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Intravenous acetaminophen reduces postoperative nausea and vomiting: A systematic review and meta-analysis

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ABSTRACT

Opioids are a key risk factor for postoperative nausea and vomiting (PONV). As intravenous (i.v.) acetaminophen reduces postoperative pain and opioid requirements, one would expect i.v. acetaminophen to be associated with a lower incidence of opioid-induced side effects, including PONV. We conducted a systematic search using Medline and Cochrane databases supplemented with hand search of abstract proceedings to identify randomized-controlled trials of i.v. acetaminophen. Inclusion criteria were (a) randomized for i.v. acetaminophen vs a placebo control, (b) general anesthesia, and (c) reported or obtainable PONV outcomes. Primary outcome was postoperative nausea and secondary outcome was postoperative vomiting. We included 30 studies with 2364 patients (1223 in the acetaminophen group, 1141 in the placebo group). The relative risk (95% confidence interval) was 0.73 (0.60–0.88) for nausea and 0.63 (0.45–0.88) for vomiting. Data showed significant heterogeneity for both nausea ($P = 0.02$, $I^2 = 38\%$) and vomiting ($P = 0.006$, $I^2 = 47\%$), but were homogeneous when studies were grouped according to timing of first administration: i.v. acetaminophen reduced nausea when given prophylactically either before surgery, 0.54 (0.40–0.74), or before arrival in the postanesthesia care unit, 0.67 (0.55–0.83); but not when given after the onset of pain, 1.12 (0.85–1.48). When i.v. acetaminophen was given prophylactically, the reduction of nausea correlated with the reduction of pain (odds ratio 0.66, 0.47–0.93), but not with reduction in postoperative opioids (odds ratio 0.89, 0.64–1.22). Prophylactically administered i.v. acetaminophen reduced PONV, mainly mediated through superior pain control.

1. Introduction

Postoperative nausea and vomiting (PONV) occurs in about 30% of all patients undergoing general anesthesia, and the main triggers are known to be inhalational anesthetics and opioids [2,3,27,51]. While the emetogenic inhalational anesthetics may be substituted with intravenous (i.v.) propofol infusions, it is more difficult to replace or at least minimize the use of opioids [2,50]. However, even if it may not be generally possible to eliminate opioids, the reduction of opioid consumption is generally thought to be associated with fewer opioid-related side effects. For example, systematic reviews and meta-analyses of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and pregabalin as part of multimodal analgesia have demonstrated a reduction in PONV by about 30%, which is comparable to the efficacy known from conventional antiemetics [29,54].

While oral and rectal acetaminophen has been on the market for many decades, i.v. acetaminophen was introduced only about 10 years ago in Europe and 2 years ago in the United States. The key advantage of i.v. acetaminophen seems to be that 1 g of i.v. acetaminophen is associated with about twice the plasma and effect site concentrations as 1 g of its oral or rectal applications, resulting in greater central nervous system penetration [44], which corroborates the superior analgesic efficacy seen with i.v. compared to oral acetaminophen in the surgical setting [38].

According to systematic reviews and meta-analyses, acetaminophen has also been shown to reduce opioid requirements [32,47]. However, to our surprise, this did not translate to a reduced incidence of PONV. A closer look revealed that those reviews focused on studies with pain or opioid consumption as the primary end

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point, and very few studies did actually report PONV. Furthermore, in the last 2 years, a number of new studies have been published reviewing PONV and acetaminophen [15,30].

Thus, our objective was to systematically review the effect of i.v. acetaminophen on nausea and vomiting in randomized controlled trials in patients who received general anesthesia.

2. Material and methods

According to a prospectively drafted protocol, we searched Medline using the search string "(acetaminophen OR paracetamol) AND (PONV)" using the limits "(human AND clinical trial AND randomized controlled trial)" on March 4, 2012. Eligible studies were abstracts or full papers with no language restrictions, but all studies had to be randomized, placebo-controlled, and report the incidences or number of patients with nausea, vomiting, or both.

Nausea and vomiting are 2 distinct phenomena and, as we have pointed out before, the study of PONV should assess and report these variables separately [4]. But because few patients experience vomiting without nausea, the incidence of postoperative nausea (PON) and PONV is generally fairly similar and thus, original papers often do not distinguish between these variables [50]. Thus, when both PON and PONV were reported, we used the nausea values, and if PONV but not PON was reported, we considered the PONV variables as a very close surrogate for PON. The most commonly reported time interval to measure the efficacy of antiemetics is 24 hours [4]. If another shorter or longer time interval was reported, we used the time interval that was closest relative to the 24-hour interval. If data were unclear or missing, we contacted the authors to ask for additional information.

Included studies had to report PON, PONV, or postoperative vomiting, either as a primary end point, secondary end point, or as adverse events. Our primary hypothesis was that i.v. acetaminophen will reduce PON, possibly through reduction in postoperative opioid requirements. In addition, we expected the effect size for vomiting to be similar; acknowledging that due to the much lower incidence of vomiting compared to nausea, there could be insufficient power for a statistically significant effect even though the effect size could be similar to that for nausea. Furthermore, we planned sensitivity analyses for the source of funding, dosage, and meta-regressions to study the effects of postoperative opioid and pain reduction. Because we found that i.v. acetaminophen did not reduce PONV when it was dosed many hours and often the following days after surgery as a rescue medication, we conducted sensitivity analyses on patients in whom i.v. acetaminophen was given prophylactically. We analyzed all reported outcomes for potential publication bias by examining funnel plots and performing Egger's regression tests [16].

This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [35]. Analyses were primarily conducted with RevMan 5.1 (Cochrane Collaboration, Copenhagen, Denmark), and we calculated the relative risk of the events for the intervention versus the placebo control group using the more conservative random-effects model. We also calculated the number needed to treat; however, this measure needs to be cautiously interpreted since numbers needed to treat for prophylactic interventions are highly dependent on baseline incidences and thus should not be used to compare interventions among trials with different baseline incidence [8]. For meta-regressions and Egger's regression tests, we used Comprehensive Meta-Analysis 2.2 (Biostat; Englewood, NJ, USA) and confirmed the results with STATA 9.0 (StataCorp LP, College Station, TX, USA). Postoperative opioid consumption was converted to morphine equivalents and the regression was conducted on 10-mg morphine equivalents to make the coefficient more comparable to other factors. Reporting of postoperative pain was rather heterogeneous, and conversions were performed as necessary. First, we converted pain values to an 11-point pain scale (0–10). Second, we calculated the area under the pain curve for each group and divided the between-group differences by the duration of observation (usually 24 hours), which resulted in an average pain intensity difference.

