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Review Article

Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials

V. Martinez[1,2], H. Beloeil[3], E. Marret[4], D. Fletcher[1,2], P. Ravaud[2,5,6,7] and L. Trinquart[2,8]

[1]Service d'Anesthésie Réanimation Chirurgicale, Hôpital Raymond Poincaré, Assistance Publique Hôpitaux de Paris, 104 boulevard Raymond Poincaré F-92380 Garches, France, [2]INSERM, U-987, Hôpital Ambroise Paré, Centre d'Evaluation et de Traitement de la Douleur, F-92100 France, Université Versailles Saint-Quentin, F-78035, France, [3]INSERM, UMR 1153, Centre of Research in Epidemiology and Statistics, Sorbonne Paris Cité—(CRESS), METHODS team, Paris, France, [4]American hospital of Paris, 92 200 Neuilly-sur-Seine, Paris, France, [5]CHU de Rennes, université Rennes 1, pôle anesthésie-réanimation-urgences-SAMU, Inserm UMR 991, 2, avenue H.-Le-Guillou, 35033 Rennes, France, [6]Assistance Publique-Hôpitaux de Paris, Centre d'Epidémiologie Clinique, Hôpital Hôtel-Dieu, 1 place du Parvis Notre-Dame, 75004 Paris, [7]Université Paris Descartes-Sorbonne Paris Cité, 12 Rue de l'École de Médecine, 75006 Paris, France and [8]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York City, USA

*Corresponding author. E-mail: valeria.martinez@rpc.aphp.fr

Abstract

Background. Morphine, and analgesics other than morphine (AOM), are commonly used to treat postoperative pain after major surgery. However, which AOM provides the best efficacy-safety profile remains unclear.
Methods. Randomized trials of any AOM alone or any combination of AOM compared with placebo or another AOM in adults undergoing major surgery and receiving morphine patient-controlled analgesia were included in a network meta-analysis. The outcomes were morphine consumption, pain, incidence of nausea, vomiting at 24 h and severe adverse effects.
Results. 135 trials (13,287 patients) assessing 14 AOM alone or in combination were included. For all outcomes, comparisons with placebo were over-represented. Few trials assessed combinations of two AOM and none the combination of three or more. Network meta-analysis found morphine consumption reduction was greatest with the combination of two AOM (acetaminophen + nefopam, acetaminophen + NSAID, and tramadol + metamizol): -23.9 (95% CI -40;-7.7), -22.8 (-31.5;-14) and -19.8 (35.4;-4.2) mg per 24 h, respectively. For AOM used alone, morphine consumption reduction was greatest with α-2 agonists, NSAIDs, and COX-2 inhibitors. When considering the risk of nausea, NSAIDs, corticosteroids and α-2 agonists used alone were the most efficacious (OR 0.7 [95% CI: 0.6-0.8], 0.36 [0.18-0.79], 0.41 [0.15-.64], respectively). The paucity of severe adverse effects data did not allow assessment of efficacy-safety balance.
Conclusions. A combination of aetaminophen with either an NSAID or nefopam was superior to most AOM used alone, in reducing morphine consumption. Efficacy was best with three AOM used alone (α-2 agonists, NSAIDs and COX-2 inhibitors) and least with tramadol and acetaminophen. There is insufficient trial data reporting adverse events.
Clinical trial registration. PROSPERO: CRD42013003912.

Key words: analgesics; balanced analgesia; postoperative pain; surgery; systematic review

Editor's Key Points

- A network meta-analysis analyses treatment effects across studies that did not conduct direct head-to-head comparisons.
- This analysis confirmed morphine-sparing with some combinations of non-opioid drugs.
- Morphine-sparing analgesic techniques can reduce the risk of postoperative nausea and vomiting.
- Adverse event reporting must be included when conducting clinical trials.

More than 230 million major surgeries are performed annually in the world.[1] Severe pain after surgery remains a major problem, occurring in 20% to 40% of patients.[2] Administration of morphine by patient-controlled analgesia (PCA) has extensively improved the management of postoperative pain,[3] and can be considered a gold standard to alleviate pain after major surgery.[4] Among analgesics, morphine is considered the reference agent but it has limits: moderate efficacy on relieving pain during movement, side-effects such as nausea and vomiting, which can be incapacitating for the patient and delay postoperative rehabilitation.

Balanced analgesia was proposed 25 yr ago to improve postoperative management;[5] it is based on a combination of different analgesic drugs to reduce pain while decreasing the postoperative use of morphine and associated side-effects.[6–8] Therefore, non-opioid analgesics and weak opioids (defined as analgesics other than morphine [AOM]) are often used alone or in combination along with morphine PCA after major surgery.

Many randomized trials and meta-analyses have compared the effects of AOM monotherapy combined with morphine, to that of placebo on pain and postoperative nausea and vomiting (PONV).[9–17] However, few trials have compared these AOM against each other, few trials have assessed AOM combination regimens, and few meta-analyses have synthesized the adverse-effect profile of AOM. As a consequence, which AOM has the best efficacy-safety balance when combined with morphine is unclear.

We undertook a systematic review with network meta-analysis of randomized controlled trials that compared AOM to a placebo or another AOM for treating pain after major surgery. We assessed clinical efficacy and safety using network meta-analysis to integrate data from direct and indirect comparisons,[18–21] thereby determining the relative efficacy and safety of all treatments against each other.

