A |
| Ma et al,\[27\], 2014 [Systematic review] | 27 | >20,000 | Safety of preoperative aspirin in patients undergoing CABG | - Doses <100 mg represent minimal risk of bleeding  
- Not clear cutoff value for risk of bleeding  
- Doses >325 mg are related to increased risk of postoperative bleeding and increased packed red blood cells requirements | 0–88 |
| Wong et al,\[28\], 2013 [Systematic review] | 31 | Not reported | Effect of acetaminophen and NSAIDs on opioid consumption in children | - Better analgesic effect when NSAIDs are given with acetaminophen than when given alone  
- NSAIDs produce an opioid-sparing effect in both, bolus and infusion  
- No increased risk of bleeding or adverse effects overall | N/A |
| De Oliveira et al,\[29\], 2012 | 13 RCT | 782 | Efficacy and dose of ketorolac in postoperative pain | - Overall postoperative pain intensity decreased with the use of ketorolac 60 mg at rest and with movement in the first 24 h  
- Doses of 30 mg did not show reduction in pain  
- PO opioid consumption and PONV were decreased | 0–93 |
| Michelet et al,\[30\], 2012 | 27 | 985 | Pediatric use of NSAIDs for PO pain | - Postoperative: NSAIDs decreased opioid consumption in PACU and during the next 24 h  
- Decreased PONV after 24 h adenotonsillectomy  
- No general difference between nonselective NSAIDs and coxibs | 0–90 |
| Bainbridge et al,\[31\], 2006 | 20 | 1065 | Analgesia and opioid sparing effect of NSAIDs in cardiothoracic surgery | - Significant pain score reduction  
- Significantly less need of opioids in the 24 h postoperative  
- No difference on heart, renal and GI functioning | 0–89 |
| Straube et al,\[32\], 2005 [Systematic review] | 22 CT | 2246 | Effect of coxibs in postoperative outcomes compared with placebo | - Reduction in postoperative pain, opioid consumption  
- No significant difference in intraoperative blood loss  
- Overall, no significant difference in PONV | N/A |

**Abbreviations:** CABG, coronary artery bypass grafting; coxibs, cyclooxygenase inhibitors; CT, controlled trial; $I^2$, index of heterogeneity of the analysis; N/A, not applicable; NNT, number needed to treat; NSAIDs, nonsteroidal antiinflammatory drugs; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; RCT, randomized, controlled trial.
preoperative long-term doses of less than 100 mg/d, the risk of bleeding was not statistically increased in patients undergoing coronary artery bypass grafting (MD, 103 [95% CI, -65 to 272]; P = .23). However, at higher doses, the risks of postoperative bleeding, PRBC (packed red blood cells) transfusion requirements and reoperation for rebleeding had a statistically significant increase.27

In a different metaanalysis, comparing NSAIDs with opioids, Mezentsev37 showed that there was no difference in the analgesia provided by these 2 classes of drugs during modern shock wave lithotripsy.

Scientific review on the use of ibuprofen indicates that ibuprofen is a racemic mixture of S- and R-isomers.4 The R-isomer is inactive and the S-isomer is the one responsible for the therapeutic effects. However, approximately 60% of the R-enantiomer is metabolized to the S-isomer (dexibuprofen), helping in the maintenance of the pharmacologic effects. Derry and colleagues38 aimed to determine the role of the oral dexibuprofen on postoperative pain in adults and showed that 400 mg of racemic ibuprofen was related to a 50% pain relief in 51% of patients, and 70% of the patients receiving 400 mg dexibuprofen use showed a 50% pain reduction. These results lacked statistical power owing to the low number of subjects and lack of convincing evidence available. Koh and colleagues4 mentioned 3 studies on the therapeutic efficacy in postoperative analgesia of ibuprofen compared with placebo, and the results showed a statistically significant reduction in postoperative pain and opioid consumption with no significant variance on the incidence of adverse effects even with a daily dose of 3200 mg of ibuprofen.