3. Results

3.1. Search

Search using Medline and Cochrane databases revealed 178 and 62 hits, respectively, with 33 duplicates (Fig. 1). Hand search of references and contacting Cadence Pharmaceuticals, Inc (San Diego, CA) revealed 10 additional references, leading to a total of 217 references. After reviewing the title and abstracts, 143 references were excluded because they did not meet the inclusion criteria (eg, treatment of acetaminophen overdose) and 74 full-text articles were assessed for final eligibility. Of those, a further 44 articles were excluded for the following reasons (note that one study could have more than one reason): not randomized for i.v. acetaminophen (n = 15), no inactive control (n = 20), patients did not receive surgery under general anesthesia (n = 12), and PONV data were missing and not obtainable (n = 4). Thus, we identified 30 papers (with 32 comparisons) with 2364 patients (1223 in the acetaminophen group, 1141 in the placebo group; Table 1 [5–7,9–11,13,17–23,25,26,28,33,34,36,37,39,42,43,45,46,48,49,52]).

3.2. Efficacy data

Intravenous acetaminophen was associated with a relative risk (95% confidence interval) of 0.73 (0.60–0.88) for nausea (Fig. 2) and 0.63 (0.45–0.88) for vomiting (Fig. 3), but with significant heterogeneity for both nausea ($P = 0.02$) and vomiting ($P = 0.006$; Table 2). Number needed to treat for i.v. acetaminophen was 12.3 (7.6–32.3) for nausea and 14.2 (8.3–50.8) for vomiting. Sensitivity analysis revealed that i.v. acetaminophen reduced nausea (0.63, 0.54–0.75) and vomiting (0.42, 0.31–0.56) in investigator-initiated trials, but did not reduce nausea (1.12, 0.85–1.48) and even increased vomiting (1.41, 1.02–1.96) in industry-sponsored clinical trials. A closer look showed that i.v. acetaminophen was generally started prophylactically in investigator-initiated trials, while it was generally

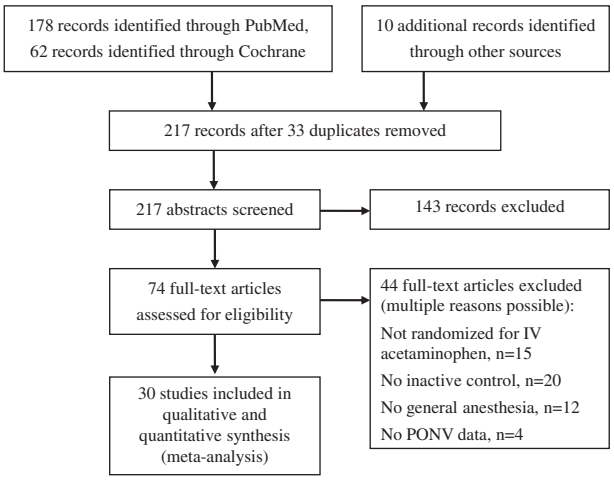

Fig. 1. Flow chart of systematic identification, screening, and eligibility assessment of studies. IV, intravenous; PONV, postoperative nausea and vomiting.

Table 1
Characteristics of included studies.

Study (first author) Year	Number of patients acetaminophen	Number of patients placebo	Risk of bias assessment[a]	Patients/type of surgery	Intervention	Outcomes	Comments
Arici [5] 2009	55	27	U/U/H/H/U	ASA I-II, elective abdominal hysterectomy	1 g i.v. paracetamol before surgery 1 g i.v. paracetamol (prior to skin closure)	Morphine consumption 1, 2, 4, 8, 12, 24 h Pain VAS (0–10) score 1, 2, 4, 8, 12, 24 h Nausea, vomiting, itching, SpO_2 0–24 h Hospital stay	
Arslan [6] 2011	20	20	L/H/L/L/L	ASA I-II, elective thyroidectomy	1 g i.v. acetaminophen intraoperatively 8 mg lornoxicam intraoperatively	Pain VAS 0.25, 1, 2, 4, 6, 8, 12, 18, 24 Time to first analgesic (tramadol) Patient satisfaction Nausea, vomiting 0–24 h Allergy, hypotension 0–24 h	
Atef [7] 2008	38	38	L/L/L/L/L	Elective tonsillectomy	1 g i.v. paracetamol immediately after end of surgery and for every 6 h for 18 h	Pain VAS 1, 2, 3, 4, 24 h Number of pethidine doses Nausea and vomiting 0–24 h Headache 0–24 h	
Brodner [9] 2010	49	49	L/L/L/L/L	ASA I-III, minor-to-intermediate surgery	1 g i.v. acetaminophen every 6 h intraoperatively 1 g dipyrone every 6 h intraoperatively 40 mg parecoxib every 12 h intraoperatively	Pain VAS 1,6, 18, 30, 42 h Time to first piritramide Piritramide consumption Patient satisfaction Respiratory depression Nausea and vomiting Sedation, sweating	
Cakan [10] 2008	20	20	L/L/H/L/L	ASA I-III, elective lumbar laminectomy and diskectomy	1 g i.v. acetaminophen at end of surgery and for every 6 h for 24 h	Pain VAS 1, 2, 4, 6, 12, 18, 24 h Patient satisfaction Nausea and vomiting 0–24 h Sedation 0–24 h Dizziness, headache, drowsiness, hypotension 0–24 h	
Candiotti [11] 2008	166	165	L/L/L/L/U	ASA I-III, lower abdominal, non-laparoscopic, gynecological surgery	1 g i.v. acetaminophen after surgery and for every 6 h for 48 h	Sum of pain intensity at 24 and 48 h Pain relief Time to first rescue morphine Total morphine consumption after 24 and 48 h Patients' satisfaction	
Cattabriga [13] 2007	56	57	L/L/L/L/L	Elective cardiac surgery	1 g i.v. acetaminophen at end of surgery And for every 6 h for 72 h	Pain VAS 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72 h Morphine consumption 0–72 h Nausea and vomiting Cardiorespiratory parameters	
Cok [15] 2011	41	45	L/L/L/L/L	ASA I-II, strabismus surgery in children 2–14 years	15 mg kg^{-1} i.v. paracetamol	Faces pain scale 0–24 h Number of analgesic interventions Nausea and vomiting 0–24, 24-48 h	All patients received dexamethasone 0.1 mg kg^{-1} 10 mg kg^{-1} paracetamol as analgesic rescue medication
Emir [17] 2010	30	30	L/H/H/H/U	Elective spinal vertebral surgery	1 g i.v. paracetamol + 0.75 mg kg^{-1} tramadol immediately after surgery 1.5 mg kg^{-1} tramadol immediately after surgery	0, 0.25, 0.5, 1, 2, 4, 6, 12, 18, 24 h Numeric rating scale for pain assessment 4-point nausea scale Cardiorespiratory parameters	Average was taken Group T: 17/7 = 2.43 Group P: 4/3 = 1.33
Fadly [18] 2006	10	10	U/U/H/H/U	ASA I-II, surgical release of post burn neck contractures	1 g paracetamol + 0.05 mg kg^{-1} morphine 1 g paracetamol Study drug given immediately after extubation	Pain score 0, 0.25, 0.5, 0.75 1, 2, 4, 6 h Time to first morphine rescue dose Total morphine consumption Patient satisfaction Nausea or vomiting 0–6 h	Additional morphine 0.05 mg kg^{-1}

