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BRIEF COMMUNICATION

Intravenous Acetaminophen Versus Placebo in Post-bariatric Surgery Multimodal Pain Management: a Meta-analysis of Randomized Controlled Trials

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Abstract

Background Pain management after bariatric surgery is challenging. Recent trials have been exploring the role of intravenous (IV) acetaminophen in multimodal analgesic therapy. This systematic review and meta-analysis assessed the effect of IV acetaminophen compared to placebo for pain management after bariatric surgery.

Methods A comprehensive search of MEDLINE, Embase, CENTRAL, and PubMed databases were performed. Randomized controlled trials (RCTs) comparing IV acetaminophen to placebo as part of multimodal pain management after bariatric surgery in patients with obesity were included. Key outcomes were analyzed using random-effects meta-analysis, and the certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Results Four RCTs including 349 patients met the inclusion criteria, of whom 175 were provided IV acetaminophen and 174 were provided placebo. Patients given IV acetaminophen demonstrated a lower postoperative pain score (mean difference (MD) − 0.66, 95% CI − 1.03 to − 0.28, $P < 0.001$) 24 h after surgery and lower postoperative opioid use (MD − 6.44, 95% CI − 9.26 to − 3.61, $P < 0.001$; $I^2 = 0\%$) in morphine equivalent doses (MED) within 24 h compared with the placebo group. There was no significant difference in length of stay between groups (MD − 0.26, 95% CI − 0.55 to 0.03, $P = 0.08$).

Conclusions The use of IV acetaminophen after bariatric surgery is effective in reducing pain score after 24 h and postoperative opioid doses, but not length of stay. Provided the benefits of IV acetaminophen, its addition to postoperative care and enhanced recovery programs may be warranted.

Keywords Acetaminophen · Postoperative pain management · Multimodal analgesia · Meta-analysis

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Introduction

Bariatric surgery is the most effective treatment for sustained weight loss and the improvement of comorbidities in patients with obesity [1]. The number of bariatric surgeries performed has increased with the obesity epidemic, which now affects over 650 million adults worldwide [2]. Pain control after bariatric surgery is key to postoperative care, and more than 86% of patients experiencing postoperative pain rate it as moderate, severe, or extreme [3]. Insufficient control of pain can result in reduced patient satisfaction, reduced quality of life, longer lengths of stays (LOS) in the hospital, and increased costs [4].

Traditionally, options for postoperative pain relief included opioids which are associated with adverse effects including respiratory depression, postoperative nausea and vomiting (PONV), constipation, and decreased mental alertness [5]. The incidence of obstructive sleep apnea in patients undergoing bariatric surgery has been estimated to be as high as 55–70% [6, 7], and can be exacerbated by the respiratory depression caused by opioids, resulting in hypoxemia [8]. To minimize the adverse effects associated with opioid use, and improve pain control, the American Society of Anesthesiologists (ASA) has recommended the use of a multimodal pain management regimen whenever possible [9]. Multimodal pain management regimens combine analgesics including local and/or regional anesthetics, acetaminophen, and other drugs that possess different mechanisms of action to achieve additive or synergistic effects [9].

Acetaminophen is a widely used analgesic drug with a positive safety profile and an intravenous (IV) formulation approved by the US Food and Drug Administration (FDA) in 2010 for mild to moderate pain, severe pain as an adjunct to opioids, and fever reduction [10]. The analgesic has been previously demonstrated to decrease pain scores, length of hospitalization, and opioid consumption while increasing patient satisfaction; however, results varied depending on the surgery [10]. IV acetaminophen use decreased rescue opioid consumption in patients by 33% for total hip or knee replacement, 61% for major abdominal surgery, and 78% for tonsillectomy [10–13]. In comparison, the utility of IV acetaminophen for the management of post-bariatric surgery pain is relatively unclear as randomized controlled trials on the topic have achieved mixed results. While IV acetaminophen is commonly available in many countries, it is often provided at a substantial cost, and in some countries including Canada, IV acetaminophen has not yet been approved and is not commonly used in bariatric surgery [14]. A recent meta-analysis by Blank et al. found that there was no significant difference in pain scores according to studies comparing IV acetaminophen to placebo in adult patients undergoing abdominal surgery [15]. Furthermore, the clinical significance of acetaminophen's effects is uncertain, with recent studies questioning its clinical significance in other abdominal surgeries [16].