De Oliveira and colleagues29 studied the effects of a single dose of systemic (IV or IM) ketorolac on postsurgical pain. A metaanalysis of 13 randomized clinical trials including 782 patients showed a statistical significance (WMD, -0.64 [95% CI, -1.11 to -0.18]) in the first 4 hours for postoperative pain over placebo. Other benefits included decreased opioid consumption (MD, -1.71 [95% CI, -2.83 to -0.60]) and PONV (odds ratio (OR) 0.57). Differences between the intramuscular or intravenous routes were difficult to analyze because of a low number of patients in each subgroup. However, it seems that ketorolac provided a better analgesic effect when the dose is given IM. Two doses were studied: 30 mg (4 RCTs) and 60 mg (9 RCTs). Doses of 30 mg did not seem to have a clinically important benefit on outcomes.

As expected, oral NSAIDs have also proven to be beneficial for postoperative analgesia. Oral diclofenac (sodium and potassium) was studied by Derry and colleagues,39 who compared the NSAID versus placebo in 18 studies including 3714 subjects. The study showed an increase in the efficacy of the drug, related to the dose used, of up to 100 mg. The effect was greater for the potassium formulation of Diclofenac, and the maximum pain relief (for 50 mg) compared with placebo was evident with a number needed to treat of 2.1 (95% CI, 1.9–2.5).39 Moore and colleagues26 extended this study to general analgesics, with an analysis of 39 reviews. Forty-one different NSAIDs were studied, and the overall effect was similar to the one of diclofenac (the average number needed to treat ranged from 1.6 for ibuprofen 200 mg + acetaminophen 500 mg; to 3.5 for acetaminophen alone 500 mg). Certain drugs like etodolac and aspirin had a considerable change in efficacy related to the different doses.

GI events and renal impairment are two of the most common adverse effect of NSAIDs and usually become manifest in the first weeks of therapy, even though GI bleeding can occur much later. Other systems affected include central nervous system (headache, vertigo, dizziness, confusion, depression), blood (inhibited platelet activation, increased risk of bleeding), uterine (tocolysis), vascular (closure of ductus arteriosus), and hypersensitivity reactions.24
Related to the renal impairment, a metaanalysis on the effect of NSAIDs on the post-operative renal function of 1459 healthy adults found that NSAID use only led to a mild transient reduction of the creatinine clearance (16 mL/min [95% CI, 5–28]) 1 day after surgery, which was insignificant when compared with placebo (difference placebo/NSAIDs: 0 mL/min). Therefore, NSAIDs should not be avoided in healthy individuals owing to concern for renal side effects.

An increased incidence of gastric or duodenal ulcers and upper GI tract bleeding varies according to the specific NSAID. For instance, the odds ratio for upper GI tract bleeding for diclofenac is 9.1, ibuprofen 8.2, and meloxicam 13.1. An interesting exception is metamizole (Dipyrone), which odds ratio is 0.9 (95% CI, 0.7–1.2) and has been proposed as the drug to use in patients with GI or renal impairment (odds ratio, 1.2 [95% CI, 1.0–1.3]). IV coadministration of H₂ blockers and proton pump inhibitors, 1 hour before surgery, has been proven to decrease gastric volume and increase the pH.

CORTICOSTEROIDS

The hormonal steroids synthetized in the outer adrenal cortex belong to 1 of 2 classes: glucocorticoids (cortisol), with effects in the intermediary metabolism, or mineralocorticoids (aldosterone), with mainly salt-retaining activity. Synthetic analogs of glucocorticoids, especially methylprednisolone, betamethasone, and dexamethasone, have been found to have several uses in perioperative medicine. The differences between these medications are predominantly based on their antiinflammatory potency, sodium-retaining potency, and duration of action (ranging from several minutes to several days).

The main mechanism of action of glucocorticoids involves interaction with specific proteins and regulation of gene expression, which usually takes hours to become apparent. However, receptor-independent mechanisms have been described. Altogether, this affects several metabolic pathways, generating anabolic, catabolic, anti-inflammatory, immunosuppressive, vascular, endocrine, and many other effects.

Regarding purposeful perioperative use, studies have described several effects. For instance, decreased nausea and vomiting, relief of inflammation, analgesia, opioid-sparing effect, cardiovascular uses, positive pulmonary effects, and neuraxial involvement have been the subjects of intensive research. A summary of the included most relevant studies regarding perioperative use of corticosteroids is shown in Table 3.