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Table 1 (*continued*)

Study (first author) Year	Number of patients acetaminophen	Number of patients placebo	Risk of bias assessment[a]	Patients/type of surgery	Intervention	Outcomes	Comments
						Sedation SpO_2	
Gimbel [19] 2008	30	31	L/L/L/L/L	Elective hip arthroplasty	1 g i.v. acetaminophen first morning after surgery and repeated after 4, 10, 16 h	First dose: Pain intensity difference 0.25, 0.5, 0.75, 1, 2, 3, 4 h post dose Pain intensity and pain relief derived scores PAR, SPID, TOTPAR, MAXPID, MAXPAR Rescue, frequency, administration, amount Repeated doses: PID at 1, 5, 11, and 17 h Nausea	
Gokten [20] 2011	20	20	U/H/H/L/L	Percutaneous nephrolithotomy	1 g i.v. paracetamol postoperatively and repeated 4/day 20 mL 0.25% levobupivacaine + 1 g i.v. paracetamol postoperatively repeated 4/day 20 mL 0.25% levobupivacaine	Pain VAS at 6 and 24 h Percentage meperidine rescue medication Side effects: Nausea or vomiting Sedation, respiratory depression, hypotension, pruritus, dizziness, sweating, dry mouth	Additional 0.25% levobupivacaine infiltration
Grundmann [21] 2006	20	20	L/L/L/L/L	ASA I-II, unilateral microsurgical lumbar diskectomy	1 g i.v. paracetamol 40 mg parecoxib 1 g metamizol Before the end of surgery	All outcomes for first 2 h postsurgery Pain VAS Patients requiring additional pain therapy Time to rescue piritramide Cumulative piritramide dose Nausea and vomiting Shivering, pruritus, mean arterial pressure, heart rate	
Hong 1 [23] 2010	31	32	L/L/L/L/L	Children 6-24 months, elective ureteroneocystostomy	15 mg kg^{-1} iv acetaminophen + 0.5 μg kg^{-1} intraoperatively 0.5 μg kg^{-1} intraoperatively Parent nurse-controlled analgesia with i.v. acetaminophen in treatment group	Postoperative fentanyl dose at 1,6, 12, 24, 36, 48, 60, 72 h Children's Hospital of Eastern Ontario Pain Scale at 1,6, 12, 24, 36, 48, 60, 72 h Parent satisfaction Side effects (0–72 h): Vomiting, sedation, pruritus, poor oral feeding, desaturation	Additional fentanyl 0.5 mg kg^{-1}
Hong 2 [22] 2010	63	61	L/U/L/L/L	ASA I-II, women, robot-assisted endoscopic total thyroidectomy	1 g i.v. paracetamol before induction of anesthesia and for every 6 h for 24 h	Pain VAS at 1, 3, 6, 12, 24, 48, 72 h Time to rescue fentanyl Side effects: Nausea and vomiting Drain output	
Jokela [25] 2010	40	40	L/L/L/L/L	ASA I-III, laparoscopic hysterectomy	1 g acetaminophen at induction of anesthesia and for every 6 h for 24 h 1 g acetaminophen at induction of anesthesia and for every 6 h for 24 h + 4 mg ondansetron	NRS pain scale at 1, 2, 4, 6, 8, 18, 24 h Time to first rescue oxycodone Total oxycodone dose 0–24 h Patient satisfaction Side effects (0–24 h): PONV, vomiting, dizziness, headache, lack of concentration, pruritus	
Kiliçaslan [26] 2010	25	25	L/L/L/L/L	ASA I-II, cesarean section	1 g paracetamol before end of surgery and for every 6 h for 24 h Patient-controlled tramadol analgesia	Pain (VAS) 1, 3, 6, 12, 24 h postoperative Sedation score (5-point) 1, 3, 6, 12, 24 h postoperative PCA demand and delivery first 24 h Total tramadol consumption first 24 h Side effects (0–24 h): Nausea, vomiting, use of antiemetics, dry mouth, dizziness-drowsiness	

Table 1 (*continued*)