Methods

Data sources and search strategy

The study was registered at PROSPERO (CRD42013003912). We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS databases for reports of randomized trials included from the inception of each database to August, 2015, with no limits on publication language, date, or status. The search equation is available in Supplementary data 1. We also searched the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects for previous relevant systematic reviews. We hand-searched the annual conference proceedings of the American Society of Anesthesiology and European Society of Anaesthesiology from June 2008 to June 2015 and searched for completed trials in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. We systematically contacted primary authors and manufacturers for studies with incomplete data.

Study selection

We included all trials involving adults who underwent major surgery as defined by Earl[22] and who received morphine by PCA for a least 24 h that compared at least one AOM to a placebo or another AOM. Treatment classes of interest were AOM with systemic administration, whatever the timing, dose, route and mode of administration (single or multiple bolus, continuous). Eligible AOM classes included 1) nonsteroidal anti-inflammatory drugs (NSAIDs) 2) COX-2 inhibitors, 3) acetaminophen, 4) tramadol, 5) nefopam, 6) metamizol, 7) corticosteroids and 8) α-2 agonists. Trials assessing the combination of these drugs were eligible. We included trials comparing one drug to two different doses or the timing of administration (pre- or post-incision) of another drug, or one drug to two other drugs in the same class. In such trials, we grouped the arms assessing different doses or timings of administration, or different drugs of the same class.

We excluded trials in which 1) continuous morphine infusion was administered in addition to PCA, 2) PCA involved an opioid other than morphine, 3) PCA was used for less than 24 h, 4) regional analgesia was used in addition to PCA, or 5) an anti-hyperalgesic was used. We also excluded trials of surgery requiring postoperative ventilation during the first 24 h. Finally, we excluded reports authored by Reuben who allegedly fabricated data.[23]

Two pairs of authors independently screened titles, abstracts and full manuscripts according to the selection criteria. Any disagreement was discussed with a third author until consensus was reached.

Data extraction and risk of bias assessment

After developing a data extraction form, we tested it on 20 included studies selected at random and refined it accordingly. Pairs of reviewers independently extracted data from each study. Disagreements were resolved by consensus with a statistician. We extracted information about the trial setting (country), participants (age, gender, weight), type of surgery (abdominal, gynaecologic, orthopedic, mixed), treatments (drug, dose, route, mode and timing of administration) and outcome measures. Drug doses were converted to number of defined daily doses as established by the WHO and corresponding to the average maintenance dose per day, for a drug used for its main indication in adults (Supplementary data Table 1).[24] Two independent reviewers assessed trial methodological quality by using the Cochrane Risk of Bias tool, with any discrepancies resolved by consensus.[25]

Outcome measures

The co-primary outcomes were cumulative morphine consumption (in milligrams of morphine equivalent) and pain (on a 100-mm visual analog scale [VAS]), both at 24 h. Pain scores reported on a numerical rating scale were converted to a 100-mm VAS. The secondary outcomes were the occurrence of nausea and of vomiting at 24 h. If 24-h data were not available, we used the data point closest to 24 h. Because many articles did not report the occurrence of nausea and vomiting separately, we used the

Apfel classification.[24 26 27] Secondary outcomes also included severe adverse events (SAEs) (as defined in each trial). Intention-to-treat analysis was used whenever available.

Review of network geometry

We examined the pattern of comparisons among the different AOM within the network of trials (i.e. we assessed the geometry of the networks for each outcome separately) and produced network graphs with nodes representing the competing AOM and two nodes linked together by an edge, if at least one trial compared the two corresponding AOM. We examined the connections between AOM (i.e. which of the considered treatments were compared head-to-head in trials and which were connected only indirectly by one or more "common comparators" and the amount of evidence informing each comparison.

Data synthesis and analysis

For morphine consumption and pain, the treatment effect measure was a mean difference. For nausea and vomiting and SAEs the treatment effect measure was an odds ratio. The network meta-analysis simultaneously synthesizes data from all available trials within a consistent network and combines direct evidence (comparison of treatments within head-to-head trials) with indirect evidence (comparison of treatments across trials against a common comparator).[28] We used random-effect consistency models within a Bayesian framework.[29] These models accounted for the correlation between the treatment effects by different comparisons from multi-arm trials. We fitted models with Markov chain Monte Carlo simulations with non-informative priors. We derived a rank order of treatments by determining the mean rank and 95% credible interval, based on draws from the estimated effect size distributions in Markov chain Monte Carlo simulations. We plotted rank probabilities against the possible ranks for all competing treatments. All analyses involved use of Rv3.1.2 (R Development Core Team, Vienna, Austria) with the R2WinBUGS package and WinBUGS 1.4.3 (MRC Biostatistics Unit).