The Society of Ambulatory Anesthesiology included the use of steroids in the guidelines for the management of PONV, primarily dexamethasone 4 to 5 mg IV at induction (level of evidence: A1), and methylprednisolone 40 mg IV (level of evidence: A2) among the first-line therapy of drugs used for prophylaxis. Wang and colleagues included 7 studies comparing ondansetron with dexamethasone in a metaanalysis and concluded that in the first 6 hours postoperative, ondansetron was more effective (relative risk [RR], 1.71 [95% CI, 1.05–2.77] but dexamethasone was more effective in the next 24 hours (range, 6–24 hours; RR, 0.51 [95% CI, 0.27–0.93]).

Because PONV and pain are the 2 most common reasons for delaying discharge for patients undergoing laparoscopic cholecystectomy, these could be prevented with the co-administration of dexamethasone and NSAIDs.

Allen and colleagues analyzed 8 RCTs and found that, in patients who received neuraxial morphine as part of the anesthetic technique, dexamethasone was an effective drug for prophylaxis of PONV (decreased incidence of PON: RR, 0.57 [95%
### Table 3
Summary of the included most relevant studies regarding perioperative use of corticosteroids

<table>
<thead>
<tr>
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<th>I² Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jebaraj et al.45 2016</td>
<td>5 RCT</td>
<td>Not reported</td>
<td>Epidural local analgesia using dexamethasone and local anesthetics</td>
<td>• Decreased demand for rescue analgesia, decreased amount of morphine needed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Knezevic et al.46 2015 [Systematic review]</td>
<td>14</td>
<td>1022</td>
<td>Dose-related perineural dexamethasone effect in brachial plexus block</td>
<td>• Better PO analgesia at 24 and 48 h for doses between 4 and 10 mg • Increased latency for sensory and motor block • Longer duration of motor block • No effect in the incidence of complications</td>
<td>N/A</td>
</tr>
<tr>
<td>Huynh et al.47 2015</td>
<td>12</td>
<td>1054</td>
<td>Effect of dexamethasone in the combination of local anesthetics on peripheral blockade in adults</td>
<td>• 26 min longer analgesia in average • 76 min longer motor blockade in average • Lower incidence of PONV (9% vs 27% in control group) • No difference on pain intensity</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wang et al.48 2015</td>
<td>7</td>
<td>608</td>
<td>Dexamethasone vs ondansetron for PONV after laparoscopic surgery</td>
<td>• Comparable effectiveness for PONV • Postoperative, in the first 6 h, ondansetron was more effective (RR, 1.71) • Postoperative, 6–24 h dexamethasone was more effective (RR, 0.51) • Ondansetron has higher cost benefit ratio • Overall PONV: dexamethasone 33.3%, ondansetron 36.7%</td>
<td>0–65</td>
</tr>
<tr>
<td>Viviano et al.49 2013 [Systematic review]</td>
<td>70</td>
<td>&gt;5000</td>
<td>Perioperative corticosteroids for prevention of postoperative atrial fibrillation</td>
<td>• Hydrocortisone (100 mg/d) shows an ARR 18% (48%–30%) • Methylprednisolone + dexamethasone: ARR: 30% (51%–21%) • Dexamethasone 50-210 mg risk difference, −0.12</td>
<td>N/A</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>No.</td>
<td>Sample</td>
<td>Study Design</td>
<td>Main Findings</td>
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<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Allen et al</td>
<td>2012</td>
<td>8</td>
<td>768</td>
<td>8 RCT</td>
<td>Dexamethasone reduced the incidence of PONV, the use of rescue antiemetic therapy, pain scores, and rescue analgesics</td>
</tr>
<tr>
<td>Waldron et al</td>
<td>2012</td>
<td>45</td>
<td>5796</td>
<td></td>
<td>Effect of dexamethasone (1.25–20 mg) in PO pain and adverse effects</td>
</tr>
<tr>
<td>De Oliveira et al</td>
<td>2011</td>
<td>24</td>
<td>2751</td>
<td>24 RCT</td>
<td>Efficacy and dose of dexamethasone in PO pain</td>
</tr>
<tr>
<td>Baker et al</td>
<td>2007</td>
<td>9</td>
<td>990</td>
<td></td>
<td>Corticosteroids in postcardiothoracic surgery atrial fibrillation</td>
</tr>
<tr>
<td>Sauerland et al</td>
<td>2000</td>
<td>51</td>
<td>1696</td>
<td></td>
<td>Risk-benefit analysis of the use of high dose of methylprednisolone (15–30 mg/kg) in surgical patients</td>
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Abbreviations: ARR, absolute risk reduction; I², index of heterogeneity of the analysis; N/A, not applicable; OR, odds ratio; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; RCT, randomized control trials; RR, relative risk.
CI, 0.45–0.72]; POV: RR, 0.56 [95% CI, 0.43–0.72] and the use of rescue antiemetic drugs (RR, 0.47 [95% CI, 0.36–0.61]). There was also a statistically significant effect on 24-hour pain scores and the use of rescue analgesics.

