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The Efficacy of Acetaminophen in ERAS Protocols for Total Laparoscopic Hysterectomy

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ABSTRACT

Objective: Despite limited data, acetaminophen, along with other agents, is commonly included in enhanced recovery after surgery (ERAS) protocols following laparoscopic hysterectomy. We aimed to systematically review the efficacy of acetaminophen on the management of postoperative pain after laparoscopic hysterectomy.

Methods: We searched PubMed, SCOPUS, Web of Science, and Cochrane Library databases for relevant clinical trials investigating the role of acetaminophen in the management of pain after laparoscopic hysterectomy. We performed the risk of bias according to Cochrane's risk of bias tool. We performed the analysis of homogeneous data under the fixed-effects model during the analysis of heterogeneous data under the random-effects model. The primary outcome was the assessment of pain score after 2, 6, 12, and 24 h.

Results: A total of 495 patients in 13 trials were included in our meta-analysis. Acetaminophen was not superior at reducing postoperative pain scores. Further analysis at progressive temporal points revealed no further significance; effect size at after 2 h (SMD = −0.020, 95% CI (−0.216; 0.176)), 6 h (SMD = −0.115, 95% CI (−0.312; 0.083)), 12 h (SMD = −0.126, 95% CI (−0.277; 0.025)), or 24 h (SMD = 0.063, 95% CI (−0.065; 0.191)). Pooled analysis was heterogeneous ($P < 0.1$); therefore, we conducted a sensitivity analysis yielding homogeneous results. The drug did not reduce opioid need (MD = −0.16, 95% CI (−2.39, 2.06), $P = 0.89$).

Conclusion: We conclude that acetaminophen is not beneficial for reducing pain after laparoscopic hysterectomy. Other alternatives have better results. Caution should be given to the inclusion of acetaminophen in ERAS protocols designed for laparoscopic hysterectomy, especially as a single agent or to reduce opioid consumption.

Key Words: Acetaminophen, Hysterectomy, Pain, Enhanced recovery after surgery, ERAS.

INTRODUCTION

Despite being an irreversible line of treatment, laparoscopic hysterectomy is ranked by the Centers for Disease Control and Prevention as the second most common gynecological procedure during the childbearing period. The United States alone records 600,000 cases every year.[1] The procedure includes removal of the uterus either

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Informed consent: Dr. Marchand declares that written informed consent was obtained from the patient's for publication of this study/report and any accompanying images.

IRB Approval: This manuscript has been reviewed by the institutional IRB board at Marchand Institute and was found to be exempt from IRB review. (Sep 2020).

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wholly with its cervix or subtotal (supracervical) without the cervix via minimal invasive technique.[2] This helps in decreasing the complication rate as well as the average hospital stay compared to laparotomy.[3] The trend towards laparoscopic hysterectomy has increased over the last decade, and it has become widely used for many indications, including both benign and malignant conditions like endometriosis, adenomyosis, pelvic pain, vaginal prolapse, placenta accreta, placenta percreta, and different gynecological cancers.[4] This increasing usage is attributed to many factors, including better cosmetic outcomes, earlier discharge, reduced hospitalization costs, and earlier rehabilitation.[5–8] However, postoperative pain remains an issue that undermines the advantages of laparoscopic hysterectomy. Although many authors have suggested protocols for the management of postoperative pain, to date the authors have not found data specific to recovery after laparoscopic hysterectomy.[9,10]

Opioids are commonly used as postoperative analgesics; their side effects are commonly reported, including nausea and vomiting, constipation, respiratory depression, urine retention, and sedation.[11] As a result, a need for novel alternatives exists. Therefore recent studies have proposed several multimodal pain management plans to reduce the dependence on opioids as a postoperative analgesic. A multimodal approach, often referred to as enhanced recovery after surgery (ERAS), usually refers to the usage of several classes of analgesics with a different mode of action to achieve the maximum pain relieving effect, and may include other non medication modalities.[11] Acetaminophen is almost invariably included in these protocols. Acetaminophen is a pain relief medication that is available in many different doses and forms, including orally, intravenous (IV) infusion, and a rectal suppository. It is commonly used in many conditions such as headache, toothache, and arthralgia, and has recently been proposed by The American Society of Anesthesiologists (ASA) to be considered for wider usage in the management of postoperative pain.[12] Its mechanism of action as a pain reliever is not completely understood, but the most common hypothesis suggested that it exerts its effect by central inhibition of prostaglandin release.[13]