To assess clinical heterogeneity and transitivity, we generated descriptive statistics and we compared the distributions of participant age, gender, weight, defined daily dose, and types of surgery across trials and treatment comparisons. To evaluate statistical heterogeneity, we calculated between-trial variances, assuming a common estimate for the heterogeneity variance across the different comparisons. We conducted subgroup analyses according to the type of surgery, and administration timing which did not show evidence of differences. The consistency assumption may be violated in network meta-analysis, if indirect evidence conflicts with direct evidence. To assess consistency, we fitted inconsistency models estimating independent mean treatment effects; we compared the fit (assessed by posterior means of the residual deviance and the Deviance Information Criteria) of the consistency and the inconsistency models; if inconsistency models provided a better fit, then the network exhibited inconsistency.[30] We also used the node-splitting method to assess local inconsistencies.[31]

Results

Characteristics of trials and patients

Of 3,843 potentially eligible reports, we examined 311 full-text articles and selected 135 reports of trials including 13,287 patients and assessing 15 treatments (Supplementary data eFig. 1). Tables 1 and 2 present the characteristics of the selected trials (detailed description in Supplementary data Table 2). About half of the trials concerned abdominal surgery and about one quarter gynaecologic surgery. All included trials were published between 1986 and 2014.

The overall risk of bias was low for 36 (27%) trials, high for 13 (10%) and unclear for 86 (63%). More specifically, the risk of selection bias (sequence generation and allocation concealment) was low for 43% of trials and was unclear for 57%. The risk of performance bias (blinding of patients and personnel) and detection bias (blinding of outcome assessors) was low for 62% and 57% of trials, respectively. Finally, 70% of trials featured low risk of bias regarding incomplete outcome data (Supplementary data eFig. 2). Detailed assessments of the risk of bias for each trial are in Supplementary data eTable 3.

Summary of network geometry

Because the reporting of outcomes differed across trials, we included 131 trials (13,083 patients) for the analysis of morphine consumption, 111 (10,133 patients) for pain, 92 (9,568 patients) for nausea, 56 (6,759 patients) for vomiting and 34 (4,697 patients) for SAEs, representing 97% of trials (98% of patients) for morphine consumption, 82% (76%) for pain, 68% (72%) for nausea, 41% (51%) for vomiting, and 26% (36%) for SAEs.

Figures 1 and 2A-3D show the networks of evidence for each outcome. Among 105 possible pairwise comparisons between the 15 treatments, evidence was available for only 27 (26%) for morphine consumption, 25 (24%) for pain, 22 (21%) for nausea, 14 (13%) for vomiting and 10 (9%) for SAEs. For all outcomes, comparisons *vs* placebo were over-represented. For morphine consumption, 143 comparisons were to a placebo and 28 were head-to-head comparisons between drugs. NSAIDs, COX-2 inhibitors and acetaminophen were the most evaluated, with metamizol, nefopam and tramadol the least evaluated (3, 8, and 11 trials, respectively). The combination of two AOM was not

Table 1 Characteristics of the included randomized trials ($n = 135$). Data are number (%) unless stated otherwise. Data for number of centres, age, gender and weight were not available for 3, 15, 19, and 27 trials, respectively.

Characteristics	
Publication yr, median (range)	2003 [1986–2014]
Single-centre trials	117(86)
Trial size, median no. of patients (range)	61 [16–540]
Sponsorship	
Industry	43 (32)
Non-industry	12 (8)
Mixed	3 (1)
Not clear	80 (59)
Population characteristics	
Age, yr, overall mean (range)	50 [18–73]
Women, overall proportion (range of proportion)	69 [0–100]
Weight, kg, overall mean (SD)	71 []
Type of surgery	
Abdominal	64 (47)
Gynaecologic	26 (28)
Orthopaedic	26 (19)
Mixed	19 (5)

Table 2 Trial characteristics by analgesic monotherapy. Data are number (percentage) unless stated otherwise. Data for number of age, weight and gender were not available for 15, 27, and 19 trials, respectively. DDD, defined daily dose; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase.

Analgesic other than morphine	Dose ≥ 1 DDD	Pre-incision administration	Single-bolus administration	Yr of publication, median (range)	Industry funding source	Age, mean (range)	Weight, mean (Range)	Proportion of women, mean (range of proportion)
NSAIDs	72 (84)	32 (38)	28 (33)	2007 (1987-2014)	19 (31)	50 [18.1-66.4]	71.6 [53-96.6]	73% [3-100]
COX-2 inhibitor	37 (97)	26 (67)	19 (49)	2007 (2001-2013)	10 (40)	52.3 [32.3-68.5]	69.5 [54.7-93]	51% [0-100]
Acetaminophen	19 (70)	3 (12)	8 (31)	2008 (1995-2013)	7 (29)	60.5 [42.3-55]	55.8 [51.4-65]	70% [55-93]
Corticosteroids	6 (55)	10 (91)	11 (100)	2004 (1999-2008)	1 (20)	47.3 [25.5-62.6]	73.3 [65-85.7]	61% [30-100]
A-2 agonist	8 (80)	7 (70)	3 (30)	2005 (1992-2008)	1 (10)	48.8 [27-73.3]	76.8 [57.8-88.7]	63% [40-80]
Tramadol	4 (33)	5 (42)	5 (42)	2001 (1992-2008)	2 (16)	47.5 [42-53]	69.1 [58.4-74]	73% [36-100]
Nefopam	5 (56)	2 (22)	1 (11)	2003 (1990-2010)	1 (11)	57.8 [46-73]	70.9 [62.5-77]	71% [63-77]
Metamizol	3 (100)	0(0)	0 (0)	2009 (1996-2009)	1 (33)	54.3 [52-58.5]	75.8 [75.8-75.8]	50% [18-100]

