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Effects of Nonsteroidal Antiinflammatory Drugs on Patient-controlled Analgesia Morphine Side Effects

Meta-analysis of Randomized Controlled Trials

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Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly combined with intravenous morphine patient-controlled analgesia to relieve postoperative pain. NSAIDs have a documented 30–50% sparing effect on morphine consumption. However, most of the studies have not demonstrated a decrease in morphine adverse effects. A meta-analysis of randomized controlled trials was performed to evaluate the risk of morphine adverse effects in patients treated with NSAIDs. Twenty-two prospective, randomized, double-blind studies including 2,307 patients were selected. NSAIDs decreased significantly postoperative nausea and vomiting by 30%, nausea alone by 12%, vomiting alone by 32% and sedation by 29%. A regression analysis yielded findings indicating that morphine consumption was positively correlated with the incidence of nausea and vomiting. Pruritus, urinary retention, and respiratory depression were not significantly decreased by NSAIDs.

OPIOIDS are considered the treatment cornerstone of severe postoperative pain.[1] Consequently, in the United States, more than 60% of the patients who have experienced moderate or severe postoperative have received morphine as a postoperative pain therapy.[2] Patient-controlled analgesia (PCA) is the most frequent mode of postoperative morphine administration.[2] Significantly greater analgesic efficacy and higher patient satisfaction were observed with administration of opioid by PCA, in comparison with as-needed opioid administration.[3] Although opioids are highly efficacious, unwanted side effects, such as postoperative nausea and vomiting (PONV), drowsiness, respiratory depression, and gastrointestinal and bladder dysfunction, are frequently observed during opioid PCA.[4] Multimodal or balanced analgesia, *i.e.*, the combination of nonopioid analgesics and/or regional analgesic techniques to opioid, have been proposed to decrease morphine consumption and to improve postoperative analgesia after severely painful surgery.[5]

Nonsteroidal antiinflammatory drugs (NSAIDs) have been shown to reduce the opioid analgesic requirement in most of the clinical trials with a 30–50% sparing effect on morphine consumption.[6,7] However, most of the studies have not demonstrated a decrease in morphine adverse effects related to the reduction in postoperative morphine requirement. Although morphine adverse events such as PONV have been considered less important by physicians in comparison with other postoperative complications, such as cardiac complications, sepsis, or venous thrombosis, they are costly and are also a major concern for patients.[8,9] Patients consider nausea and vomiting as one of the most undesirable postoperative outcomes[10] and are ready to pay more than $50 US to avoid them.[11] Moreover, PONV delays return to oral feeding, recovery, and hospital discharge.[12] Other morphine adverse effects, such as sedation or urinary retention, similarly impair active mobilization and rehabilitation. Although there is no doubt that NSAIDs reduce pain intensity and improve postoperative analgesia, concern remains regarding the real clinical benefit of NSAIDs to reduce adverse effects of opioids in a multimodal analgesic approach.[13]

Therefore, we performed a meta-analysis to evaluate the effect of NSAIDs in postoperative patients treated with PCA morphine on opioid adverse effects.

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Materials and Methods

Identification of the Studies

Two electronic databases were searched *via* the Internet for studies published between January 1966 and December 2003, PubMed® (MEDLINE/*Index Medicus*)

and the Cochrane Controlled Trials Register published by the Cochrane Library. The Medical Subject Heading terms used for the search were *patient controlled analgesia*, *morphine*, and *NSAIDs*. Supplementary manuscripts were searched by changing the Medical Subject Heading term *NSAIDs* to *celecoxib*, *rofecoxib*, *parecoxib*, *lumiracoxib*, or *etoricoxib*. Additional articles were also retrieved by clicking on hyperlinks and by manually searching reference lists in original published articles, review articles, and correspondence. Four drug companies (Aventis [Paris, France], Pharmacia [Saint-quentin en Yvelines, France], Pfizer [Paris, France], and Abbot [Rungis, France]) were also contacted for research of additional unpublished trials. Only trials published in English were reviewed. For some articles, the authors were contacted for additional information on the results.

Quality Assessment of the Studies

Each study was subjected to a quality assessment by two investigators, who were not blinded to the authors or results. Disagreements between the two investigators were resolved by discussion. In the case of persistent disagreement, a third reviewer helped to reach a consensus after separately reviewing the report. Each article was scored using a five-point scale that evaluates randomization, blinding, and completeness of patient follow-up (Oxford validity scale).[14] One point was given if the study was described as randomized. An additional point was given if the randomization method was described and was appropriate (*e.g.*, computer-generated table of random numbers), whereas a point was subtracted if the randomization method was described and inappropriate (*e.g.*, alternate allocation or allocation by date of birth). Similarly, one point was assigned to studies described as double-blind, two points were assigned to studies for which the double-blinding method was described and appropriate (identical placebo, active placebo, double-dummy), and zero points were assigned to studies for which the double-blinding method was described and inappropriate. One point was given if the article specified the numbers of and reasons for withdrawals and dropouts. Thus, the minimum score for a randomized study was 1, and the highest possible score was 5. We included studies with a score of 3 or greater.

Selection Criteria

Criteria for study selection were as follows: randomized, double-blind design; quality assessment score of 3 or greater[14]; inclusion of adolescents (aged $>$ 12 yr) or adults who underwent major surgery that necessitated morphine administrated by a patient-controlled-analgesia device; NSAID therapy compared to a placebo; report of data on morphine adverse effects such as nausea, vomiting, sedation urinary retention, and respiratory depression; and report of patient satisfaction. We included studies regarding nonselective NSAIDs and selective cyclooxygenase-2 inhibitors.

Criteria for study exclusion were a score of 2 or lower on the three-item Oxford quality five-point scale[14]; inclusion of children (aged $<$ 12 yr); use of a continuous morphine infusion in addition to PCA; use of a continuous regional analgesia in addition to PCA or other regional techniques exclusively; need for postoperative ventilation during the first 24 h (*i.e.*, cardiac surgery); duration of the study less than 24 h; PCA with an opioid other than morphine (*e.g.*, meperidine, alfentanil, fentanyl, hydromorphone, oxycodone); control group with an NSAID; administration of another nonopioid analgesic in both groups (*i.e.*, acetaminophen, nefopam); and NSAID intrarectal administration.