Study (first author) Year	Number of patients acetaminophen	Number of patients placebo	Risk of bias assessment[a]	Patients/type of surgery	Intervention	Outcomes	Comments
Lee [28] 2010	20	20	U/U/H/L/L	ASA I-II, thyroidectomy	1 g i.v. paracetamol 700 mg i.v. paracetamol + 3 mg i.v. morphine 30 mg i.v. Ketorolac 30 min before end of surgery	VAS pain score 0.5, 1, 2, 4, 6 h postoperative Incidence of rescue pethidine Patient satisfaction Side effects (0–6 h): Nausea, vomiting, headache, sedation, dizziness, respiratory depression	
Memis [33] 2010	20	20	L/L/H/H/L	ASA II-III, major surgery, ICU patients	1 g i.v. paracetamol + i.v. meperidine i.v. meperidine every 6 h for 24 h after arrival in ICU	Behavioral pain scale (10-point scale) until extubation VAS 10-point pain scale after extubation at 24 h Sedation score at extubation Sedation score at 24 h Adverse effects: respiratory depression, reintubation, nausea and vomiting, treatment for nausea and vomiting, pruritus	
Minkowitz [34] 2008	23	21	L/L/L/L/U	ASA I-III, vaginal hysterectomy	1 g acetaminophen on morning of postsurgery day 1 and after 4, 10, 16 h	Pain relief and pain intensity difference (4-point) at 0,1,2,3, 4 h Time to maximum pain relief, maximum pain relief SPID4, TOTPAR4 Nausea and vomiting, liver enzymes	Early study termination due to particulates in placebo vials
Moon [36] 2011	36	35	L/L/L/L/H	ASA I-II, abdominal hysterectomy	2 g acetaminophen 30min before induction of anesthesia	Total patient controlled hydromorphone consumption 0-24 h VAS pain score at 1, 2, 6, 12, 24 h after surgery Side effects (0-24 h): Nausea and vomiting, sedation, respiratory depression, pruritus, use of antiemetics	
Ohnesorge [37] 2009	27	26	L/U/L/LU	ASA I-III, elective breast surgery	1 g i.v. paracetamol 1 g i.v. metamizol 20 min before end of surgery and 4, 10, 16 h after surgery	NRS (11-point) pain scale, vigilance, nausea 0.5, 1, 2, 4, 6, 10, 24 h after surgery Need for rescue morphine Total morphine consumption 24 h Patient satisfaction, cognitive function Time to first ambulation	
Platzer [39] 2011	40	39	L/L/H/L/L	ASA I-II, children age 3–13 years, tonsillectomy, adenoidectomy or adenotonsillectomy	15 mg kg^{-1} paracetamol 2 mg kg^{-1} ketoprofen	5-point smiley scale at 0.5, 1 2, 3, 4 h after PACU arrival Morphine consumption Time to rescue morphine Vomiting	Additional 2 mg kg^{-1} ketoprofen additional propofol
Salihoglu [42] 2009	20	20	L/L/L/L/L	ASA I-II, laparoscopic cholecystectomy	1 g i.v. paracetamol after intubation	Verbal (4-point) and VAS (11-point) pain scales at 5, 10, 15, 30, 60 min after recovery Time of first rescue morphine in PACU Total morphine consumption Duration of stay in PACU Awakening time, extubation time Nausea, vomiting	
Sinatra [43] 2005	49	52	L/L/L/L/L	ASA I-III, orthopedic surgery	1 g i.v. acetaminophen on morning of postsurgery day 1 and for every 6 h for 24 h 2 g i.v. propacetamol	VAS (0-100) pain scale, verbal pain scale (4-point), pain relief (5-point) at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 18, 20, 24 h after first dose Time to rescue medication Total morphine consumption Patients satisfaction over	Patient-controlled morphine analgesia

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Table 1 (*continued*)

Study (first author) Year	Number of patients acetaminophen	Number of patients placebo	Risk of bias assessment[a]	Patients/type of surgery	Intervention	Outcomes	Comments
						24 h TOTPAR6, SPID6, SPRID 6 Side effects: nausea, vomiting, constipation, abdominal enlargement, injection site pain/reaction, fever, anemia, pruritus, coughing	
Topal [45] 2009	20	20	U/U/H/U/L	ASA I-II, inguinal hernia repair	1 g paracetamol before end of surgery and for every 6 h for 24 h	VAS (11-point) pain scale and sedation at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24 h postsurgery Total morphine consumption Nausea, vomiting, antiemetic use, respiratory depression, pruritus	Additional 0.05 mg kg^{-1} morphine at end of surgery and patient controlled morphine analgesia
Toygar [46] 2008	60	30	U/H/H/H/U	Lumbar diskectomy	1 g paracetamol 15 min before induction of anesthesia 1 g paracetamol 15 min before end of surgery	VAS pain scale 0, 1, 2, 3, 6, 12, 24 h Time to rescue morphine Total morphine consumption Side effects: Nausea, vomiting, urinary retention	
Uvarov [48] 2008	25	24	L/U/H/H/L	Thoracotomy	1 g i.v. paracetamol before end of surgery and every 6 h for 24 h Rectal paracetamol	VAS pain scale 3,6,12,18,24 h total consumption ropivacaine/fentanyl Side effects: Nausea or vomiting, skin itching, urinary retention	Additional epidural patient controlled analgesia with ropivacaine and fentanyl and 30 mg i.m. ketorolac
Viscusi [49] 2008	35	34	L/L/L/L/L	Total hip arthroplasty	On postsurgery day 1: 1 g paracetamol vs. placebo.	Nausea: i.v. acetaminophen 2/35 Placebo 0/34 Vomiting: i.v. acetaminophen 13/35 Placebo 7/34	BMS study data per study report received from Cadence Pharmaceutical
Wininger [52] 2010	134	110	L/L/L/L/L	Abdominal laparoscopic surgery	Start of medication at postsurgery day 1: 650 mg acetaminophen every 4 h for 24 h 1000 mg acetaminophen every 6 h for 24 h	Pain intensity (4-point), VAS (100 mm) pain scale, Pain relief(5-point) at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24 h on postsurgery day 1 Amount of and time to first morphine or hydromorphone Patient satisfaction (4-point) after 24 h TOTPAR at 4, 6, 24 h, SPID at 4, 6, 24 h Side effects: Nausea, vomiting, constipation, diarrhea, flatulence, infusion-site pain, pyrexia, incision-site pain, back pain, headache, psychiatric disorders, insomnia, dyspnea	

U, unclear; L, low; H, high; ASA, American Society of Anesthesiology; i.v., intravenous; VAS, visual analogue scale; PAR, pain relief; SPID, summed pain intensity difference; TOTPAR, total pain relief; MAXPID, maximum pain intensity difference; MAXPAR, maximum pain relief; PID, pain intensity difference; NRS, numerical rating scale; PONV, postoperative nausea and vomiting; PCA, patient-controlled analgesia; PACU, postanesthesia care unit; SPRID, sum of pain relief and pain intensity difference; BMS, Bristol-Myers Squibb.

[a] The categories in Risk of Bias Assessment are: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data.

given the day following surgery in industry-sponsored registration trials.

Further sensitivity analyses revealed that prophylactically administered i.v. acetaminophen reduced nausea and vomiting irrespective of whether it was started before surgery, intraoperatively, or immediately after surgery (Fig. 4, Table 2). However, a single prophylactic dose of i.v. acetaminophen was associated with less nausea (0.50, 0.38–0.66) than if the dose was repeated (0.72,