As both the use of bariatric surgery and concerns over opioids are growing topics of interest, and doubts remain regarding the benefit of IV acetaminophen in bariatric surgery, the effectiveness of IV acetaminophen in patients undergoing bariatric surgery is an increasingly important question with a literature that has not yet been systematically reviewed and synthesized to our knowledge. This systematic review and meta-analysis aims to establish the effects of IV acetaminophen administration compared to placebo on postoperative pain scores, amount of postoperative opioid use, and the length of stay in obese patients after bariatric surgery.

Methods

Search Strategy

We conducted a systematic search of the following databases covering the period from database inception through August 2018: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL). PubMed and the major clinical trial registries (ClinicalTrials.gov: http://clinicaltrials.gov/; International Clinical Trials Registry Platform Search Portal (ICTRP): http://apps.who.int/trialsearch/) were searched for ongoing trials. The search terms were designed and conducted with the help of an expert medical librarian with input from study investigators. The search strategy included keywords such as "bariatric surgery," "intravenous," "acetaminophen," "randomized trial," and more. Appendix S1 shows the details of the search strategy. We also searched the references of published studies and searched gray literature manually to ensure that relevant articles were not missed. We did not discriminate full texts by language. This systematic review and meta-analysis is reported in accordance with the Preferred Reporting items for Systematic Reviews and Meta-analyses (PRISMA) [17]. The protocol of this study was registered before commencement in the Prospective Register of Systematic Review (PROSPERO).

Eligibility Criteria

We included RCTs that compared IV acetaminophen versus placebo as part of a multimodal analgesia pain management after bariatric surgery in patients with obesity (body mass index (BMI) >40 kg/m^2 or >35 kg/m^2 with obesity-related comorbidities). Exclusion criteria were as follows: (1) non-randomized studies, (2) studies that did not provide any primary or secondary outcomes of interest, (3) studies with non-obese patients, (4) duplicate publications or substudies of included trials.

Outcomes

Primary outcomes were as follows: (1) postoperative visual analogue pain scale (VAS) 24 h after surgery, (2) postoperative opioid consumption in morphine equivalent doses. Due to

the heterogeneity of the different types of opioids administered (e.g., hydromorphone, morphine, oxycodone, fentanyl), doses of opioids other than morphine were converted to morphine equivalent dose (MED) using standard conversion factors [18, 19] (refer to Table S1 for conversion). Secondary outcomes were as follows: (1) length of stay (LOS), (2) postoperative VAS nausea score 24 h after surgery, (3) adverse events related to medications.

Data Abstraction

The systematically searched titles and abstracts were independently evaluated by two reviewers using a standardized, pilot-tested form. Reviewers were not blinded to authors, institution, or the journal where the manuscript was published. Discrepancies that occurred at the title and abstract screening stages were resolved by automatic inclusion to ensure that all relevant papers were not missed. Discrepancies at the full-text stage were resolved by consensus between two reviewers, and if disagreement persisted, a third reviewer was consulted. The two reviewers independently conducted data abstraction onto a data collection manual designed a priori. Abstracted data included study characteristics (e.g., author, year of publication, study design, funding source), patient demographics (e.g., age, % female, number of patients per treatment arm, preoperative BMI), intervention description (e.g., type of bariatric surgery, dosing and frequency of intervention), and outcomes.

Risk of Bias and Certainty of Evidence

Risk of bias for individual RCTs was assessed using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs [20]. Certainty of evidence for estimates derived from each meta-analyzed outcome was assessed by Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [21, 22].