Outcome Measures

The primary evaluation criterion was the presence of nausea and/or vomiting in the postoperative setting. Three different events were extracted from each trial as mentioned by the authors: nausea, vomiting, and any emetic event. Any emetic event was defined as PONV when authors did not report nausea and vomiting separately in their results section. The regimen of prophylactic antiemetic was also extracted. Other endpoints, such as postoperative urinary retention, sedation defined by the report as sedation or drowsiness, pruritus, apnea, and respiratory depression, were analyzed. Morphine requirement was extracted at 24, 36, and/or 48 h. When trials compared more than two groups, data were extracted in two groups: NSAIDs and control. In dose-ranging studies with a placebo group, we extracted the events of the control group and the highest study-dose group. When authors compared two types of administration with the same dose of NSAIDs (*i.e.*, continuous infusion *vs.* intermittent or bolus group or preoperative *vs.* postoperative), patients receiving NSAIDs were pooled and compared to those receiving placebo. Sensitivity analysis was performed to explore the effect of NSAIDs in different procedures, namely peripheral *versus* pelvic or abdominal surgery, on significant endpoints. Similarly, subgroup analysis for PONV was conducted in groups of patients who did or did not receive opioid intraoperatively and did or did not have reversal of muscle relaxant.

Statistics

When not reported in the article, an intention-to-treat analysis was performed based on the original data. The Mantel-Haenszel–like procedure for relative risk (RR) was used to pool RRs.[15] Analyses were performed with WeasyMA software (ClinInfo, Lyon, France) for dichotomous data.[16] The RRs (and 95% confidence intervals [CIs]) were calculated, and the results were expressed graphically. All criteria were analyzed separately. In the case that the result of a Q Cochran heterogeneity test

was significant ($P < 0.1$), a random-effects analysis was conducted. For the significant criteria, we computed the number needed to treat (NNT) as the inverse of the difference of the proportion of patients who had any PONV in the NSAID groups and the control groups. CIs of the NNT were constructed by inverting and exchanging the limits of the 95% CI for the RR. The NNT and 95% CI were calculated with the Internet-based program Visual Rx.‖ Relations between morphine requirements and PONV were studied in a weighted linear regression model (Software S-PLUS 2000; MathSoft, Seattle, WA). The model was constructed from aggregated variables. The independent variable was the mean morphine consumption (in milligrams). Dependent variables were the incidence of nausea or vomiting weighted by the inverse variance of the incidence of each trial. All tests were two sided, and *P* values less than 0.05 were considered statistically significant.

A funnel plot (plot of treatment effect against trial precision) was also created to determine the presence of publication bias and possible other biases (English language, citation, and multiple publication), true heterogeneity, data irregularities, and choice of effect measure in the meta-analysis.[17] In the presence of bias that usually leads to an overestimate of the treatment effect, the funnel plot is skewed and asymmetrical. The degree of asymmetry was measured by the Egger test[17] using WeasyMA software.[16] A *P* value less than 0.1 was considered statistically significant for asymmetry.[17]

Results

One hundred ninety controlled trials were identified by the MEDLINE and the Cochrane Library search. One hundred sixty-eight were excluded for the following reasons: 100 studies considered morphine administration but not by PCA, and/or used opioid other than morphine, and/or had no control group managed without NSAIDs; 32 used regional analgesia/anesthesia; 12 were performed in children; 9 had a quality score lower than 3; 10 reported insufficient clinical data and/or duration of study period less than 24 h; and 5 reported NSAID administration by the rectal route. A manual search of cross-references from the manuscripts and contact with the pharmaceutical companies did not identify additional studies or data. Thus, a total of 22 randomized controlled trials studying intravenous morphine PCA side effects after major surgery were identified by a systematic search of the two databases (table 1).

Study Designs, Patients, and Type of Anesthesia and Surgery

All twenty-two randomized, double-blind studies were published in or after 1991. Most of the studies reported intramuscular or intravenous NSAID administration with a placebo-controlled intramuscular or intravenous saline. Three placebo-controlled comparisons were performed with an active drug administrated *per os* (ibuprofen for one, rofecoxib and naproxen for two).[18–20]

Four trials, two with ketorolac[21,22] and two with parecoxib,[23,24] were dose-ranging studies. In these cases, 30 mg ketorolac every 6 h and 40 mg parecoxib every 12 h were the highest study doses. Two trials compared two modes of NSAID administration (*i.e.*, continuous or intermittent injection) with placebo injection.[7,25] In one study, intravenous ketorolac was administrated preoperatively in one group, postoperatively in another group, and compared with a placebo.[26] One trial compared two types of NSAIDs administrated preoperatively with a placebo.[27] Another compared two types of NSAIDs (tenoxicam *vs.* piroxicam) with two modes of administration for tenoxicam (intramuscular *vs.* intravenous) with a placebo.[28] One thousand three hundred sixteen patients received NSAID therapy that consisted of intravenous or intramuscular ketorolac (596 patients), intravenous tenoxicam (273 patients), intravenous ketoprofen (93 patients), intravenous parecoxib (82 patients), intravenous dexketoprofen (59 patients), intravenous diclofenac (36 patients), intravenous lysine acetyl salicylate (25 patients), intravenous indomethacin (15 patients), intramuscular tenoxicam (15 patients), intramuscular piroxicam (15 patients), oral ibuprofen (52 patients), oral naproxen (20 patients), or oral rofecoxib (35 patients) (table 1). In the control groups, patients received intravenous saline or placebo tablets. Treatment duration ranged from 24 to 72 h (table 1). Most of the studies demonstrated a significant morphine-sparing effect with NSAIDs (table 1).

The PCA system was programmed to deliver morphine with a bolus dose of 1 mg in 12 trials,[7,18,19,22–24,26–32] 1.5 mg in 2 trials,[21,33] 2 mg in 3 trials,[20,23,24] 2.5 mg in 1 trial,[34] 5 mg in 1 trial,[35] and 0.02 mg/kg in 2 trials.[25,36] In one study, the bolus dose was increased in case of inadequate analgesia.[7] The lockout intervals were fixed at 2 min,[25] 5 min,[18,27,28,30,32] 6 min,[7,22–24,36] 7 min,[33] 8 min,[21] or 10 min.[19,20,26,29,31,34,35] Most of the studies did not fix limitation to the dose of morphine administered. However, 9 studies reported a maximum cumulative dose: 5 mg every hour in 1 study,[28] 15 mg every 4 h in 1 study,[34] 20 mg during any 4-h interval in 2 studies,[24,33] 24 mg every 4 h in 1 study,[26] or 30 mg every 4 h in 4 studies.[7,21,22,27] The maximum dose could be increased in case of inadequate analgesia in one study.[33]

Anesthesia was maintained with inhaled agents: halogenates in 19 trials[6,18–22,24–27,29–31,33–37] and nitrous oxide in 19 trials.[6,18–22,24–31,33–36] Residual muscle relaxation antagonism was described in the methods section in 6 studies.[19–21,27,34,35]

‖ Visual Rx. Available at: http://www.nntonline.net/. Accessed June 10, 2004.