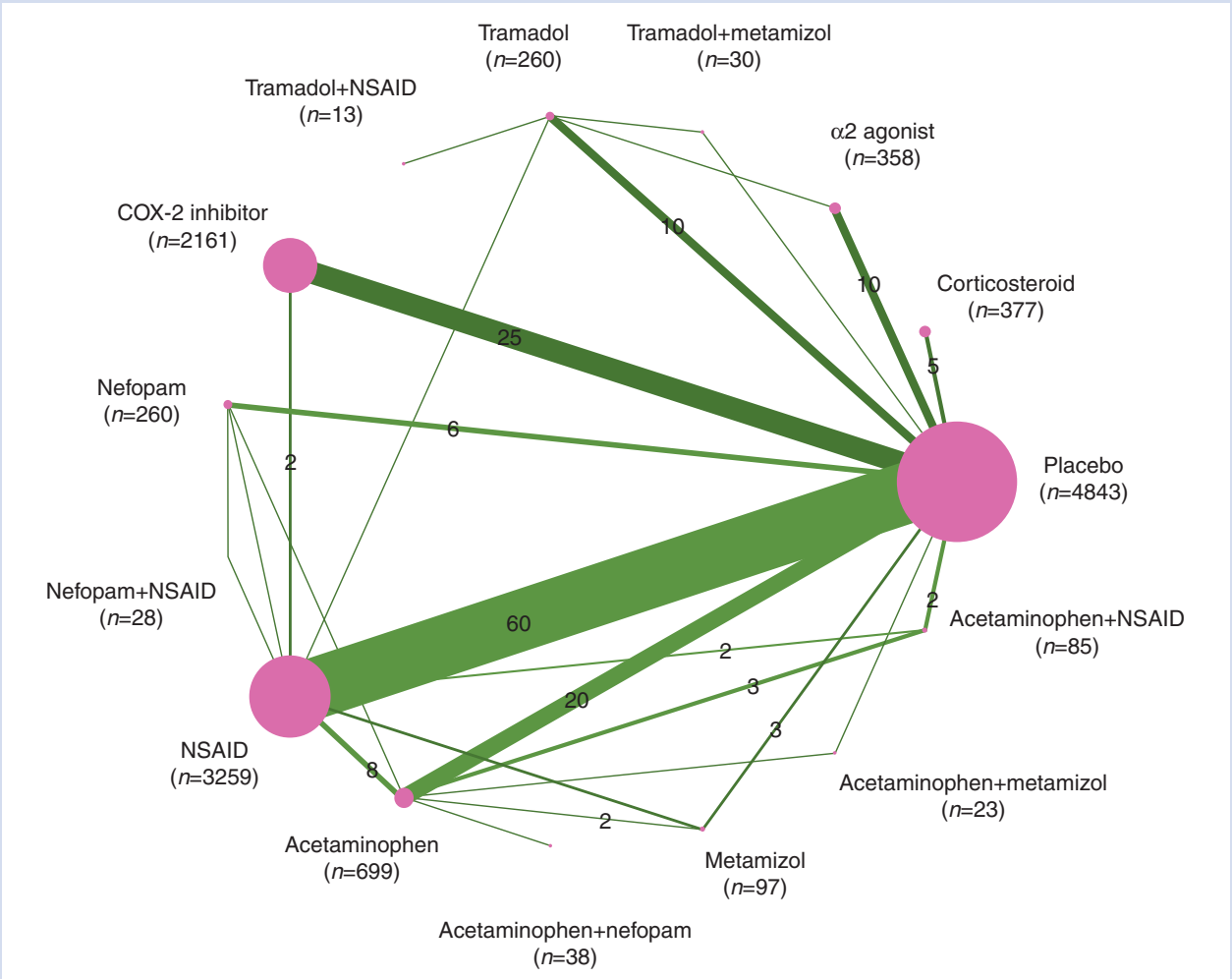

Fig 1 Network geometry for trials reporting treatment effect for morphine consumption.