Dexamethasone has also shown an effect on pain scores and need for rescue medication. In 2011, De Oliveira performed a metaanalysis using 24 randomized clinical trials, studying the effect of 3 different single doses of IV dexamethasone (<0.1 mg/kg; 0.11–0.2 mg/kg; >0.21 mg/kg), given in a range from 2 hours preoperatively to use during surgery. The outcomes studied were the effects on postoperative pain and the incidence of adverse events. Results, comparing SD, indicated that dexamethasone decreased the overall postoperative opioid consumption (SD, –0.41 [95% CI, -0.58 to -0.24]) and postoperative pain during the first 24 hours, either at rest (SD, –0.49 [95% CI, -0.67 to -0.31]) or with movement (SD, –0.47 [95% CI, 0.71 to -0.24]). No change was evident at low doses on either early pain at rest (<4 hours; SD, –0.33 [95% CI, -0.7 to 0.04]) or postoperative opioid consumption (SD, –0.17 [95% CI, -0.38–0.03]). Nor was there evidence of a dose-dependent increased risk of adverse effects, but, according to the authors, this may not apply for patients with a high risk of wound infections. In a larger metaanalysis involving 45 studies and 5796 patients, Waldron and colleagues reached similar conclusions. Nevertheless, heterogeneity was high, ranging from 0% to 97%.

A recent metaanalysis has reported an effect of combining dexamethasone (4–10 mg) to the local anesthetics used for peripheral nerve block. JebraJ and colleagues found that the need of postoperative analgesia rescues (RR, 0.51 [95% CI, 0.41–0.63]) and the consumption of morphine (MD, –7.89 mg [95% CI, -11.66 to -3.71]), significantly decreased when epidural dexamethasone was administered combined with local anesthetic.

Similarly, Huynh and colleagues based a metaanalysis on 12 trials including 1054 patients, and identified several results of combinations of steroids and local anesthetics. A longer duration of analgesia and faster onset of analgesic action were found to be statistically significant; patients receiving the combination had analgesia for around 351 minutes (WSD, 351 [95% CI, 288–413]), versus control patients who had analgesia lasting around 325 minutes (range, 98–888). However, there was no difference on pain intensity. Time of motor blockade also increased (WSD, 276 minutes [95% CI, 167–387]) approximately 76 minutes more than the control group. PONV was reduced with the use of the combination, resulting in an absolute risk reduction of 18% (PONV 9% vs 27%).

Knezcic and colleagues, after a systematic review of 14 studies and a total of 1022 patients, concluded that adding dexamethasone to the local anesthetics used for brachial plexus blocks was related to longer postoperative analgesia at 24 hours (SMD, –1.46 [95% CI, -2.43 to -0.50]) and 48 hours (SMD, –1.20 [95% CI, -2.26 to -0.13]); longer postoperative analgesia with dose between 4 and 5 mg (SMD, 2.41 [95% CI, 1.47–3.35]) and doses of 8 to 10 mg (SMD, 4.46 [95% CI, 3.54–5.38]) of dexamethasone; increased duration of sensory and motor block (SMD, –0.56 [95% CI, -1.13 to 0.00]), increased latency for the block, and no effect in the incidence of complications.

Corticosteroids have been shown to improve the respiratory dynamics by different mechanisms, including an antiinflammatory effect linked to cytokine production, cell recruitment, and decreased bronchial hyperactivity. Along with anticholinergic agents and beta2 agonists, parenteral corticosteroids are used for acute control of reactive airways in asthmatic patients. In a systematic review of 51 randomized clinical trials with a total of 1696 patients, Sauerland and colleagues showed that the use of high dose methylprednisolone (>15 mg/kg), used no more than 3 days after surgery and...
discontinued afterward, did not increase significantly the complication rates and was actually related to better outcomes on lung function associated with reduction of pulmonary complications (risk difference of −3.5 [95% CI, −6.1 to −1.0]). Unfortunately, no metaanalysis was found regarding the dose and use of corticosteroids in intraoperative bronchospasm or used to reduce airway edema.