Table 1. Characteristics of the 22 Studies Included in the Meta-analysis

Study	Control Group (n = 991) Sex, M/F	NSAIDs Group (n = 1,316) Sex, M/F	Type of Surgery	Type of NSAIDs	Dose of NSAIDs	Route of Administration	Cumulative Dose of Morphine, mg (Control *vs.* NSAIDs)	Duration of Treatment Adverse Effects Reported
Alexander *et al.*,[27] 2002	32 13/19	67 23/44	Orthopedic	Diclofenac Ketorolac	75 mg 60 mg	Intravenous	51.6 *vs.* 47.2 (ketorolac)* *vs.* 36.3 (diclofenac)*	24 h PONV, PRU
Balestrieri *et al.*,[6] 1997	82 0/82	166 0/166	Gynecologic	Ketorolac	60 mg and 30 mg/6 h (intraoperative or postoperative)	Intramuscular	58.1 *vs.* 41.3 (intraoperative)* *vs.* 46.6 (postoperative)	24 h PONV, SED, PRU
Burns *et al.*,[25] 1991	21 10/11	42 19/13	Abdominal	Ketorolac	10 mg/4 h or 2.5 mg/h	Intramuscular	139 *vs.* 111 (bolus) *vs.* 80 (continuous)*	48 h PONV, UR
Celik *et al.*,[20] 2003	20 0/20	40 0/40	Gynecologic	Naproxen Rofecoxib	550 mg 50 mg	*Per os*	93 *vs.* 63 (naproxen)* *vs.* 50 (rofecoxib)*	24 h PONV
Chow *et al.*,[37] 2001	29 NA	26 NA	Urologic Laparoscopic	Ketorolac	15–30 mg/6 h	Intravenous	63 *vs.* 39	48 h UR, SED, PRU
De Decker *et al.*,[28] 2001	15 6/9	45 21/24	Orthopedic	Piroxicam Tenoxicam	40 mg 40 m	Intravenous Intramuscular	36.5 *vs.* 24.6 (PIM) *vs.* 24.3 (TIM) *vs.* 21.7 (TIV)*	24 h PONV
Etches *et al.*,[36] 1995	88 47/41	86 38/48	Orthopedic	Ketorolac	30 mg and 5 mg/h	Intravenous	66 *vs.* 40*	24 h PONV, UR, SED, RD
Fletcher *et al.*,[26] 1995	20 8/12	40 16/24	Orthopedic	Ketorolac	60 mg	Intravenous	NA	48 h PONV, RD, SED, PRU
Fletcher *et al.*,[29] 1997	15 8/7	15 9/6	Orthopedic	Ketoprofen	50 mg/6 h	Intravenous	59 *vs.* 34*	48 h PONV, SED, UR, RD
Hanna *et al.*,[30] 2003	55 30/25	117 57/60	Orthopedic	Ketoprofen Dexketoprofen	100 mg/12 h 50 mg/12 h	Intramuscular	65 *vs.* 41 (ketoprofen)* *vs.* 39 (dexketoprofen)*	24 h PONV
Huang *et al.*,[19] 2001	15 15/0	15 15/0	Urologic (prostate)	Rofecoxib	50 mg	*Per os*	30 *vs.* 30	24 h PONV
Malan *et al.*,[23] 2003	70 39/31	64 30/34	Orthopedic	Parecoxib	40 mg	Intravenous	72.5 *vs.* 43.1*	36 h PONV, SED, UR, RD
Pang *et al.*,[31] 1999	25 18/6	25 16/8	Orthopedic	Aspirin	90 mg/ml	Intravenous	32 *vs.* 24*	48 h PONV, SED
Plummer *et al.*,[8] 1996	56 NR	52 NR	Gynecologic	Ibuprofen	800 mg × 4/day	*Per os*	38 *vs.* 32	24 h PONV, RD
Rao *et al.*,[32] 2000	19 12/7	20 10/10	Abdominal	Ketoprofen	100 mg/12 h	Intravenous	50 *vs.* 32*	24 h PONV, RD, SED
Ready *et al.*,[7] 1994	71 16/55	136 NA	Orthopedic Gynecologic General	Ketorolac	Bolus 30 mg/6 h continuous 5 mg/h	Intravenous	42 *vs.* 31 (bolus) *vs.* 25 (continuous)*	24 h PONV, PRU, RD
Reuben *et al.*,[21] 1998	10 NR	10 NR	Orthopedic	Ketorolac	30 mg	Intravenous	118 *vs.* 69*	24 h PONV
Sevarino *et al.*,[22] 1992	12 0/12	11 0/11	Gynecologic	Ketorolac	60 mg and 30 mg/6 h	Intramuscular	69 *vs.* 40*	36 h PONV, PRU
Tang *et al.*,[24] 2002	18 0/18	18 0/18	Gynecologic	Parecoxib	40 mg/12 h	Intravenous	51 *vs.* 33*	24 h PONV, PRU
Tigerstedt *et al.*,[35] 1991	15 9/6	15 3/12	Abdominal	Indomethacin	0.5 mg/kg and 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$	Intravenous	70 *vs.* 58	24 h PONV, PRU, SED, UR
Vandermeulen *et al.*,[33] 1997	256 NA	258 NA	Orthopedic Abdominal Gynecologic	Tenoxicam	40 mg/24 h	Intravenous	NA	72 h PONV, PRU, SED
Varassi *et al.*,[34] 1994	47 15/32	48 17/31	Abdominal	Ketorolac	30 mg and 2 mg/h	Intramuscular	22 *vs.* 15	24 h PONV, PRU, UR, SED, RD

Morphine consumption is expressed as mean or median.

* Significant morphine-sparing effect ($P < 0.05$).

NA = not available; NR = not reported; NSAID = nonsteroidal antiinflammatory drug; PIM = piroxicam intramuscular; PONV = postoperative nausea and/or vomiting; PRU = pruritus; RD = respiratory depression; SED = sedation; TIM = tenoxicam intramuscular; TIV = tenoxicam intravenous; UR = urinary retention.