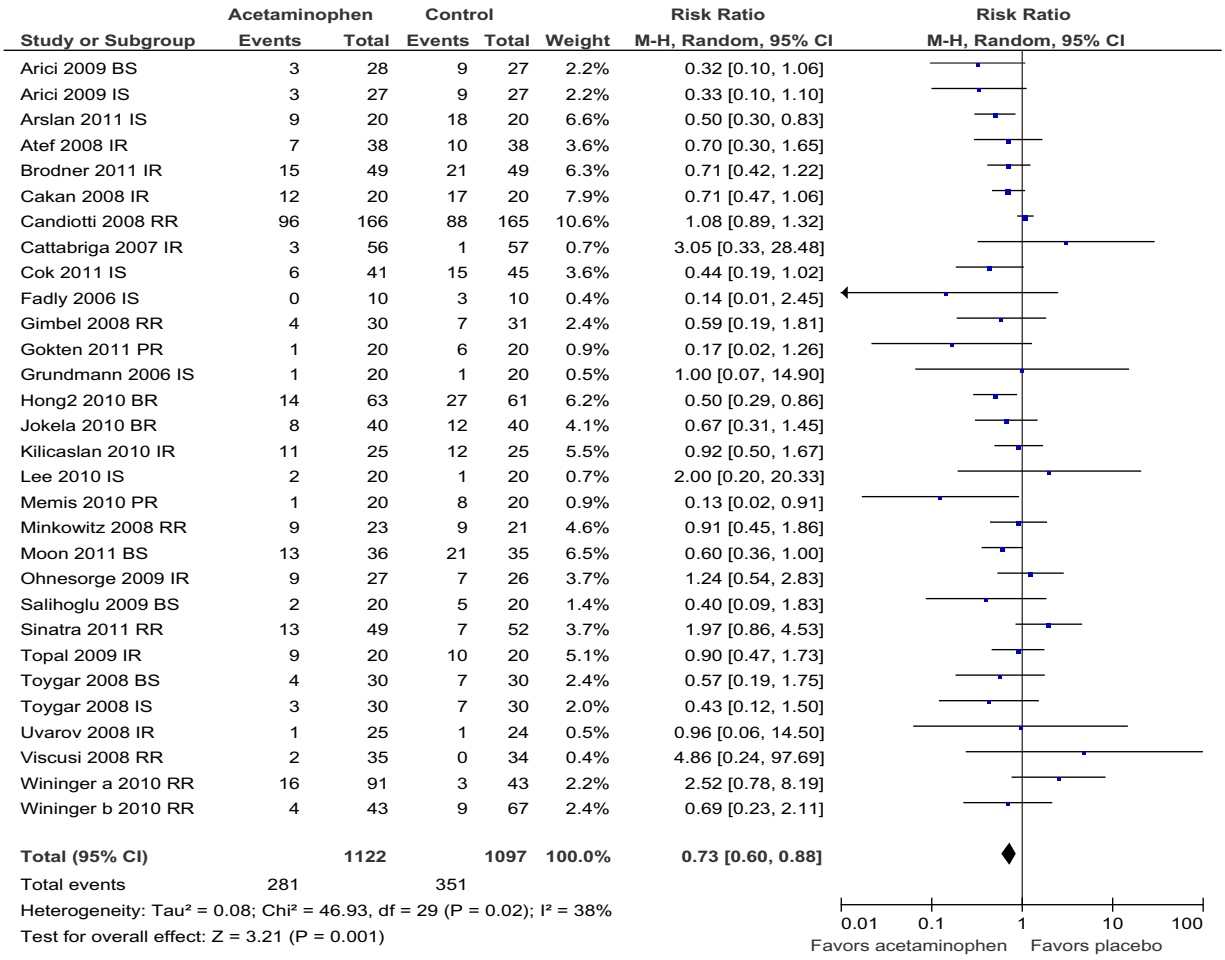

Fig. 2. Effect of intravenous acetaminophen on postoperative nausea. CI, confidence interval; BS, before surgery, single dose; IS, during or immediately after surgery, single dose; IR, during or immediately after surgery, repeated dose; RR, rescue medication, repeated dose; PR, postoperative, repeated dose; BR, before surgery, repeated dose.

0.58–0.89, *P*-value for sub-group differences 0.04, Fig. 5). Results for vomiting were similar, with *P*-value for sub-group differences of 0.13 (Table 2). Reduction of postoperative opioids (average reductions were about 9 mg of morphine equivalents) did not contribute to the antiemetic effect of prophylactic i.v. acetaminophen, with an odds ratio of 0.89 (0.64–1.22) for 10 mg of morphine equivalents (Fig. 6, $P = 0.45$). However, reduction in postoperative pain (average reduction was about 0.9 points on a 0–10 scale) was associated with a significant reduction in postoperative nausea, with an odds ratio of 0.66 (0.47–0.93) per 1 point (Fig. 7, $P = 0.02$). Egger's regression tests did not reveal any evidence of publication bias for any of the outcomes studied ($P > 0.05$ for all outcomes, Table 2).

4. Discussion

We found that prophylactic i.v. acetaminophen reduced PONV. Interestingly, timing of treatment markedly influenced the treatment effect: i.v. acetaminophen was most effective against PONV when given before surgery and intraoperatively, but not when treatment was initiated after onset of pain. Further, when i.v. acetaminophen was given prophylactically, the reduction of PONV correlated with the reported reduction of pain, but not postoperative opioid consumption.

4.1. Critique against previous systematic reviews

At the time this manuscript was being written, several systematic and narrative reviews have been published, all noting that i.v. acetaminophen does not reduce PONV [24,30,31,40,41,47,53]. This includes a Cochrane review that identified only 4 papers, even though at the time of the last search, May 2010, 19 of the 30 papers that we identified had already been published [47]. It is disconcerting that so many studies had not been identified in the Cochrane review, despite the explicit reporting and application of fairly complex search strategies. Further research into why this happens is certainly indicated if we want to improve the reliability of systematic reviews. Therefore, we investigated the effect of i.v. acetaminophen as our main outcome and included the new evidence in our analysis.

4.2. Timing of i.v. administration

Cumulative results showed a high degree of heterogeneity, which prompted further sensitivity analyses. We analyzed the results according to the source of funding. To our surprise, industry-sponsored trials did not show a reduction of PONV, while independent, investigator-initiated trials showed a clear reduction in PONV. We thus reviewed the study designs and found that i.v. acetaminophen was given for rescue treatment only in industry-