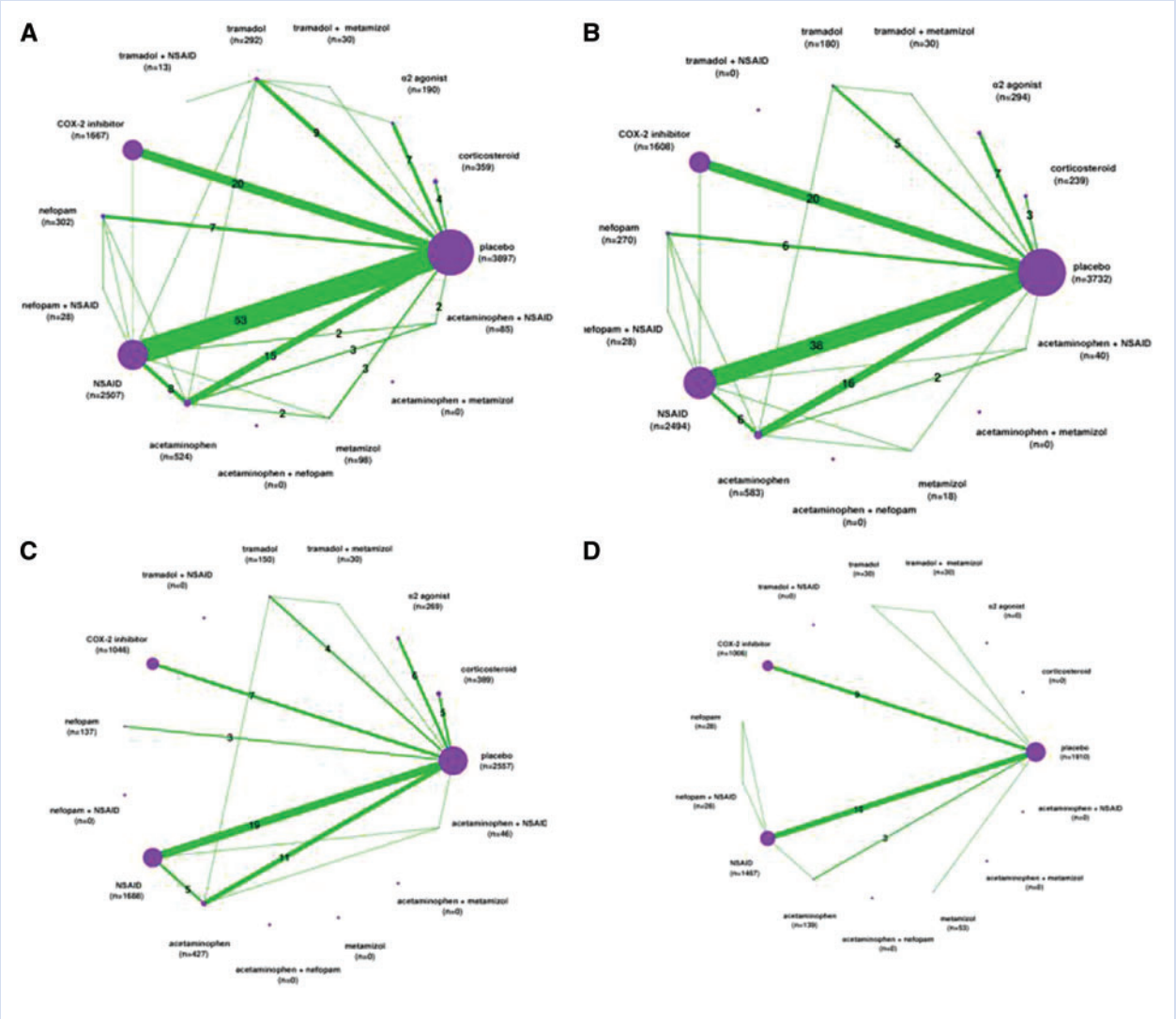

Fig 2 Network geometry for trials reporting treatment effect for A) pain, B) nausea, C) vomiting, and D) severe adverse events.

frequently evaluated; 15 trials assessed six different combinations of two AOM. No trial assessed the combination of three or more AOM (Fig. 1). The difference in the reporting of outcomes varied by the AOM: the ratio between the number of trials reporting nausea and that reporting morphine consumption ranged from 0% to 100% (Supplementary data eFig. 3).

Synthesis of results

Morphine consumption and pain at 24 h

Pooled analysis revealed that morphine consumption was significantly lower with six AOM administered alone (tramadol, nefopam, acetaminophen, NSAIDs, COX-2 inhibitors, and α2-adrenergic agonists) as compared with placebo, with mean reductions ranging from 7.4 to 14.6 mg per 24 h; mean reduction was $\geq$ 20 mg per 24 h with three associations of AOM (acetaminophen + NSAIDs, acetaminophen + nefopam, and tramadol + metamizol) (Fig. 3). In the absence of direct comparisons, network meta-analysis revealed that the morphine-sparing effect was significantly greater for NSAIDs than corticosteroids. Some combinations were associated with a significantly superior effect: acetaminophen + NSAIDs was superior to tramadol, nefopam, corticosteroids, and metamizol, and acetaminophen + nefopam was superior to corticosteroids (Supplementary data eTable 4).

Pain

Pain was significantly decreased with two AOM used alone (NSAIDs and COX-2 inhibitors) and two associations of AOM (acetaminophen + NSAID and tramadol) as compared with placebo, with mean reductions ranging from 5.2 to 23 mm/100 at 24 h (Fig. 3). The treatment effects did not reach a clinically meaningful level for any AOM for pain (Supplementary data eTable 4).