Statistical Analysis

All statistical analyses and meta-analysis were performed using the Cochrane Review Manager 5.3 (London, UK) with a level of significance set at P of < 0.05. We performed pairwise meta-analyses using a DerSimonian and Laird random-effects model for continuous outcomes. Pooled effect estimates were obtained by calculating the mean difference (MD) for continuous outcomes along with their respective 95% confidence intervals (CI) to confirm the effect estimation. In addition, the mean and standard deviation was estimated for studies that only reported the median and interquartile range using the estimation method proposed by Wan et al. [23]. For studies that only reported the mean without standard deviation, we contacted the authors for the missing information. This allowed for one unified measure that could allow for the pooling of continuous outcome [18]. Assessment of heterogeneity was completed using the inconsistency (I^2) statistic. We considered I^2 higher than 50% to represent considerable heterogeneity.

Results

Study Characteristics

From 486 potentially relevant citations from the search, four RCTs met the inclusion criteria [24–27]. Figure 1 depicts a PRISMA flow diagram of study selection process. All studies were double-blind, placebo-controlled, randomized trials comparing IV acetaminophen versus placebo as part of multimodal pain management. All trials used 1000 mg of IV acetaminophen every 6 h for 1 day as an intervention and IV saline placebo every 6 h for 1 day as control. In total, 349 patients were enrolled across four RCTs. Of these patients, 75% were female with a weighted mean age of 42.8 ± 2.9 years, and a weighted mean preoperative BMI of 47.1 ± 2.4 kg/m^2. All trials had strict exclusion criteria where patients with a history of chronic opioid use or any opioid use in the last 6 h before the operation were excluded. The types of postoperative opioids used were IV hydromorphone (3 studies), IV fentanyl (2 studies), IV morphine (1 study), and oral (PO) oxycodone (1 study). The detailed RCT characteristics are reported in Tables 1 and 2.

Primary Outcomes

From the four trials included, all trials reported pain score and opioid consumption 24 h after surgery. In total, 175 patients were enrolled in the IV acetaminophen group and 174 were in the placebo group. Most studies assessed pain levels using the VAS system from 0 to 10 with 0 representing no pain and 10 representing the most severe pain. For one study that used the VAS system from 0 to 100, scores were converted to the 10-point maximum scale to allow for pooling. Compared to the placebo group, the IV acetaminophen group had a significantly lower postoperative pain score by 0.66 points (MD − 0.66, 95% CI − 1.03 to − 0.28, $P < 0.001$; $I^2 = 18\%$) 24 h after surgery (Fig. 2). Moreover, the IV acetaminophen group had significantly lower postoperative opioid use than placebo group by 6.44 mg in MED (MD − 6.44, 95% CI − 9.26 to − 3.61, $P < 0.001$; $I^2 = 0\%$) (Fig. 3).

Secondary Outcomes

The length of stay after bariatric surgery was reported in three trials ($n = 316$), with 157 patients in the IV acetaminophen group and 159 in the placebo group. There was no significant difference in the length of stay between IV acetaminophen and the placebo