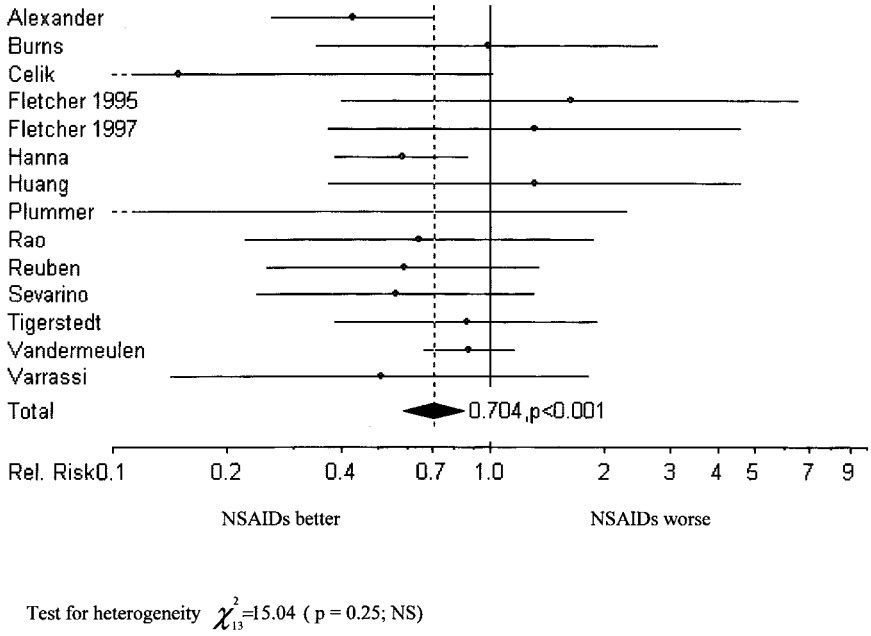

Fig. 1. Effect of administration of nonsteroidal antiinflammatory drugs (NSAIDs) in addition to patient-controlled analgesia intravenous morphine after surgery on the relative risk (Rel. Risk) of postoperative nausea and vomiting.[18–22,25–27,29,30,32–35] NS = not significant.

Postoperative Nausea and Vomiting

Postoperative nausea and vomiting were the most frequently reported morphine adverse effects in 21 trials. Nausea and vomiting were reported indistinctly in 14 trials[18–22,25–27,29,30,32–35] (n = 1,343; fig. 1) and separately in 7 trials[6,7,23,24,28,31,36] (n = 909; figs. 2 and 3). No prophylactic antiemetic treatment, such as droperidol, dexamethasone, or setron, was used to prevent PONV in any of the 21 trials. Curative antiemetic treatment was reported in only 9 studies. Intravenous metoclopramide, 10 mg, was the most commonly antiemetic treatment used.[6,7,18,27,31,32,36] The other curative treatments were alizapride,[33] dimenhydrinate,[36] and/or droperidol.[6]

In the control group, the incidences of nausea, vomiting, and PONV were 55% (extremes, 16–78%), 21% (extremes, 0–27%), and 30% (extremes, 10–70%), respectively. In the NSAIDs group, the overall incidences of postoperative nausea, vomiting, and PONV were 50% (extremes, 8–66%), 14% (extremes, 0–26%), and 22% (extremes, 0–40%), respectively. NSAIDs reduced the risk of PONV from 30% to 22% (RR, 0.704; 95% CI, 0.590–0.841; $P < 0.001$; fig. 1). The NNT to prevent one

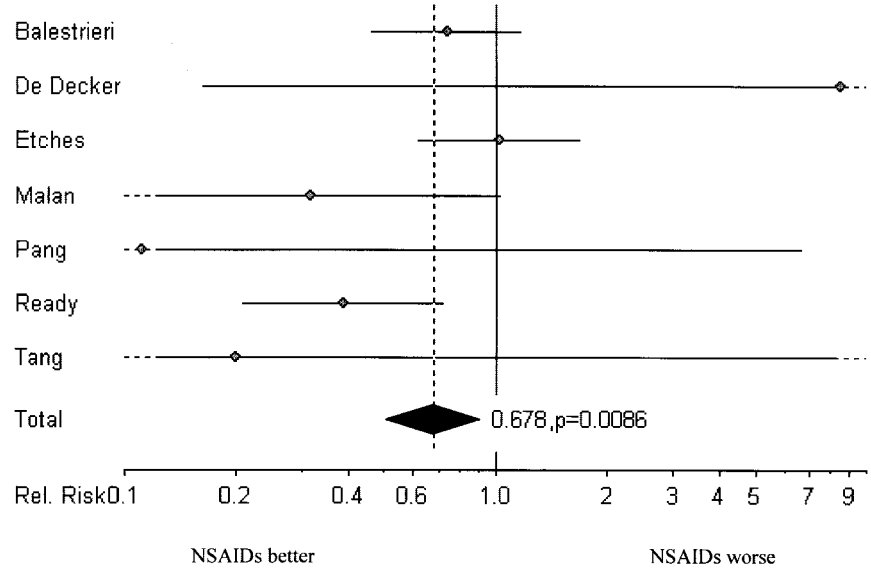

Fig. 2. Effect of administration of nonsteroidal antiinflammatory drugs (NSAIDs) in addition to patient-controlled analgesia intravenous morphine after surgery on the relative risk (Rel. Risk) of postoperative vomiting.[6,7,23,24,28,31,36] NS = not significant.

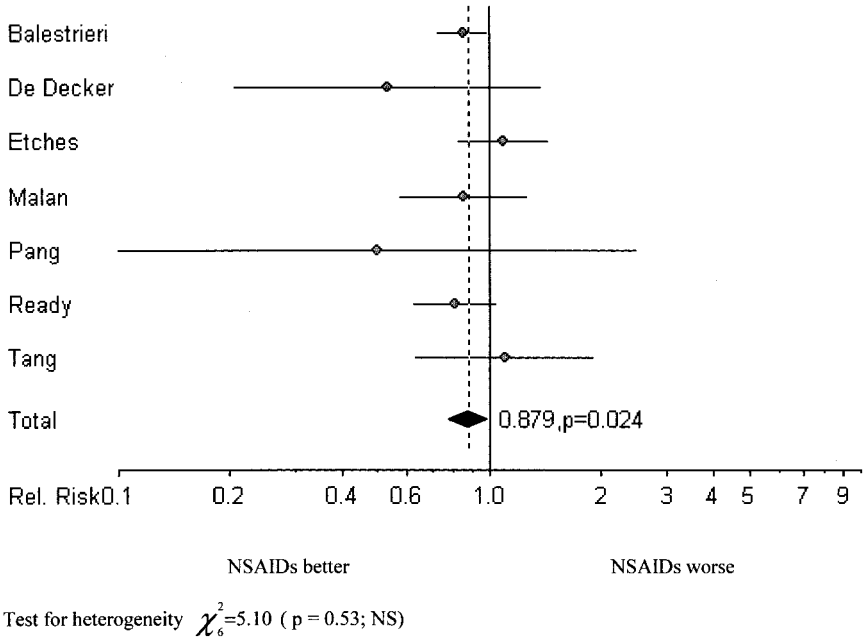

Fig. 3. Effect of administration of nonsteroidal antiinflammatory drugs (NSAIDs) in addition to patient-controlled analgesia intravenous morphine after surgery on the relative risk (Rel. Risk) of postoperative nausea.[6,7,23,24,28,31,36] NS = not significant.