Postoperative nausea and vomiting

The risk of PONV was significantly decreased with three AOM used alone (NSAIDs, corticosteroids, α-2 agonists) as compared

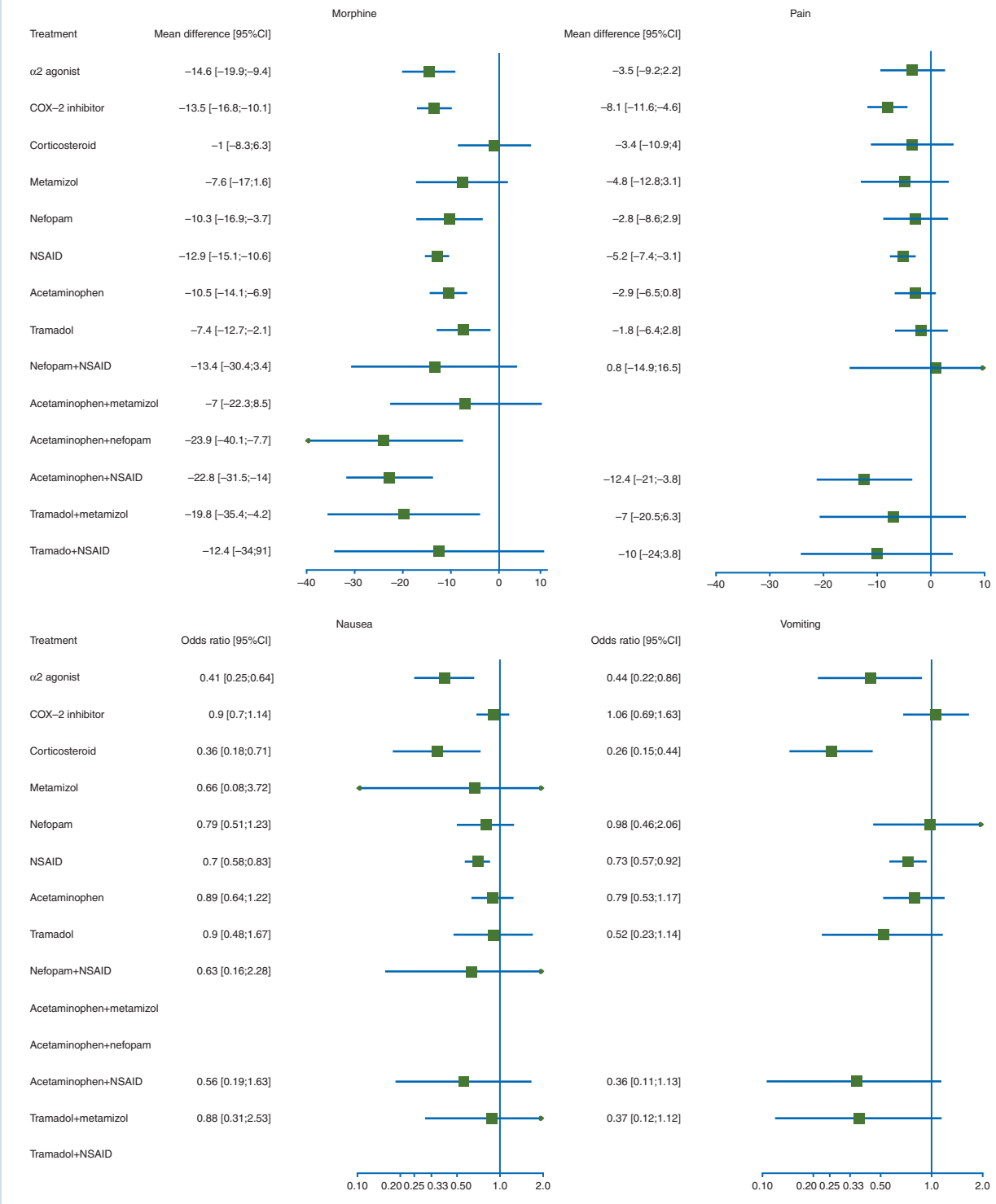

Fig 3 Forest plots of network meta-analysis estimates of analgesics other than morphine *vs* placebo for morphine consumption, pain, nausea, and vomiting.

with placebo. Across all drugs, the ORs ranged from 0.36 to 0.89 for nausea and 0.26 to 0.98 for vomiting. The largest reduction was obtained with corticosteroids (OR 0.36 for nausea and 0.26 for vomiting) and α-2 agonists (OR 0.41 for nausea and 0.44 for vomiting) (Fig. 3). Use of α-2 agonists and corticosteroids did not differ in reducing the risk of PONV. α-2 agonists were significantly superior to NSAIDs for nausea, and corticosteroids were significantly superior to NSAIDs for vomiting. In the absence of

direct comparisons, network meta-analysis revealed that corticosteroids were significantly superior to COX-2 inhibitors in preventing nausea and to COX-2 inhibitors, nefopam, NSAIDs, and acetaminophen in preventing vomiting (Supplementary data eTable 4). Evidence was not sufficient to show reduced risk of PONV with any association of AOM.

Serious adverse events

The network of trials reporting treatment effects on serious adverse events was sparse, which precluded synthesizing data. In conventional random-effects meta-analysis, evidence was insufficient for increased risk of SAEs with NSAIDs (nine trials, OR 1.28 [95% CI 0.65;2.53], with low between-trial heterogeneity, $I^2 = 10\%$), acetaminophen (two trials, OR 3.09 [95% CI 0.33;28.60], with moderate heterogeneity, $I^2 = 18\%$), and COX-2 inhibitors (five trials, OR 2.85 [95% CI 0.75;10.83], with substantial heterogeneity, $I^2 = 79\%$) (Supplementary data eFig. 4).