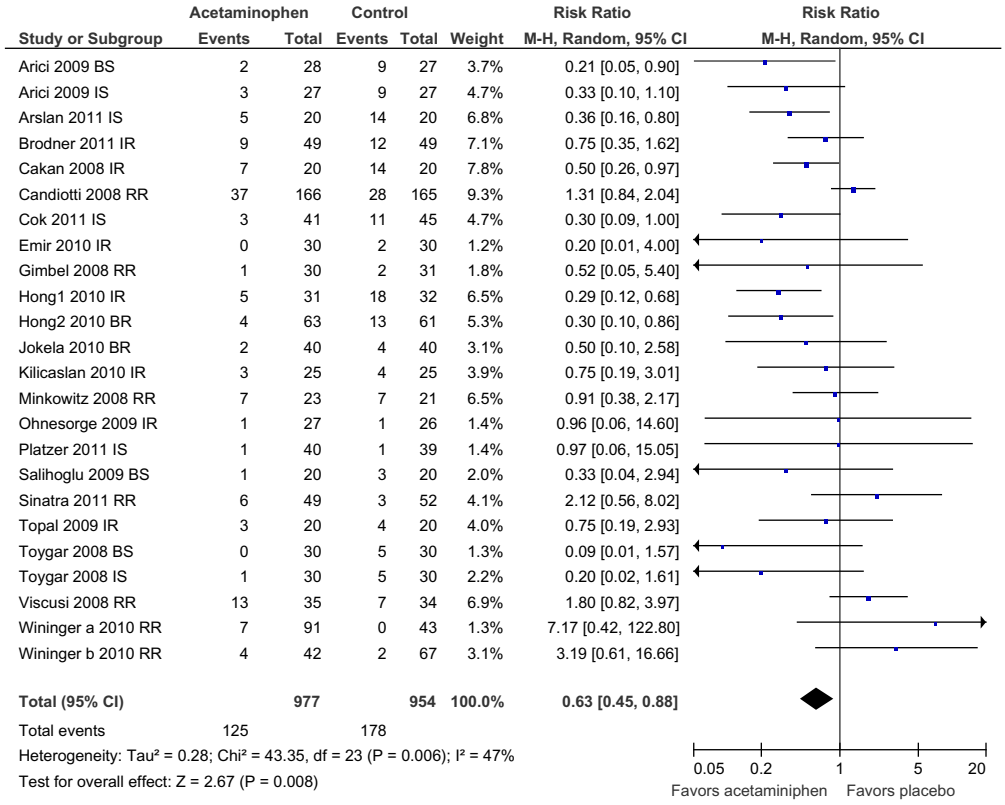

Fig. 3. Effect of intravenous acetaminophen on postoperative vomiting. CI, confidence interval; BS, before surgery, single dose; IS, during or immediately after surgery, single dose; IR, during or immediately after surgery, repeated dose; RR, rescue medication, repeated dose; PR, postoperative, repeated dose; BR, before surgery, repeated dose.

Table 2
Efficacy of i.v. acetaminophen to reduce nausea and vomiting.

Comparison	Acetaminophen	Control	Risk ratio	95% CI	*P*-value of effect	*P*-value heterogeneity	*P*-value Egger's test
Nausea	281/1122	351/1097	0.73	0.60–0.88	0.001	0.02	0.07
Industry sponsored trials/as rescue	144/437	123/413	1.12	0.85–1.48	0.42	0.32	0.60
Investigator initiated trials/prophylactic	137/685	228/684	0.63	0.54–0.75	< 0.001	0.60	0.36
Before surgery	44/217	81/213	0.54	0.40–0.74	<0.001	0.92	0.31
During or immediately after surgery	93/468	147/471	0.67	0.55–0.83	<0.001	0.39	0.50
Prophylactic single dose	46/282	96/284	0.50	0.38–0.66	<0.001	0.94	0.64
Prophylactic repeated doses	91/403	132/400	0.72	0.58–0.89	0.002	0.41	0.74
Vomiting	125/977	178/954	0.63	0.45–0.88	0.008	0.006	0.20
Industry-sponsored trials/as rescue	75/436	49/413	1.41	1.02–1.96	0.04	0.57	0.40
Investigator-initiated trials/prophylactic	50/541	129/541	0.42	0.31–0.56	<0.001	0.90	0.40
Before surgery	9/181	34/178	0.29	0.14–0.57	<0.001	0.87	0.55
During or immediately after surgery	41/360	95/363	0.46	0.33–0.63	<0.001	0.84	0.93
Prophylactic single dose	16/236	57/238	0.31	0.19–0.51	<0.001	0.96	0.52
Prophylactic repeated doses	34/305	72/303	0.49	0.35–0.70	<0.001	0.77	0.96

i.v., intravenous; CI, confidence interval.

sponsored trials, and i.v. acetaminophen was given prophylactically in investigator-initiated trials. Furthermore, heterogeneity vanished when the studies were stratified for timing. We classified the studies into 3 main subgroups: studies in which i.v. acetaminophen was administered a) before surgery, b) during or shortly after the end of surgery, and c) after recovery from anesthesia at onset of pain. Intravenous acetaminophen was shown to be effective for both nausea and vomiting only when administered prophylactically. In contrast, in industry-sponsored trials in which i.v. acetaminophen was given after the onset of pain (often only initiated on the first postoperative day), it did not reduce PONV. Hence, the differences between investigator-initiated and industry-sponsored trials can be attributed to the differences in timing of treatment.

4.3. Prophylactic single versus repeated dosage

As a secondary sensitivity analysis, we separated studies with prophylactically applied i.v. acetaminophen into those where a single dose was given, compared to repeated dosage. While the reduction of vomiting was not statistically significantly different between single and repeated doses, nausea was more reduced by the single dose (risk ratio 0.31) compared to repeated doses (risk ratio 0.49, *P*-value for single vs. repeated comparison = 0.04). These data suggest that i.v. acetaminophen reduces PONV at least as well as established antiemetics, which generally have a risk ratio of 0.60 to 0.80 [1,12]. However, it would be surprising if a single dose of i.v. acetaminophen would be more than twice as effective as con-