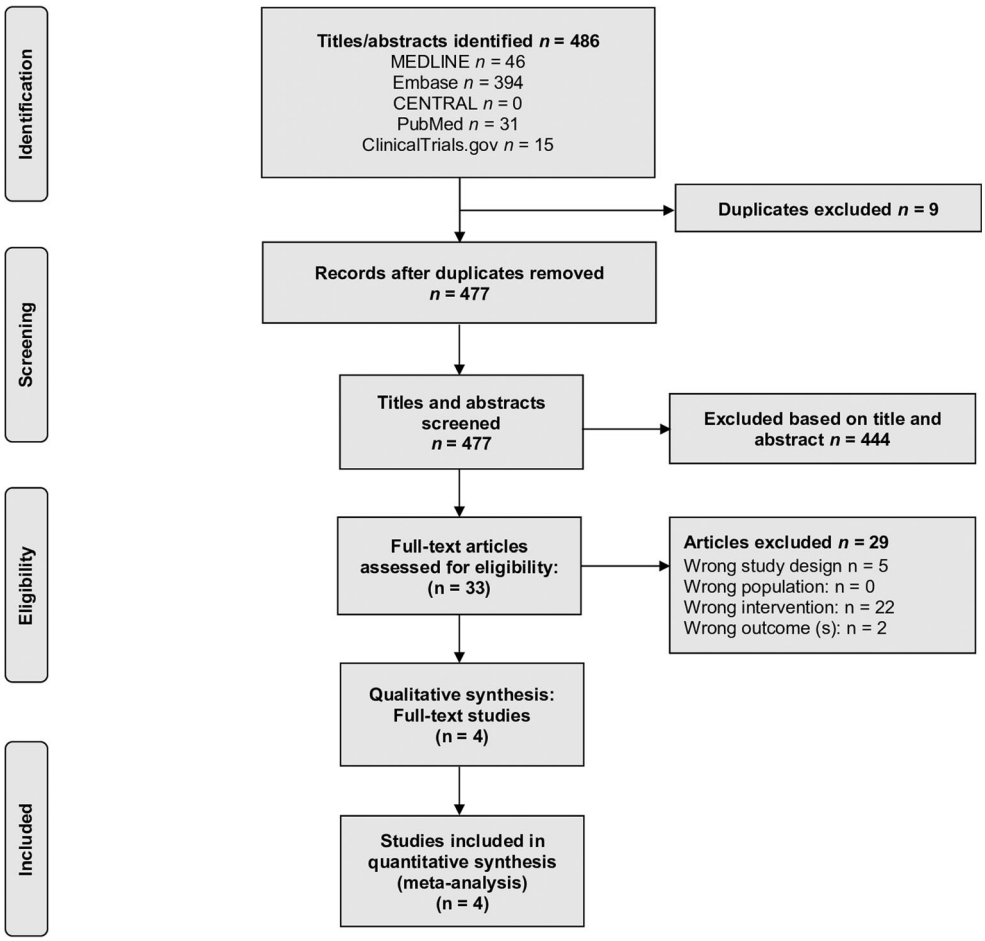

Fig. 1 PRISMA diagram—transparent reporting of systematic reviews and meta-analysis flow diagram outlining the search strategy results from the initial search to included studies

group in the length of stay (MD −0.26, 95% CI −0.55 to 0.03, $P = 0.08$, $I^2 = 66\%$) (Figure S1). Postoperative nausea score 24 h after surgery was reported in only two trials [26, 27]. Both trials did not show a significant difference in nausea score between the IV acetaminophen and placebo group. This outcome could not be included in a meta-analysis due to a high risk of publication bias and a lack of standard deviation reported in one of the trials. In terms of adverse events, only one patient in the IV acetaminophen group experienced generalized swelling of the face and had a rash, which then led this patient to be removed from the study. Otherwise, all patients did not experience any adverse events related to medications (Table S2).

Quality Assessment of Studies

A summary of the risk of bias across all studies is provided in Figure S2. All included studies had random sequence generation, allocation concealment, blinding of participants, and blinding of healthcare providers. Blinding of outcome assessment was present in 75% of the studies, and 50% adequately explained incomplete outcome data or lost to follow-up. No study had selective reporting of outcomes. Therefore, following the Cochrane risk of bias tool, the majority of the studies had low selection bias, performance bias, detection bias, and reporting bias.

GRADE quality of evidence profiled is summarized in Table 3. All outcomes were rated down for imprecision due to total sample size being less than 400 patients [29]. Moreover, the length of stay outcomes were rated down for inconsistency due to high heterogeneity [29]. Overall, there was a moderate certainty of evidence for postoperative pain score and postoperative opioid consumption outcomes, which indicate that IV acetaminophen probably reduces postoperative pain score and opioid consumption compared to placebo after surgery. In addition, there was a low certainty of evidence for the length of stay, which demonstrates that IV acetaminophen may lower the length of stay after surgery.