Exploration of inconsistency

Across all outcomes, the global approach to the assessment of inconsistency always supported the assumption of consistency between direct and indirect evidence; in fact, we always found a better trade-off between model fit and complexity when consistency was assumed than not assumed. Across all outcomes, the local approach to the assessment of inconsistency showed similar findings; we identified significant disagreement between direct and indirect estimates (inconsistency) in a few cases: one discrepancy for morphine consumption (NSAIDs vs nefopam: direct evidence -22.0 [-42.0;-1.9] mg per 24 h in one trial *vs* indirect evidence 0.12 [-7.2;7.4] mg per 24 h); none for pain; one discrepancy for nausea (NSAIDs vs. COX-2 inhibitor: 0.0 [0.0;0.7] vs indirect evidence 0.8 [0.6;1.1]) and (Supplementary data eTable 5).

Discussion

This network meta-analysis is the largest review, including 135 randomized trials and 13,287 patients, assessing the efficacy and safety of AOM associated with morphine PCA after major surgery. It provides opportunity to both explore the network of evidence and to combine all data available for treatment comparisons.

Geometry of evidence

The geometry of our network of treatments revealed that the research agenda did not take into account key clinical issues. First, our network appears as a star with placebo in the centre – that is, placebo was the most evaluated intervention. Head-to-head comparisons were few. Indeed, comparisons *vs* placebo were five times more frequent than head-to-head comparisons and only one-quarter of the evidence was available among 105 possible pairwise comparisons of the 15 treatments. Second, the analyses of geometry revealed that the amount of evidence differed between interventions and outcomes. The most investigated treatment classes (NSAIDs and COX-2 inhibitors) were funded by pharmaceutical sponsors, whereas others classes less supported are less explored (tramadol, nefopam, α-2 agonists). The amount of evidence differed largely between outcomes and among all available trials, from 26% for SAEs to 97% for morphine consumption. The reporting of SAEs was poor. Only one quarter of patients included in trials contributed to the analyses of SAEs. Among 105 possible pairwise comparisons between the 15 treatments, only 9% featured at least one trial for SAE. Furthermore, the differential reporting of SAEs varied greatly by the AOM tested: the ratio between the number of trials reporting SAEs and reporting morphine consumption ranged from 0% for α2 agonists, tramadol, nefopam, metamizol and all combinations, to 36% for COX-2 inhibitors. Third, the trials of combinations of AOM were few. Only 1.5% of all trials evaluated the efficacy of the combination of two AOM and no trial evaluated the combination of three AOM. All combinations deserve more investigation, especially those involving the most effective analgesics, such as NSAIDs and α-2 agonists, which have never been assessed. This lack of evidence contrasts greatly with clinical practice. National and European surveys reported the use of more than two analgesics for 30% to 75% of patients.[32 33] Altogether, 30 yr of clinical research on the subject has not met clinicians' needs, who still need an answer to which AOM or AOM combination has the best efficacy/safety balance?

Relative effectiveness

Our network meta-analysis provided the following novel information. First, the greatest morphine-sparing effect was obtained with the combination of two AOM: acetaminophen plus nefopam, acetaminophen plus NSAIDs, and tramadol plus metamizol. The reduction in morphine consumption with these drug combinations was twice as large, approximately 20 mg per 24 h, as compared with any AOM prescribed alone. The network meta-analysis highlighted the benefit of several combinations. In particular, acetaminophen plus nefopam produced the largest reduction in morphine consumption. However, these results cannot be considered definitive because of the relatively small number of patients included in this group. Within these three drug combinations, the association of acetaminophen and NSAIDs was the only one compared with three AOM used alone in a previous network meta-analysis.[14] Our analysis confirms the previous results showing a benefit of this combination. Moreover, we found this combination allowed for the largest reduction in morphine consumption as compared with acetaminophen and NSAIDs used alone, and also as compared with tramadol, nefopam, corticosteroids and metamizol used alone. All combinations of AOM seemed to reduce the risk of PONV but not all were statistically significant. We could have expected that any effect on morphine sparing would translate into reduced risk of PONV.[12] However, the absence of a statistically significant effect could be as a result of lack of statistical power; in particular, the amount of evidence in the network for nausea and vomiting was reduced, because of poor outcome reporting, as compared with the network for morphine consumption.

Second, our results showed that NSAIDs, COX-2 inhibitors and α-2 agonists were the most efficacious when administered alone. The morphine-sparing effect with NSAIDs and α-2 agonists was associated with a significant decrease in PONV incidence, defining these last two drugs as the most efficient. NSAIDs have long been shown to be superior to other analgesics for postoperative pain relief.[1012] A recent meta-anlaysis[9] on ketorolac reported a significant opioid dose-sparing effect and reduction in PONV incidence as compared with placebo. Studies have reported the superiority of NSAIDs compared with analgesics containing opioids.[3435] The lack of significant reduction in PONV incidence associated with COX-2 inhibitors despite an opioid-sparing effect could be because of lack of data. Our results for α-2 agonists are compelling. Indeed, our analysis revealed that α-2 agonists were similar to NSAIDs and COX-2 inhibitors in terms of morphine-sparing and pain relief but also in reducing risk of PONV. Our findings are novel as compared