In the interest of improving women's health and comfort in the care surrounding laparoscopic hysterectomy, we conduct this study to systematically review the efficacy of acetaminophen on the management of postoperative pain after laparoscopic hysterectomy.

MATERIALS and METHODS

We followed the PRISMA statement guidelines[14] during the preparation of this systematic review and meta-analysis and performed all steps in strict accordance with the Cochrane handbook of systematic reviews of intervention.[15]

Literature Search Strategy

We searched PubMed, SCOPUS, Embase, and Cochrane CENTRAL, using relevant keywords "laparoscopic hysterectomy", "abdominal hysterectomy", "open hysterectomy", "laparotomic hysterectomy", "hysterectomy", "acetaminophen", "paracetamol", "panadol", "placebo", "saline", "pain score", "pain", "VAS". All published articles were considered with no restriction in terms of language. We searched the bibliography of included studies for additional relevant records.

Eligibility Criteria and Study Selection

We included all studies satisfying the following criteria: 1) population: women who were scheduled to undergo a laparoscopic hysterectomy under general anesthesia; 2) intervention: acetaminophen either intravenous or rectal; 3) comparator: placebo (saline); 4) outcomes: pain scores and mean consumption of opioids; and 5) study design: randomized controlled trials (RCTs). We excluded the following: 1) nonrandomized trials, 2) in vitro and animal studies, and 3) studies whose data were unreliable for extraction and analysis. Duplicate studies were removed, and retrieved references were screened in two steps: the first step was to screen titles/abstracts for matching our inclusion criteria, and the second step was to screen the full-text articles of eligible abstracts for eligibility for the meta-analysis.

Data Extraction

Two independent authors extracted the relevant data from the included studies. Disagreements were resolved through discussion and consensus among the reviewers. The extracted data included the following: 1) study design; 2) study population; 3) risk of bias domains; and 4) study outcomes: pain scores.

Risk of Bias Assessment

The risk of bias and quality of the eligible studies was assessed by three independent reviewers. We used the

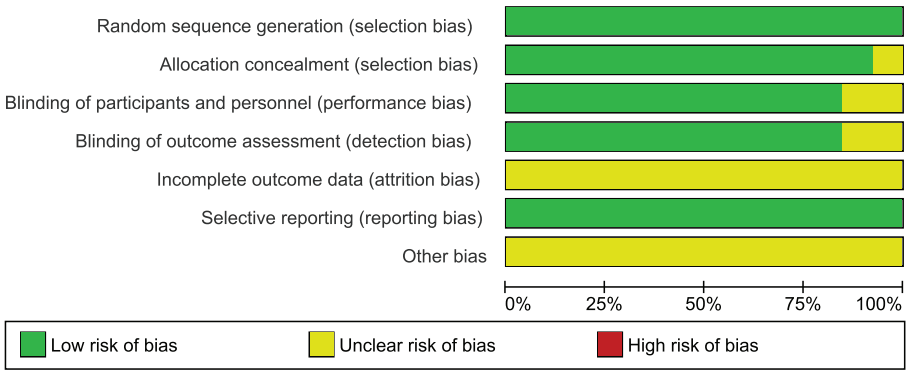

Figure 1. Risk of bias graph.

