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| **STUDY** | **DESIGN** | **PARTICIPANTS AND COMPARATORS** | **RESULTS AND CONCLUSION** |
| Strom *et al.* 199627 | Post-marketing surveillance study (35 hospitals in Pennsylvania, USA) | * Adults/children undergoing oral or general surgery * Ketorolac IV or IM, daily dose range <15mg to >150mg (n=9,900) * Parenteral or oral opiates (n=10,247) | * + - * Increased risk of gastrointestinal bleeding, but not operative site bleeding, with ketorolac vs. opiates; overall associations between ketorolac use and bleeding are small       * Risk greater and clinically significant when ketorolac used in higher doses (>105 mg/day) and in elderly adult subjects (≥75 years) |
| Moiniche *et al*. 200329 | Systematic literature review and meta-analysis (25 US RCTs) | * Adults/children undergoing tonsillectomy * NSAIDs (ketorolac, diclofenac, ibuprofen, naproxen, among others); IV, IM, oral, or rectal admin. (n=970) * Placebo or non-NSAID (opioid, acetaminophen, acetaminophen-codeine); IV, IM, or oral admin (n=883) | * Incidence of reoperation increased in NSAID group vs. placebo/non-NSAID group * Non-significant difference in intraoperative blood loss, rate of postoperative bleeding, or hospital readmission due to bleeding in NSAID group vs. placebo/non-NSAID group |
| Lewis *et al.* 201331 | Systematic literature review and meta-analysis (15 US RCTs) | * Children undergoing tonsillectomy (n=1,101) * NSAIDs (ketorolac, ibuprofen, diclofenac, ketoprofen, tenoxicam); IV, IM, or oral admin * Placebo or non-NSAID (morphine, fentanyl, codeine, acetaminophen, tramadol, papaveretum); IV, IM, or oral admin | * Non-significant increase in bleeding requiring surgical intervention or number of perioperative events requiring non-surgical intervention in NSAID group * Concluded that there was insufficient evidence to exclude risk of increased risk of bleeding when NSAIDs are used in pediatric tonsillectomy |
| Devereaux *et al.*  201434 | International RCT with 2-by-2 factorial design | * Adults undergoing non-cardiac surgery * Aspirin initial presurgical oral dose of 200 mg , followed by a daily 100 mg dose for 30 days (n=4,998) * Placebo (n=5,012) | * Major bleeding more common in the aspirin group than in the placebo group * Administration of aspirin increased risk of bleeding |
| Dirkmann *et al.* 201535 | Prospective RCT at 3 German hospitals | * Adult men undergoing radical open prostatectomy * Parecoxib (40 mg IV) for 48 h postoperatively (n=48) * Placebo for 48 h postoperatively (n=48) | * Blood loss 24 h post-surgery significantly greater in patients receiving parecoxib, but no difference in intraoperative bleeding between comparator groups |
| Forrest *et al.* 200233 | RCT, multicenter trial at 49 European hospitals | * Adults undergoing elective major surgery * Ketorolac; parenteral or oral admin (n=5,634) * Ketoprofen or diclofenac; parenteral or oral admin (n=5,611) | * No significant differences between ketorolac and comparators with respect to postoperative site bleeding * Postoperative anticoagulants increased the risk of surgical site bleeding in ketorolac and comparator groups |
| Riggin *et al.*  201330 | Systematic review and meta-analysis (36 studies, various designs) | * Tonsillectomy patients (n=1,446 adults; n=1,747 children) * NSAID (e.g. ASA, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac); IV, IM, rectal, or oral admin * Placebo or opioid analgesic (e.g. paracetamol + codeine, tramadol, morphine, codeine, meperidine, fentanyl, propacetamol) | * Use of NSAID not associated with increased risk of severe bleeding, hospital readmission, or need of reoperation due to bleeding in the overall study population or in children * NSAIDs can be considered as a safe method of analgesia in children undergoing tonsillectomy |
| Moss *et al.* 201436 | Multicenter, double-blind placebo RCT in 6 US hospitals | * Children undergoing tonsillectomy * Ibuprofen IV, 10 mg/kg preoperatively (n=82) * Placebo (n=79) | * No significant difference in incidence of serious AEs, surgical blood loss or incidence of postoperative bleeding |
| Gan *et al.*  201537 | Multicenter, open-label, clinical surveillance study (21 US hospitals) | * Adult patients undergoing surgery requiring analgesia, excluding coronary artery bypass graft surgery (n=300) * All patients received IV ibuprofen 800 mg preoperatively, infused over 5-10 minutes | * No cases of perioperative bleeding, cardiovascular and hepatorenal complications, or GI ulceration observed * Most common AE was pain or discomfort at the infusion site; all serious AEs judged to be unrelated to ibuprofen * IV ibuprofen provided a significant reduction in both pain intensity and narcotic use in the postoperative period |
| Gobble *et al.* 201428 | Systematic literature review and meta-analysis (27 US RCTs) | * Adults undergoing various surgical procedures (neurosurgical, abdominal, urological, endoscopic) * Ketorolac, (variety of routes of admin, including IV, IM); 16 studies using dose >30 mg, 11 studies using ≤30 mg dose (n=1,304 patients) * Placebo, acetaminophen, or opioid (e.g. morphine, meperidine, metamizole, hydrocodone; n=1,010 patients) | * Incidence of postoperative bleeding not significantly increased with ketorolac when compared to patients receiving placebo or opioid |

AE = adverse event; ASA = acetylsalicylic acid; GI = gastrointestinal; IM = intramuscular; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; RCT = randomized controlled trial