episode of PONV was 12 (95% CI, 9–22). No significant heterogeneity was observed among the six studies that reported postoperative vomiting and nausea separately (figs. 2 and 3). A significant reduction was observed for postoperative vomiting (RR, 0.678; 95% CI, 0.508–0.906; $P = 0.008$) and also for postoperative nausea (RR, 0.879; 95% CI, 0.785–0.983; $P = 0.02$). For postoperative vomiting, the NNT value was 15 (95% CI, 10–51), and for postoperative nausea, it was 16 (95% CI, 9–108). A linear relation was documented between the incidence of postoperative nausea ($r = 0.61$; $P = 0.007$) and vomiting ($r = 0.51$; $P = 0.02$) and morphine consumption in the postoperative period (fig. 4). For each milligram of morphine spared by NSAIDs, the incidences of postoperative nausea and vomiting decreased by 0.9% and 0.3%, respectively.

A subgroup analysis was conducted to explore the effects of NSAIDs on PONV in different procedures. Studies were classified into two groups: orthopedic (peripheral) surgery and pelvic or abdominal surgery. One trial had been conducted in different types of procedures, including orthopedic but also pelvic or abdominal surgery, with no subgroup analysis.[33] NSAIDs decreased PONV significantly in the orthopedic subgroup (RR, 0.655; 95% CI, 0.467–0.920; $P = 0.01$).[21,26,29,30] Similarly, NSAIDs were associated with a decrease in PONV after a pelvic or abdominal procedure (RR, 0.684; 95% CI, 0.459–1.020; $P = 0.06$).[18–20,22,25,32,34,35] NSAIDs also decreased PONV in patients in whom reversal neuromuscular block was described in the methods section (RR, 0.546; 95% CI, 0.388–0.770; $P < 0.001$)[19–21,27,34,35] or not described (RR, 0.773; 95% CI, 0.628–0.95; $P = 0.01$).[18,22,25,26,29,30,32,33] Most of the trials studied patients during the first 24 h (table 1). Meta-analysis of these trials showed a significant decrease in PONV (RR, 0.559; 95% CI, 0.434–0.720; $P < 0.001$),[18,20,21,27,30,32,34,35] nausea (RR, 0.883; 95% CI, 0.785–0.994; $P = 0.04$), or vomiting (RR, 0.719; 95% CI, 0.533–0.970; $P = 0.03$).[6,7,24,28,36]

A funnel plot of the treatment effect (logarithm RR of PONV or nausea) *versus* trial precision (inverse of SD) was symmetric and centered around an RR of less than 1.0, suggesting that there is no publication bias or other biases (fig. 5).[17] Therefore, there was no evidence of asymmetry and bias in this meta-analysis as shown by the symmetry in the funnel plot for PONV ($r = -0.36$, intercept [SE] = −0.38 [0.53]; $P = 0.49$; fig. 4) and nausea ($r = -0.36$, intercept [SE] = −0.28 [0.69]; $P = 0.70$; fig. 5).

Sedation

Postoperative sedation was reported in 10 studies,[6,7,20,26,29,31–35] 6 of them including a definition referring to a sedation score. Sedation was measured with a four-point scale in 4 trials[26,29,31,34] and with a five-point scale in 2 studies.[7,32] Sedation was the second most frequent side effect of intravenous morphine PCA. Among the 570 patients who did not receive NSAIDs, 74 experienced sedation (13%; extremes, 0–41%) The overall incidence of sedation (10%) was significantly less in the 763 patients who were treated with NSAIDs (RR, 0.714; 95% CI, 0.537–0.950; $P = 0.02$; fig. 6). The NNT to prevent sedation in one patient was 27 (95% CI, 17–154). Another subgroup analysis was conducted to explore the effects of NSAIDs on sedation in different procedures. Two trials included patients scheduled to undergo different procedures (orthopedic, gynecologic, abdominal).[7,33] NSAIDs significantly decreased sedation in the orthopedic subgroup (RR, 0.167; 95% CI, 0.031–0.914; $P = 0.04$)[26,29,31] and after pelvic or abdominal surgery (RR, 0.334; 95% CI, 0.175–0.637; $P < 0.001$).[6,20,32,34,35]