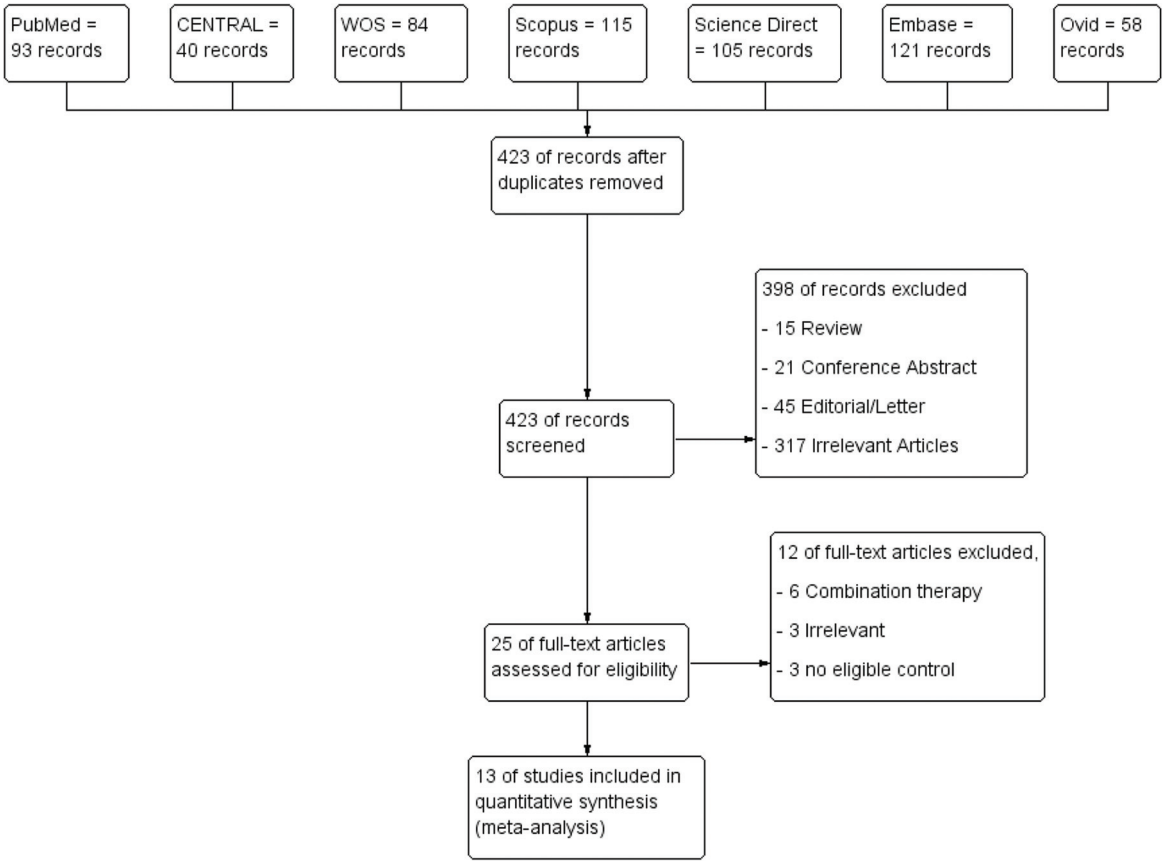

Figure 2. PRISMA flow diagram.

Cochrane Collaboration's tool for the assessment of the risk of bias. Any discrepancies were solved by discussion and consensus between reviewers. The domains upon which the included articles were assessed were: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias (other bias). The authors' judgment is categorized as "low risk", "high risk", or "unclear risk" of bias (**Figure 1**). We used the