One double-blind clinical trial comparing the effects of methylprednisolone 1 day after surgery on pain and opioid consumption in the first postoperative hours in 75 patients showed that the methylprednisolone pain-relieving effect was similar to that of ketorolac, and was statistically significantly (P<.05) better than placebo. In contrast, a more recent clinical trial comparing the effects of ketorolac (30 mg) versus betamethasone (12 mg) and dexamethasone (4 mg) showed that patients receiving ketorolac had less pain (88% of patients) and an earlier discharge (165 minutes) than did patients receiving dexamethasone (74%/192 minutes) and betamethasone (67%/203 minutes).

As mentioned, corticosteroids have not only proven to be useful in the prevention of PONV and reduction of postoperative pain after anesthesia, but also have other salutary effects on physiology. Moderate doses of corticosteroids have proven to reduce the incidence of postoperative atrial fibrillation in several RCTs and metaanalyses. Baker and colleagues reported that corticosteroids (dexamethasone 50–210 mg or equivalent) in patients postcardiothoracic surgery, significantly reduced the risk of atrial fibrillation by 45% (OR, 0.55 [95% CI, 0.39–0.78]). Corticosteroids have also been shown to decrease the needs for reintubation and the incidence of stridor in patients at risk in the intensive care unit, which was shown by Jaber and colleagues in a metaanalysis of 7 trials that included 1946 patients, and confirmed by Malhotra and colleagues in a pediatric population. This is related to their potent antiinflammatory effects on the airway. Similarly, steroids have been used to decrease the incidence of postoperative sore throat, found by prophylactically using dexamethasone 10 mg before tracheal intubation, or by adding betamethasone gel applied over the endotracheal tube.

Multiple side effects have been described with the use of corticosteroids. Most are related to discontinuation of chronic therapy or resulting from continuous use at supra-physiologic doses. Some of these side effects include suppression of the adrenal hormonal axis, hydroelectrolyte imbalances, hyperglycemia, susceptibility to infections, myopathy, and osteoporosis. However, glucocorticoids are usually used perioperatively for only short periods of time, and it is unusual for patients to develop serious adverse side effects, limiting them primarily to behavioral changes (insomnia, nervousness, changes in the mood, etc) and GI disturbances.

Additionally, a systematic review of 51 studies concluded that a single high dose of methylprednisolone was safe for use and was associated with nonsignificant increased risks, including infections and wound healing problems.

Likewise, the literature review has shown no relationship between the use of single dose steroids and an increased risk of wound infections and urinary tract infections. However, dexamethasone, as used for prophylaxis, increases glycemic levels for short periods of time, for which it is important to consider the glycemic profile individually, especially in patients with morbid obesity and poorly controlled diabetes mellitus.

**SUMMARY**

In this review, we have focused on systematic reviews and metaanalyses that included randomized, controlled studies regarding the perioperative use of acetaminophen,
NSAIDs, and steroids. IV acetaminophen used perioperatively reduces opioid consumption in the first 24 hours after surgery and some of the metaanalyses confirmed its effect on the reduction of PONV. NSAIDs showed significant pain reduction and opioid consumption when used perioperatively, both in adults and the pediatric population, when used alone or in combination with acetaminophen. However, there is a concern regarding the safety profile on NSAIDs when used perioperatively with an increased risk of GI events and renal impairment in nonhealthy individuals. Dexamethasone showed an effect on reducing postoperative pain and the need for opioids besides its effect on prophylaxes of PONV. Dexamethasone is useful in the prolongation of peripheral nerve blocks when added to local anesthetics. Corticosteroids decrease the need for reintubation and the incidence of stridor in intensive care unit patients. Studies showed that even a high dose of corticosteroids used perioperatively does not increase the risk of infection wound healing. However, precaution is required in morbidly obese patients and patients with poorly controlled diabetes. Nevertheless, the indications and safety of some of these drugs are still controversial and the information provided should be analyzed with caution. Anesthesiologists should always use their clinical judgment when making decisions for the management of these drugs.

REFERENCES