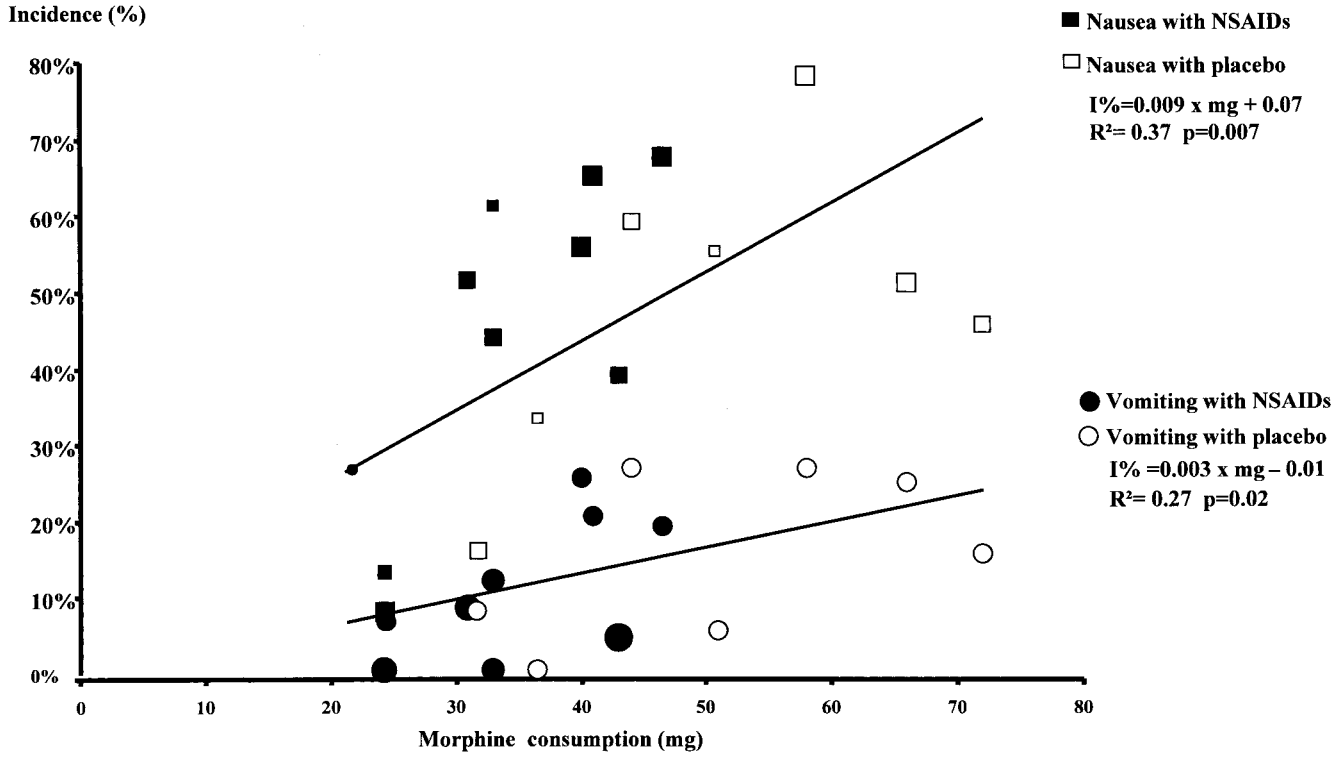

Fig. 4. Dose–effect relation between the mean dose of morphine consumed in the postoperative period and the incidence of postoperative nausea or vomiting.[6,7,23,24,28,31,36] Data were analyzed by linear regression; the model predicts an increase of 0.9% (SE, 0.2%) for nausea and of 0.3% for vomiting (SE, 0.1%) for each increase in morphine consumption of 1 mg. *Squares* represent nausea (*open* for placebo group and *filled* for nonsteroidal antiinflammatory drugs [NSAIDs] group), and *circles* represent vomiting (*open* for placebo group and *filled* for NSAIDs group). The size of the circles and squares corresponds to the inverse variance of the incidence in that trial.

Pruritus

Pruritus was reported in 10 trials (1,436 patients).[6,7,20–24,27,33,34] The overall incidence of pruritus was 9.5% (extremes, 2.0–50.0%) in the control group and 7.8% (extremes, 0.0–42.0%) in the NSAID group. A nonsignificant reduction in the incidence of pruritus was observed in the NSAID group (RR, 0.731; 95% CI, 0.523–1.022; $P = 0.07$).

Urinary Retention

Only seven trials with a total of 654 patients checked for urinary retention.[7,25,29,34–37] Five studies were performed in patients undergoing abdominal surgery, and two were performed in patients undergoing orthopedic surgery. None of the studies selected for the meta-analysis reported systematic bladder catheterization. No specific criteria was used to define urinary retention, and no

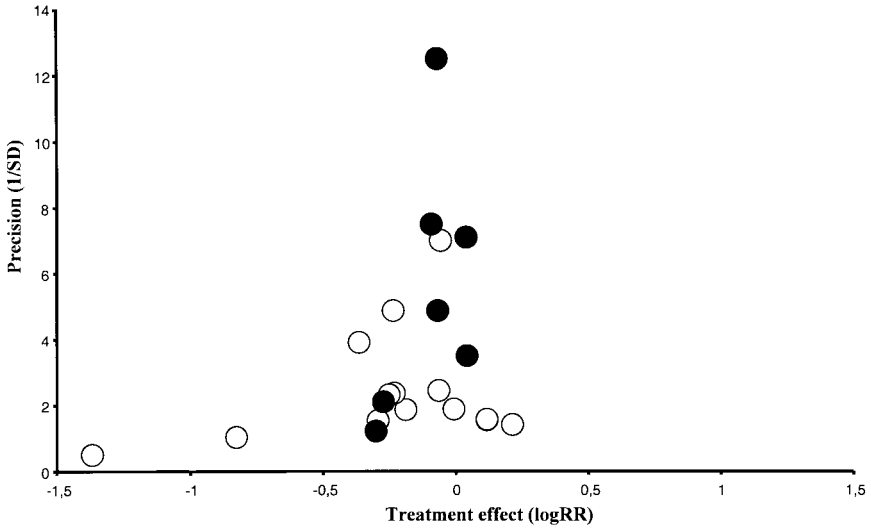

Fig. 5. Funnel plot of logarithm of relative risk (log RR) of postoperative nausea or vomiting or nausea alone *versus* precision among all studies. Data are relative risk of postoperative nausea or vomiting (*open circles*) or nausea (*closed circles*) plotted against trial precision (inverse of SD) for each trial included in the meta-analysis for postoperative nausea or vomiting[18–22,25–27,29,30,32–35] or nausea.[6,7,23,24,28,31,36] The overall SD of each trial was calculated, and the inverse was used to define the precision of the trial. A funnel plot was drawn to assess whether there was evidence of publication bias. The Egger test did not show statistical asymmetry.

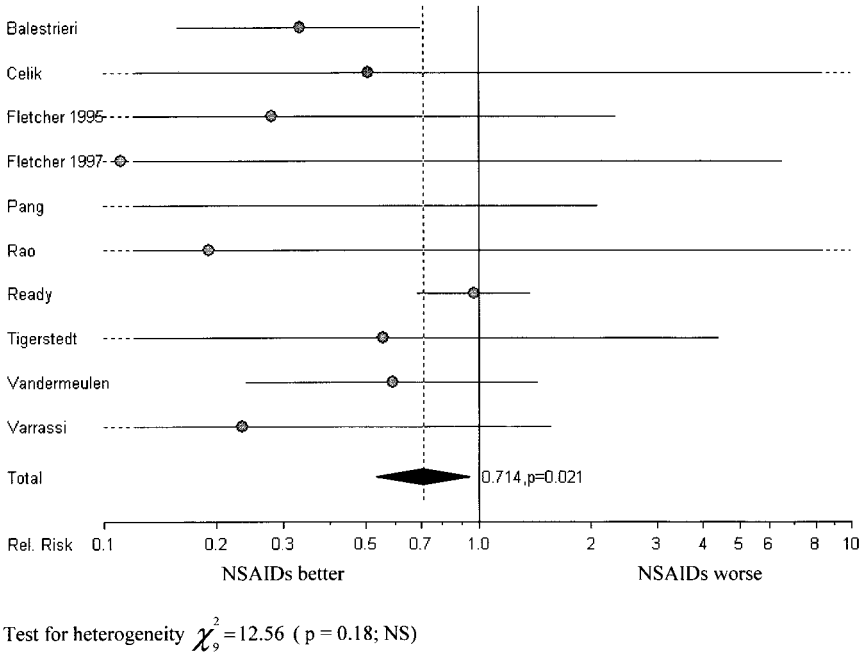

Fig. 6. Effect of administration of nonsteroidal antiinflammatory drugs (NSAIDs) in addition to patient-controlled analgesia intravenous morphine after surgery on the relative risk (Rel. Risk) of postoperative sedation.[6,7,20,26,29,31–35] NS = not significant.

precise guidelines were used to perform bladder catheterization. The incidence of urinary retention varied from 0 to 20% in the NSAIDs group (mean, 9%) and from 0 to 25% in the control group (mean, 11%). This difference was not significant (RR, 0.807; 95% CI, 0.502–1.297; $P = 0.38$).