Table 1.
Characteristics of Included Patients and Studies

Author	Year	Country	Study Design	Population	Groups	Route of administration	Dosage per day	Sample Size	Age Mean ± SD (years)	Conclusion
Rindos et al.	2019	United States	Prospective, double-blind, placebo-controlled randomized controlled trial	Subjects were 18–75 years old and were scheduled to undergo a laparoscopic hysterectomy.	Acetaminophen	Intravenous	2 g	89	41.8 ± 8.3	There was no difference between acetaminophen and placebo groups in postoperative pain.
					Placebo			91	42.1 ± 8.2	
Koyuncu et al.	2018	Turkey	Prospective, double-blind, placebo-controlled randomized controlled trial	Subjects were 18–80 years old and were scheduled to undergo a laparoscopic hysterectomy under general anesthesia over the course of a year, starting Apr 2012.	Acetaminophen	Intravenous	4 g	70	49.5 (45–62)*	Acetaminophen reduces the risk and intensity of persistent incisional pain.
					Placebo			70	50.5 (45–57)*	
Crisp et al.	2017	United States	Prospective, double-blind, placebo-controlled randomized controlled trial	Subjects had pelvic organ prolapse and were planning to undergo vaginal reconstructive surgery with a vaginal hysterectomy and intraperitoneal vault suspension and were aged between 18 and 95 years.	Acetaminophen	Intravenous	1 g	47	57.3 ± 12.8	Patients undergoing vaginal reconstructive surgery receiving perioperative intravenous acetaminophen did not experience a decrease in narcotic requirements or postoperative pain when compared with placebo.
					Placebo		100 ml	43	59.4 ± 11.4	
Abdulla et al.	2012	Germany	Prospective, double-blind, placebo-controlled randomized controlled trial	Patients were between the ages of 18 and 75 years, and had ASA physical status 1–3. Patients were scheduled for elective nonmalignant abdominal hysterectomy under general anesthesia	Acetaminophen	Intravenous	1 g	30	49.0 ± 11.3	Compared with placebo, there was no significant difference in regard to opioid-sparing effect by administering additional nonopioids, whereas VAS scores were significantly lower in the acetaminophen at 6 h after surgery.
					Placebo			30	50.6 ± 11.7	

Table 1. Continued

Author	Year	Country	Study Design	Population	Groups	Route of administration	Dosage per day	Sample Size	Age Mean ± SD (years)	Conclusion
Moon et al.	2011	South Korea	Prospective, double-blind, placebo-controlled randomized controlled trial	Women with ASA status 1 or 2, aged between 20 and 65 years, and scheduled for elective abdominal hysterectomy under general anesthesia.	Acetaminophen Placebo	Intravenous	2 g	36 35	44.5 ± 5.3 45.5 ± 6.7	Premedication with acetaminophen reducedhydromorphone consumption and opioid-related side effects in patients undergoing abdominal hysterectomy, but did not significantly reduce pain intensity.
Kvalsvik et al.	2003	Norway	Prospective, double-blind, placebo-controlled randomized controlled trial	Patients of ASA physical status 1 – 2, aged 18–70 years, weighing 50–85 kg, scheduled for nonmalignant abdominal hysterectomy.	Acetaminophen Placebo	Rectal	4 g	30 30	45 (39–64)* 45.0 (35– 55)	The effect of rectal acetaminophen after major surgery we have to increase the dose, as higher serum concentrations of acetaminophen may cause lower serum concentrations of morphine.
Gunusen et al.	2012	Turkey	Prospective, double-blind, placebo-controlled randomized controlled trial	Women, aged 44–65 years old, with ASA physical status of class I or II, scheduled for elective abdominal hysterectomy.	Acetaminophen Placebo	Intravenous	1 g	40 40	47.8 ± 4.9 48.3 ± 5	A single dose of 20 mg of tenoxicam provided effective analgesia and reduced total morphine consumption in comparison with acetaminophen and placebo after abdominal hysterectomy.
Arici et al.	2009	Turkey	Prospective, placebo-controlled randomized controlled trial	Patients undergoing an elective total abdominal hysterectomy by laparotomy in an operating room and under general anesthesia.	Acetaminophen Placebo	Intravenous	1 g	28 27	50.37 ± 6.56 49.9 ± 6.4	Acetaminophen (1 g) provided good quality postoperative analgesia, with decreased consumption of morphine and minimal side effects.