Discussion

This systematic review and meta-analysis of RCTs shows that the use of intravenous acetaminophen for the management of post-bariatric surgery pain (REVIEWER #2, Comment #2) results in a decrease in postoperative pain score after 24 h by 0.66 points (95% CI 0.28 to 1.03) and decrease in

Table 1 Study characteristics (LSG, laparoscopic sleeve gastrectomy; Robotic SG, robotic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass; BMI, body mass index; NR, not reported)

Study	Surgery	Intervention/control	*N* analyzed	Age (years)	% female	Preop BMI (kg/m^2)	Opioid naïve prior to surgery?	Duration of no acetaminophen prior to surgery	Funding Source
El Chaar 2016 [27]	LSG, LRYGB	Acetaminophen	50	43.2 (15.8)	72	45.2 (7.2)	Yes	> 7 days	Private
		Saline placebo	50	41.1 (13.9)	78	44.1 (6.1)	Yes	> 7 days	
Strode 2016 [26]	LSG	Acetaminophen	18	48 (11)	83.33	50	Yes	> 7 days	Public
		Saline placebo	15	50 (11)	86.67	44	Yes	> 7 days	
Cooke 2018 [28]	Robotic SG, LSG	Acetaminophen	63	42.2 (12.2)	71.1	46.6 (7.7)	NR	> 6 h	Private and public
		Saline placebo	64	39.1 (12.2)	73.4	47.3 (7.9)	NR	> 6 h	
Lange 2018 [29]	LRYGB	Acetaminophen	44	43.6	76	50.9	Yes	> 7 days	Private
		Saline placebo	45	45.3		49.1	Yes	> 7 days	

Table 2 Study outcomes (MED, morphine equivalent dose; VAS, visual analogue system; IV, intravenous)

Study	Intervention/control	Mean length of stay (days)	Mean fentanyl consumption (mcg)	Mean hydromorphone consumption (mg)	Mean morphine consumption (mg)	Oxycodone consumption (mg)	Total morphine equivalent dose (MED)	Pain score 24 h after surgery (VAS)	Nausea score 24 h after surgery (VAS)
El Chaar 2016 [27]	Acetaminophen 1000 mg IV q6h 1 day	1.5 (1.7)	102.5 (24.5)	1.4 (0.70)	6.7 (3.54)	36.5 (11.1)	133.7 (25.3)	6.19 (2.4)*	–
	Saline placebo IV q6h 1 day	1.5 (1.7)	103.1 (33.6)	1.5 (0.80)	7.2 (4.8)	39.2 (12.3)	141.3 (30.13)	6.31 (2.49)*	–
Strode 2016 [26]	Acetaminophen 1000 mg IV q6h 1 day	–	100.7 (22.1)	–	–	–	30.2 (6.6)	2.42 (0.50)	–
	Saline placebo IV q6h 1 day	–	152.75 (43.5)	–	–	–	45.8 (13.1)	3.33 (0.55)	–
Cooke 2018 [28]	Acetaminophen 1000 mg IV q6h 1 day	2.04 (0.81)	–	2.1 (1.6)	–	–	42 (32)	2.9 (3.4)	2.6 (1.8)
	Saline placebo IV q6h 1 day	2.16 (0.63)	–	2.4 (1.9)	–	–	48 (38)	3.6 (5.5)	3 (2.2)
Lange 2018 [29]	Acetaminophen 1000 mg IV q6h 1 day	2.72 (0.5)	–	6 (0.43)	–	–	120 (8.6)	2.55 (1.62)	7.5
	Saline placebo IV q6h 1 day	3.18 (0.25)	–	6.30 (0.30)	–	–	126 (6)	2.91 (1.61)	8.4

*Study did not report the exact time point as to when the VAS score was recorded

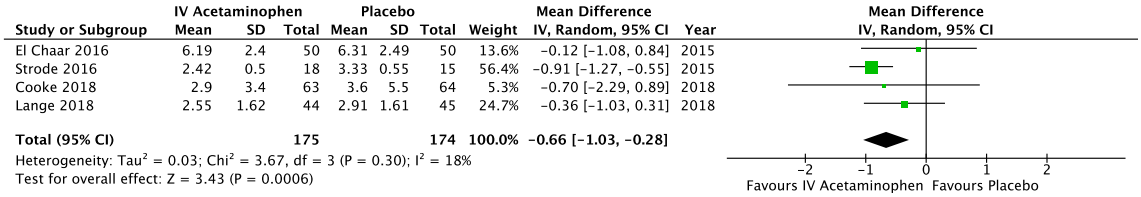

Fig. 2 Random effect meta-analysis of pain score according to the visual analogue system (VAS) 24 h after bariatric surgery

postoperative opioid dose by 6.44 mg in MED (95% CI − 9.26 to − 3.61). In contrast, there was no significant difference in the length of stay after bariatric surgery. A risk of bias assessment of the evidence using GRADE found moderate certainties of evidence for the outcome of postoperative pain score and opioid consumption and low certainty of evidence for the length of stay. Importantly, these data suggest that acetaminophen may be appropriate for use after bariatric surgery, similar to its current use in other abdominal surgeries.