Respiratory Depression

Monitoring of respiratory depression or apnea was reported in eight trials (498 patients).[21,26,29,31,32,34–36] Different criteria were used to define respiratory depression. In two trials, it was defined by a respiratory rate less than 10 breaths/min, persistent hypoxemia, pulse oximetry less than 90%, or naloxone administration.[26,29] Others considered respiratory depression when the respiratory rate was less than 10 breaths/min[21,31,34,35] or less than 8 breaths/min.[32] In two studies, respiratory depression was defined by the intravenous injection of naloxone.[7,31] One study reported significant episodes of oxygen desaturation defined by a pulse oximetry less than 84% for at least 2 min or less than 90% for at least 10 min in 15% and 17% of patients treated with NSAIDs or placebo, respectively.[36] However, no patients required treatment for clinically apparent respiratory depression.[36] At least one episode of respiratory depression was documented in only four trials.[21,31,32,35] The incidence was not different between the two groups (1.9% in the NSAIDs group *vs.* 2.5%), and NSAIDs showed no significant effect on the rate of respiratory depression (RR, 0.998; 95% CI, 0.354–2.814; not significant).

Discussion

This systematic review of 22 randomized controlled trials showed that NSAIDs decreased the incidence of postoperative nausea, vomiting, and sedation. Moreover, a significant relation was documented between morphine consumption and the incidence of PONV. The incidence of the other morphine adverse effects (pruritus, urinary retention, respiratory depression) was not significantly reduced by NSAIDs, although there was a trend toward a reduction of the risks in patients treated with NSAIDs in the postoperative period.

Morphine adverse effects are not only frequent but may be considered as a limitation of intravenous morphine PCA. In a review of 32 trials on opioid-based PCA, PONV was reported in 31% of the 252 patients studied.[4] In another systematic review on the efficacy of antiemetic treatments used during intravenous PCA, Tramer and Walder[38] found an overall 67% incidence of PONV in the control group. Several risk factors of PONV have been documented in addition to postoperative opioid, including a previous history of PONV, nonsmoking status, and/or female sex.[39] Other risks factors, such as halogenates, nitrous oxide, neostigmine use, and type of surgery (laparoscopy, breast surgery, or laparotomy), have also been identified.[40] In the studies included in this systematic review, patients were anesthetized with halogenates and nitrous oxide, were predominantly women, and could consequently be considered at risk of PONV. The risk of PONV increased with opioid use but also with previous history of PONV, with nonsmoking status, and/or in female compared with male patients.[40] Trials included in the current meta-analysis did not distinguish these last three factors, which affected the incidence of PONV. Therefore, the benefit of morphine-sparing effects of NSAIDs could not be stratified in patients with one, two, or three of these risk factors.

Several prospective studies have suggested that

NSAIDs were associated with a lesser likelihood of nausea and/or vomiting, but only a few demonstrated a significant reduction.[6,7,27,30] Most of the published randomized, controlled, prospective trials were designed to assess the analgesic efficacy of NSAIDs, but the number of patients was usually too small to draw definite conclusions regarding adverse effects. Eleven of the 14 trials that met quality criteria for inclusion in the current meta-analysis yielded a RR of less than 1 for PONV, although the difference was statistically significant in only two trials (fig. 1).[27,30] Similarly, only two randomized, double-blind studies showed a significant decrease in postoperative nausea or vomiting (figs. 2 and 3).[6,7] However, the study that included the largest population in the current meta-analysis did not find a significant difference in PONV between the NSAID and placebo groups.[33] The performance of meta-analysis, which has been developed to increase statistical power for primary or secondary endpoints and also to resolve uncertainty in view of controversial results, was especially appropriate in this setting.

The use of NSAIDs in addition to intravenous morphine PCA is supported by their synergistic interactions.[41] Therefore, a multimodal approach has been developed to improve postoperative pain relief by acting on different pain pathways.[5] Many randomized studies have demonstrated that a combination of opioid plus NSAIDs decreases morphine requirements and VAS scores. Many authors have considered that reduction in pain intensity or morphine sparing were the primary endpoints and that decreasing morphine adverse effects such as PONV or sedation was a secondary endpoint. However, most of the studies did not confirm a benefit of NSAIDs on morphine adverse effects, probably because of their lack of power. By pooling studies and their secondary endpoints, the current meta-analysis demonstrates the benefit of a multimodal analgesic approach not only on pain control, but also on the incidence of opioid adverse effects.

Sedation has been routinely monitored in many studies because it is an early indicator of respiratory depression.[42] Excessive sedation can lead to a discontinuation of PCA or a decrease in morphine consumption. Nevertheless, Paqueron *et al.*[43] noted that 25% of the patients who experienced sedation during morphine titration had visual analog scale scores of greater than 50 mm. Consequently, patients could be sedated despite persistent pain. We observed a significant decrease in postoperative sedation in the NSAIDs group that could be interpreted as the consequence of the decrease in morphine consumption. Decreasing sedation is another way to improve patient compliance to active postoperative care and to hasten recovery. Moreover, sedated patients need especially careful monitoring that could be time-consuming for nurses.

The current systematic review may have some limitations. The quality of trials included in a systematic review may alter the results.[44] Moher *et al.*[44] demonstrated that meta-analyses with low-quality trials (Jadad assessment scale score ≤ 2) compared with high-quality trials (assessment scale score > 2) were associated with an increased estimate of benefit of one third. Similarly, trials using inadequate allocation concealment may also have overestimated the benefit of treatment by as much as 37%.[44] Moreover, meta-analysis of small trials, *i.e.*, studies with less than 1,000 patients, with inadequate allocation sequence generation or no double blinding can exaggerate the benefit of the treatment in comparison with large trials and contribute to discrepancies.[45] Therefore, multiple scales have been proposed to assess the quality of trials included in a meta-analysis and to decrease bias due to the inclusion of low-quality trials. We used the Jadad composite scale to assess quality using factors such as randomization, double blinding, and patient withdrawals.[14] Meta-analyses of trials with low quality as evaluated with this scale significantly exaggerate benefits.[44] Consequently, all 22 trials selected for our systematic review were double blind and randomized and had an Oxford scale score reflecting high quality. We also limited our meta-analysis to English-language articles. Although the effect of excluding non–English-language trials on the results of a meta-analysis is unclear, in some cases, excluding trials published in other languages may have little effect on summary treatment effects and may actually result in a more conservative estimate of treatment effect.[46] In fact, trials published in non-English languages are prone to produce significant results more frequently but also to be lower in terms of methodologic quality. Publication bias and other biases may also exaggerate the benefit of the treatment of meta-analysis in comparison with large trial.[17] Consequently, we constructed a funnel plot to test the presence of bias.[17] No asymmetry was evident (fig. 5).