with the most recent conventional MAs of clonidine and dexmedetomidine, which reported a reduction in morphine consumption, pain, nausea and vomiting as compared with placebo.[36 37] A limitation of the currently available evidence is the lack of information on α-2 agonists regarding SAEs, which needs to be addressed before recommending such prescription in practice. Finally, we found that dexamethasone produced the largest reduction in PONV incidence, with no morphine-sparing effect. These results confirm that dexamethasone at commonly used dosages should be considered more as an antiemetic than as a real analgesic in the postoperative setting.[38] Other analgesics including acetaminophen, tramadol, metamizol and nefopam showed smaller benefit. As was previously shown, acetaminophen and nefopam should not be recommended alone with morphine.[7 11 14 16] The combination of tramadol, a weak opioid, with a strong opioid did not confer a significant benefit, which agrees with a recent meta-analysis.[17] Metamizol is not widely used because it has been banned in many countries because of an association with potentially life-threatening blood disorders such as immune neutropenia/agranulocytosis. Our results reported a poor benefit of metamizol used alone with morphine.

Third, the paucity of data on SAEs did not allow for NMA of this feature.

Finally, one of the primary outcomes reported in acute pain trials is pain at rest. However, the value of this outcome is questioned by our results, for which no clinically meaningful difference was found for any AOM. As all patients can use PCA, we expect that pain outcomes are the same in the two treatment groups in randomized trials of PCA. Indeed, McQuay and colleagues[39] showed that an analgesic-consumption outcome measure is valid only when treatment groups achieve similar pain scores. Several previous meta-analyses showed a non-clinical significant difference in pain reduction,[10 36 40] but none discussed this issue.

Strengths and limitations of this study

Our study has several strengths. First, we conducted a rigorous and extensive literature search, with contacts of trial authors, and searched the abstract proceedings of two main congresses up to seven yr. Therefore, the probability that we missed a trial is low. Second, our approach is novel: by looking at networks of trials, we provide, for the first time, a "big picture" of all available evidence. Moreover, network meta-analysis includes all treatments in a single synthesis, rather than separate and disconnected analyses for individual pairs of treatments and allows for estimating all comparisons. Third, we carefully developed the selected criteria for trials. We restricted our systematic review to randomized trials involving adults undergoing major surgery and excluded trials of regional analgesia or anti-hyperalgesic drugs in addition to PCA. In several previous meta-analyses assessing AOM after major surgery, most of the evidence originated from studies including several forms and types of "strong opioid rescue"[11 36 38] and combining several other analgesic strategies.[26 37 38] Fourth, when the interpretation of previous reviews was hampered by pooling data based on various morphine rescues, we restricted our systematic review to trials of morphine exclusively administrated by a PCA for at least 24 h.

We acknowledge the following limitations to our work. Our network meta-analysis was based on numerous small trials from single centres. We observed a significant imbalance in terms of quantity of evidence for each intervention, with some interventions under-represented. The power and reliability of the pooled estimates could be affected.[41 42] We observed a substantial between-trial heterogeneity, particularly for the morphine consumption outcome, which was reported previously in conventional meta-analyses.[13 17 36–38 43] There is growing evidence that morphine consumption depends more on individual pain vulnerability rather than on surgical trauma. Indeed, several factors are considered to explain pain vulnerability such as genetics, previous morphine consumption, preoperative chronic pain, and psychological factors.[44–49] None of these factors was monitored and evaluated in our dataset. Finally, our work focused only on analgesics and did not account for other drug classes or methods often used in association with the AOM, such as antihyperalgesic drugs and/or regional analgesia. Future analyses may cover larger networks of evidence including other classes. An additional limitation of our syntheses is the frequent lack of direct evidence from head-to-head trials. As a consequence, the network meta-analysis estimates rely on indirect information. However, our exploration of inconsistency did not show evidence of discrepancy between direct and indirect evidence.

Research agenda

Randomized trials evaluating associations of two or more AOM are needed. All associations, except NSAIDs with acetaminophen, deserve more investigation. Several associations, including the most effective analgesics such as NSAIDs and α-2 agonists, have never been explored. To go further, such trials should be focused on NSAIDs plus α-2 agonists, or in the comparison between acetaminophen plus α-2 agonists and acetaminophen plus NSAID. Comparative trials between AOM *vs* placebo are no longer suitable because the efficacy of these treatments has been demonstrated. NSAIDS should be used as the reference treatment. Trials of a direct comparison between AOM or between associations are needed. The outcome of pain at rest is not appropriate when morphine PCA is used. The main outcome of future studies should be focusing in reporting the reduction of morphine consumption. Moreover other clinical factors such as previous morphine consumption, preoperative pain or psychological vulnerability which could explain the variability of morphine consumption have to be considered. There is an urgent need to report SAEs.

Conclusions

Despite a lack of head-to-head comparisons and poor reporting of severe adverse effects, this network meta-analysis brings new insights to help clinicians select the best postoperative analgesic regimen. Acetaminophen combined with NSAID or with nefopam was superior to most analgesics used alone in terms of reducing morphine consumption with PCA. Three analgesics used alone (α-2 agonists, NSAIDs and COX-2 inhibitors) were the most efficient, with tramadol and acetaminophen the least efficient.

Authors' contributions

Study design/planning: V.M., L.T., H.B., E.M.
Study conduct: V.M., L.T., H.B., E.M.
Data analysis: L.T.
Writing paper: V.M., L.T., P.R., D.F.
Revising paper: all authors

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

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