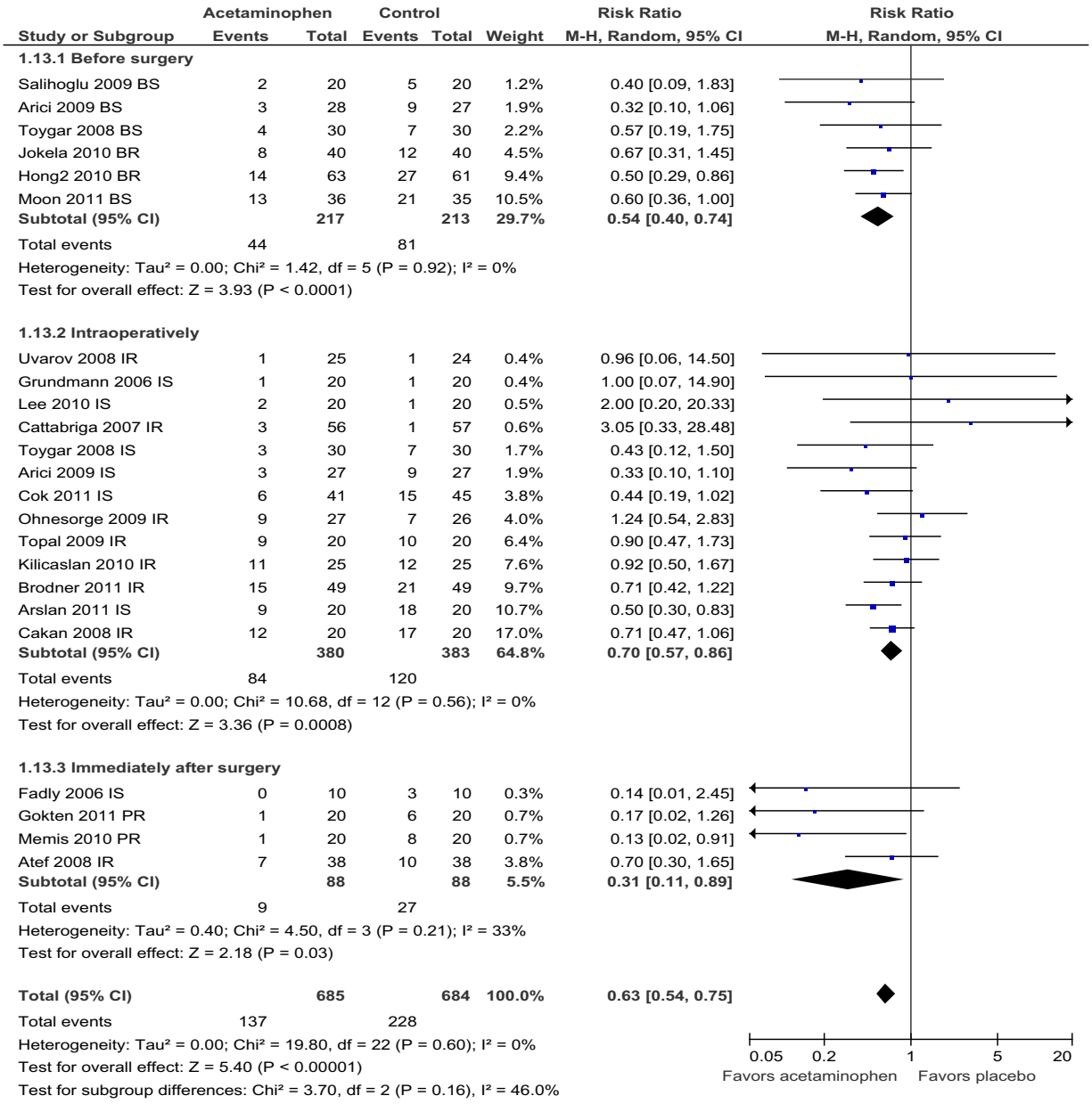

Fig. 4. Effect of prophylactic intravenous acetaminophen on postoperative nausea according to timing of administration. CI, confidence interval; BS, before surgery, single dose; BR, before surgery, repeated dose; IR, during or immediately after surgery, repeated dose; IS, during or immediately after surgery, single dose; PR, postoperative, repeated dose.

ventional antiemetics. In any event, from the perspective of PONV, a single dose of prophylactic i.v. acetaminophen is at least as effective as repeated doses or as antiemetics.

4.4. Potential mechanisms

To elucidate the mechanisms of PONV reduction by i.v. acetaminophen, we performed meta-regressions of the effects of opioid consumption and pain intensity on postoperative nausea. It is generally accepted that the antiemetic effect of NSAIDs is mediated by a dose-dependent reduction in opioid consumption; thus, it seems plausible that i.v. acetaminophen might also reduce PONV by reducing postoperative opioid requirements. In contrast to our expectations, reduction of PONV was not significantly associated with reduction of morphine equivalents; however, it was associated with a reduction in pain intensity. Pain itself is commonly believed to be a risk factor for PONV among clinicians, and this may be the first report to support this notion. Another potential mechanism could be a direct antiemetic effect of acetaminophen. In fact, acetaminophen is metabolized in the brain into AM404, a metabolite that is able to inhibit the reuptake of anandamide, a known cannabinoid CB1 and CB2 receptor agonist. It has been shown that decreased anandamide levels are associated with an increased rate of nausea and vomiting in humans [14]. Therefore, it is possible that acetaminophen simply has a direct effect on PONV by increasing anandamide levels.