The use of antiemetic was different from one study to another, but none of the studies included in the meta-analysis used preventive antiemetic treatment that could have impaired the incidence of PONV. Moreover, most of the studies reported use of metoclopramide that has been documented to be ineffective in the treatment of PONV.[47] Numerous scales, such as the visual analog scale (0–100), 11-point numerical rating scale (0–11), or verbal rating scale (none, mild, moderate, severe), are used in the literature to report PONV. Most of the studies included in the current meta-analysis reported PONV as a dichotomous variable. Only one trial reported PONV on a verbal rating scale, and patients of this study were classified into two groups (presence or absence of PONV).[20] Nausea is a subjective sensation of the desire to vomit and therefore can be expressed by *yes* or *no* or quantified on a visual analog scale. In contrast, vomiting is an objective event that is difficult to quantify on a visual analog scale graded from 0 to 100. Indeed, evalu-

ation of PONV by visual analog scale is considered by some experts to be difficult and prone to bias.[48] Therefore, the current meta-analysis explored the effect of NSAIDs only on the presence or absence of postoperative nausea and/or vomiting.

Different types of NSAIDs (nonselective cyclooxygenase inhibitors, such as ketorolac, ketoprofen, naproxen, ibuprofen, or aspirin) and selective cyclooxygenase-2 inhibitors, such as rofecoxib or parecoxib, were included in the current systematic review. All of them inhibit cyclooxygenase-2 expression induced by inflammation or surgery. NSAIDs and selective cyclooxygenase-2 inhibitors comparably decrease postoperative pain intensity.[49] Rofecoxib has been recently withdrawn from the market because of an increase in cardiovascular risk.[50] This risk was documented for long-term use of the drug. However, one study reported a trend for greater incidence of cardiovascular adverse events in patients taking parecoxib/valdecoxib after coronary artery bypass surgery.[51] Coxibs should therefore be used with caution in cardiac patients. Finally, we selected the highest dose of NSAIDs in the dose–response studies.[21–24] In these studies, the highest dose was usually associated with the greatest morphine-sparing effect. One may consider that such a decision may favor the benefit of NSAIDs. However, the dose chosen was the one commonly used in the clinical setting or the dose recommended by regulatory agencies.

We decided to exclude studies dedicated to intrarectal administration of NSAIDs because this route is considered uncomfortable by most of the adult patients, especially in the postoperative setting.[52] We also did not consider studies where morphine was administrated systematically by subcutaneous or intramuscular injection and studies where continuous infusion was associated with PCA because they were not designed to evaluate a reduction in morphine demand. We also chose to exclude the use of opioids other than morphine to avoid the risk of heterogeneity. In addition, we selected trials where only patients and not nurses or physicians titrated the morphine dose from the PCA system to achieve optimum pain relief. We chose intravenous PCA morphine administration because this technique allowed patients to maintain a balance between acceptable pain control and the occurrence of adverse effects such as PONV. Postoperative nausea and vomiting have been studied mostly in patients who received general anesthesia.[53] Most of the patients included in the current systematic review received balanced general anesthesia with halogenates, nitrous oxide, and opioid. Therefore, caution is needed before extrapolating our results to patients receiving regional anesthesia or analgesia.

This current systematic review did not demonstrate a significant reduction in some other morphine adverse effects, such as pruritus, urinary retention, or respiratory depression. These events are less frequent than PONV or sedation or less carefully monitored (pruritus, urinary retention) and consequently less reported.[4] Respiratory depression is indeed a rare event, occurring in less than 2% of the cases.[4] Although a meta-analysis increases statistical power, it is still limited by the number of events reported by investigators or the incidence of such events.

A significant relation between the incidence of nausea and vomiting and morphine consumption was observed during the postoperative period. Previous studies have documented a correlation between morphine dose and pain relief on one hand, and morphine dose and respiratory depression on the other hand.[54] Because respiratory depression has been considered a life-threatening complication, studies have focused on this point. Gal *et al.*[54] demonstrated that intravenous morphine administrated in successive doses of 0.15 mg/kg depressed the slope of the carbon dioxide–response curves, tidal volume, and mean inspiratory flow. Increasing morphine dosage was also associated with a significant increase in threshold and tolerance to experimental pain. Interestingly, the authors noted that patients who received the highest doses of morphine (0.6 mg/kg) exhibited moderate sedation and that four of six reported nausea.[54] However, they did not evaluate at each morphine dose the corresponding incidence of sedation and nausea. Morphine side effects were evaluated in more details in a dose–response study of intrathecal morphine administration in human volunteers.[55] Bailey *et al.*[55] showed that the incidence of emesis and sedation score were significantly related to the increasing intrathecal morphine dose. Conversely, they did not find a relation between pruritus and urinary retention and intrathecal morphine dose. A dose–response relation was observed between opioid use and the related adverse effects after ambulatory surgery.[56] In a randomized, double-blind, placebo-controlled trial that evaluated the use of parecoxib and valdecoxib in ambulatory surgery patients, Zhao *et al.*[56] found that every 3- to 4-mg equivalent dose of morphine increase was associated with one additional clinically significant opioid side effect. Similarly, the current metaregression suggested that a morphine sparing of 10 mg decreases the incidence of nausea by 9% and the incidence of vomiting by 3%. However, the dose–effect relation was documented by a metaregression and may have some limitations. Because trials were not randomized in respect to the dose administered, the relation between morphine dose and nausea and vomiting may also be explained by other factors, such as pain intensity or duration of treatment, even though an attempt was made to limit such bias.[57] Morphine consumption was measured during 24–48 h in the different trials included in the current meta-analysis. Nausea and vomiting are usually more frequent during the first 24 h, but morphine requirements are more important during this period of time.[40] A subgroup analysis including trials

that studied NSAIDs during the first 24 h confirmed the efficacy of NSAIDs to decrease PONV.

In conclusion, the current meta-analysis highlights the benefits of combining NSAIDs and morphine to decrease opioid-related side effects such as PONV and sedation but not pruritus, urinary retention, or respiratory depression.

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