While the present review is the first to explore the effect of IV acetaminophen post-bariatric surgery, the finding of a 6.44-mg reduction in MED for patients provided with IV acetaminophen is supported by the 20% or 9-mg morphine-sparing effect found by a 2005 systematic review of RCTs on the effect of acetaminophen on morphine consumption after major surgery [28]. While a previous meta-analysis by Blank et al. in 2018 did not find significant reductions in pain for adults given IV acetaminophen after abdominal surgery, casting uncertainty on its effectiveness in this population, their review did not include any cases of bariatric surgery and did not exclusively include randomized studies [15]. Previous trials examining the effect of IV acetaminophen have included endpoints including patient satisfaction, number of emergency department visits in 30 days, and cost of care [13, 25]. While the studies included in the present review have not reported such outcomes in sufficient frequency to warrant meta-analysis, individual studies have found significant differences in several outcomes. El Chaar et al. found that IV acetaminophen produced notable indirect cost savings ($13,185 USD vs $39,293 USD) and reduced emergency department visits for abdominal pain in the first 30 days postoperatively (1/50 patients vs 5/50 patients) [25]. Finally, Lange et al. found that IV acetaminophen significantly reduced the time to return of bowel function (1.87 days vs 2.24 days) [26].

Current guidelines for enhanced recovery after bariatric surgery (ERABS) provide a strong recommendation for the control of postoperative pain using multimodal systemic medication combined with local anesthetic infiltration techniques [30]. However, multimodal regimens can vary greatly, and the evidence supporting individual medications is relatively lower. Multimodal analgesics after bariatric surgery commonly include acetaminophen, gabapentin or pregabalin, and ketamine alongside rescue opioids [4, 31]. The efficacy of acetaminophen has been previously described as being weaker than NSAIDs, and the opioid-sparing effects may not always be clinically significant [28, 32]. While the present study has found that IV acetaminophen leads to a statistically significant decrease in pain score of 0.66 (95% CI 0.28 to 1.03) calculated using a 10-point VAS, the results are not definitively higher than the minimally clinically important difference (MCID) associated with pain which ranges from 0.8 to 4 on a 10-point scale [33]. Furthermore, while this review found an opioid-sparing effect of 6.44 mg in MED, this translates to less than a 10% reduction in morphine used. Although combinations of acetaminophen with NSAIDs are superior to either drug alone, NSAIDs have been associated with a higher risk of gastric perforation and ulceration in bariatric patients and are often contraindicated for use [34, 35].

The present study provides evidence to support the incorporation of IV acetaminophen into ERABS program with the benefit of lower postoperative pain and opioid consumption. The potential for opioid abuse is well-known, and great potential exists for reducing dependence particularly in bariatric populations in which bariatric surgery would be expected to reduce the pain associated with osteoarthritis and fibromyalgia [36, 37]. However, a 2013 retrospective cohort study found that the chronic use of opioids increased after bariatric surgery compared with before, and preoperative chronic opioid users required increased morphine equivalents after surgery [38]. The epidemic nature of opioid addiction coupled with the overrepresentation of bariatric surgery patients in substance use treatment facilities necessitates the use of better pain management and fewer postoperative opioids in these patients [39]. While the present review offers an opportunity to reduce