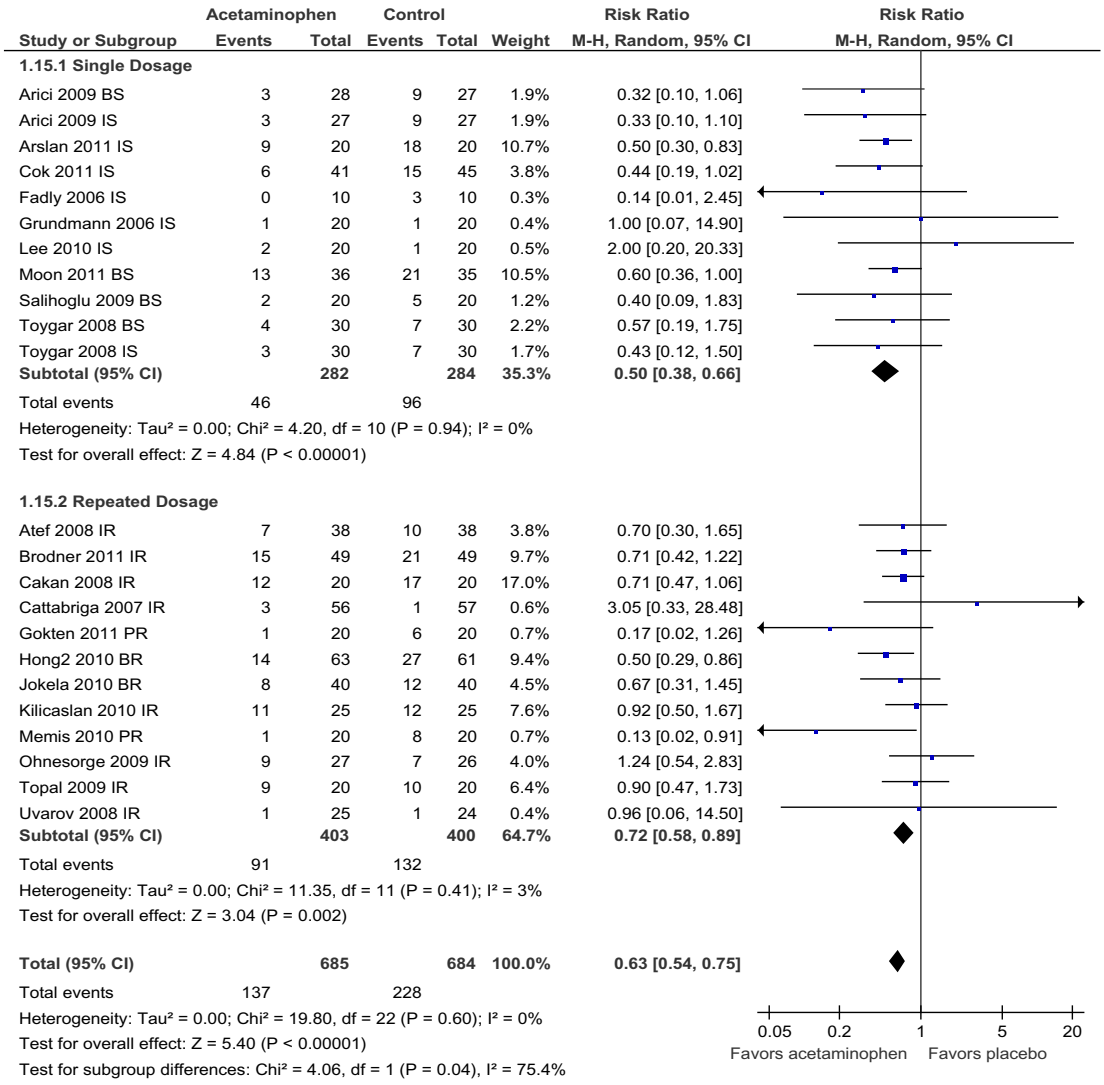

Fig. 5. Effect of single vs repeated dosing of intravenous acetaminophen on postoperative nausea. CI, confidence interval; BS, before surgery, single dose; IS, during or immediately after surgery, single dose; IR, during or immediately after surgery, repeated dose; RR, rescue medication, repeated dose; PR, postoperative, repeated dose; BR, before surgery, repeated dose.

4.5. Limitations

The validity of any systematic review and meta-analysis depends on the validity and quality of the published material, the methodological approach, and appropriate critical appraisal of the study results. We have thus analyzed the data regarding the risk of bias of various components and did not find significant differences. In particular, neither funnel plots nor Egger's regression tests suggested any evidence for a publication bias. However, investigator-initiated studies were generally small and of similar size, which limits the chance to detect publication bias. Thus, although the effectiveness of prophylactically administered i.v. acetaminophen was consistent (without any significant in-between-study heterogeneity), a large, well-designed randomized-controlled trial would be warranted to confirm these findings.

4.6. Conclusion

In summary, this systematic review and meta-analysis demonstrated that prophylactic i.v. acetaminophen reduces postoperative nausea and vomiting with an effect size that compares well with data known from other antiemetics. The results from our meta-regression suggest that the antiemetic effect of i.v. acetaminophen is not mediated through the reduction of postoperative opioid consumption, but through direct mechanisms or through the reduction of postsurgical pain.

Conflict of interest statement

Dr. Apfel was on the Speaker's Bureau of Cadence Pharmaceuticals. None of the other authors have any other potential conflict of interest to report.

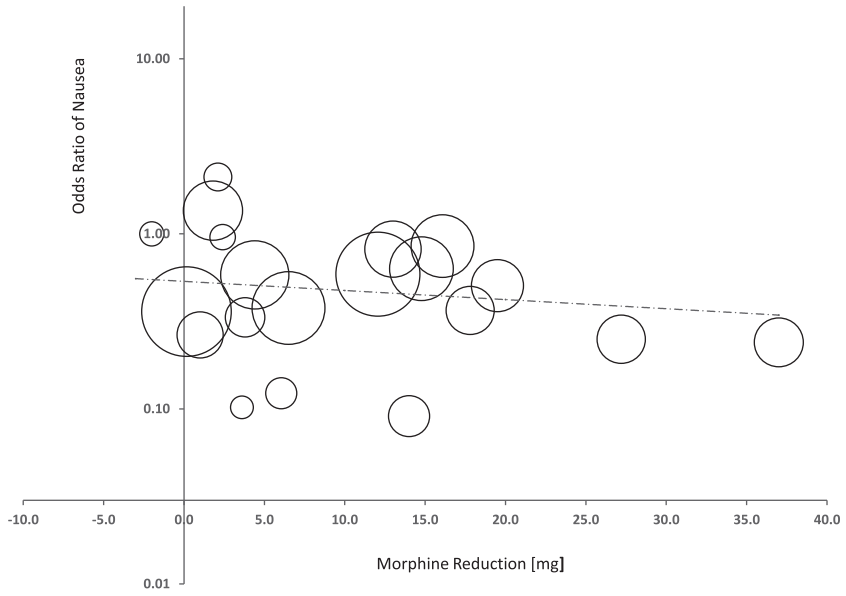

Fig. 6. Meta-regression of morphine reduction on log odds ratio for nausea Morph Reduction (mg) refers to a postoperative opioid reduction in 1-mg morphine equivalents as a result of intravenous acetaminophen vs control (for further details see Methods section).

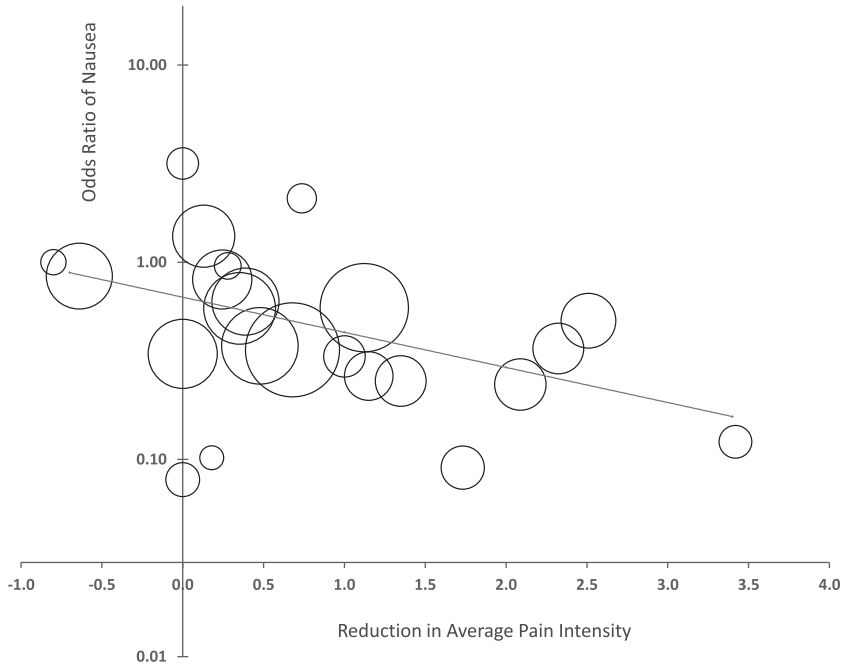

Fig. 7. Meta-regression of average pain intensity reduction on log odds ratio for nausea. Average Pain Intensity refers to a scale from 0 to 10.

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