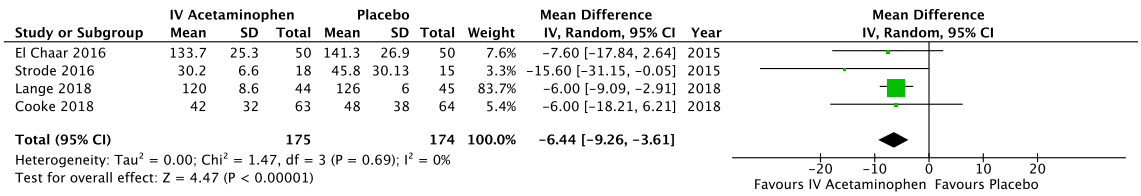

Fig. 3 Random-effect meta-analysis of opioid consumption (morphine equivalent dose, MED) after bariatric surgery

Table 3 Level of evidence according to the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria: postoperative pain score, postoperative opioid consumption, and the length of stay

Certainty assessment							No. of patients		Effect		Overall certainty of evidence
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV acetaminophen	Placebo	Relative (95% CI)	Absolute (95% CI)	
Postoperative pain score (10-point maximum)											
4	RCT	Not serious[a]	Not serious[b]	Not serious[d]	Serious[e]	None[f]	175	174	NA	MD − 0.66 (95% CI − 1.03 to − 0.28)	⊕⊕⊕○ Moderate
Postoperative opioid consumption (morphine equivalent dose, mg)											
4	RCT	Not serious[a]	Not serious[b]	Not serious[d]	Serious[e]	None[f]	175	174	NA	MD − 6.44 (95% CI − 9.26 to − 3.61)	⊕⊕⊕○ Moderate
Length of stay (days)											
3	RCT	Not serious[a]	Serious[c]	Not serious[d]	Serious[e]	None[f]	157	159	NA	MD − 0.26 (95% CI − 0.55 to 0.03)	⊕⊕○○ Low

[a] Majority of studies were adequately blinded and while lost to follow-up was high in Lange and El Chaar, participants lost to follow-up were not generally different from included participants

[b] Low heterogeneity (18% for pain score, 0% for opioid consumption) present, overlapping confidence intervals, identical intervention and comparison, and similar surgeries (either LSG or LRYGB)

[c] Downgraded one point because of high I^2 heterogeneity

[d] All included RCTs directly compare the interventions of interest, measure the outcomes of interest, and in the populations of interest

[e] Downgraded one point because the total sample size was smaller than 400

[f] No publication bias, large effect bias, or plausible confounding variables suspected

this population's exposure to opioids, IV acetaminophen is not currently widely available in several countries including Canada. Although both oral and IV formulations of acetaminophen are similarly effective, IV acetaminophen is preferred in bariatric surgery as patients may not be cleared for consumption and mechanisms of absorption may differ [14].

Our study findings should be interpreted in light of the following limitations. Firstly, while we were able to conduct a meta-analysis of RCTs, warranting a high certainty of evidence according to GRADE, only four RCTs with relevant and extractable data were found in the literature, with a total of 349 patients [24–27]. While we do not believe that additional studies would substantially alter the results of this review due to the low risk of bias of individual RCTs, further trials would allow for the evaluation of additional outcomes such as quality of life, patient satisfaction, and costs associated with care to provide a more complete picture of the effect associated with postoperative IV acetaminophen. Second, our review included studies comparing IV acetaminophen to only placebo, but it lacked comparisons to ibuprofen or other analgesics due to the scarcity of such trials. Therefore, further studies comparing acetaminophen with other analgesics may better pinpoint the role of IV acetaminophen in ERAS protocols and non-opioid multimodal analgesic regimens. Third, opioid regimens varied greatly between the trials included in this review, including morphine, hydromorphone, fentanyl, and oxycodone. While we did convert regimens to morphine equivalent doses, this conversion may not apply to all populations.

Conclusion

The current body of evidence suggests that the use of IV acetaminophen after bariatric surgery is effective in reducing postoperative pain scores and opioid doses in obese patients. However, no statistically significant benefit was noted for the hospital length of stay. Further randomized controlled trials are warranted to better determine the effect of IV acetaminophen on other outcomes including costs associated with care, patient quality of life, and satisfaction. Provided the benefits of IV acetaminophen in a vulnerable population in which proper pain management is difficult, its addition to postoperative care and enhanced recovery programs should be considered.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Statement For this type of study formal consent is not required.

Informed Consent Statement Does not apply.

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