Table 1. Continued

Author	Year	Country	Study Design	Population	Groups	Route of administration	Dosage per day	Sample Size	Age Mean ± SD (years)	Conclusion
Ünal et al.	2013	Turkey	Prospective, double-blind, placebo-controlled randomized controlled trial	Patients of ASA III group, prepared for total abdominal hysterectomy operation and between 20 years and 70 years of age.	Acetaminophen Placebo	Intravenous	1 g	20 20	48.1 ± 3.6 48.1 ± 4.5	Acetaminophen did not cause significant change in pain scores, but increased patients' comfort. Although total morphine consumption was significantly decreased, the incidence of nausea and vomiting were similar among the groups.
Yalcin et al.	2012	Turkey	Prospective, placebo-controlled randomized controlled trial	Patients of ASA physical status I–II scheduled for elective total abdominal hysterectomy.	Acetaminophen Placebo	Intravenous	1 g	26 27	47.2 ± 5.5 48.14 ± 5.98	Acetaminophen was effective in preventing remifentanil-induced hyperalgesia.
Cobby et al.	1999	UK	Prospective, double-blind, placebo-controlled randomized controlled trial	Patients with ASA I or II, aged 25–60 years, weighing 40–100 kg, undergoing elective abdominal hysterectomy.	Acetaminophen Placebo	Rectal		24 21	43.7 (28–57)* 42.4 (33–52)*	Rectal acetaminophen was an efficacious adjuvant analgesic after regular dosing.
Jokela et al.	2010	Finland	Prospective, double-blind, placebo-controlled randomized controlled trial	Patients with ASA physical status I/II/III and body mass index <35 kg/m^2 who were scheduled for laparoscopic hysterectomy with or without salpingo-oophorectomy.	Acetaminophen Placebo	Intravenous	1 g	40 40	48 ± 9 49 ± 8	Acetaminophen (as compared to placebo) in periodic doses starting at induction of anesthesia reduced the total dosage of oxycodone required over 0–24 h (P = 0.031).

Table 1. Continued

Author	Year	Country	Study Design	Population	Groups	Route of administration	Dosage per day	Sample Size	Age Mean ± SD (years)	Conclusion
Dahl et al.	1997	Norway	Prospective, double-blind, placebo-controlled randomized controlled trial	Adult females, with ASA physical status I-III, scheduled for elective hysterectomy.	Acetaminophen	Intravenous		22	46.8 ± 7.2	No differences were found between the groups in postoperative pain measured by any variable or opioid consumption at any time. Acetaminophen given preoperatively to hysterectomy patients do not have a postoperative analgesic or opioid-sparing effect. Perioperative surgical bleeding is not influenced by these drugs.
					Placebo			21	49.7 ± 5.9	

*Median (IQR); ASA: American Society of Anesthetists.

Figure 3a. Summary of quality assessment.

quality assessment table provided by the Cochrane Collaboration.[16]

Data Synthesis

Statistical analysis was performed using the Open Meta [Analyst] package from The Brown University, School of

Rindos et al, 2019	Risk of Bias	Quotations
Random sequence generation (selection bias)	Low Risk	" Each subject was assigned randomly with a sequential study number on the day of surgery to either intravenous acetaminophen or placebo in a 1:1 ratio. Randomization of participants was allocated with the use of a random sequence generator."
Allocation concealment (selection bias)	Low Risk	"Randomization of participants was allocated with the use of a random sequence generator."
Blinding of participants and personnel (performance bias)	Low Risk	" The patients, surgeons, anesthesiologist, and nursing staff were all blinded to the arm that the patient was allocated to until after the study had been completed."
Blinding of outcome assessment (detection bias)	Low Risk	" The patients, surgeons, anesthesiologist, and nursing staff were all blinded to the arm that the patient was allocated to until after the study had been completed."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Koyuncu et al, 2018	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"Randomization was web-based and out of the control of any investigator."
Allocation concealment (selection bias)	Unclear Risk	Not described.
Blinding of participants and personnel (performance bias)	Low Risk	"The web system was accessed by an independent investigator who prepared the assigned drug which was covered with opaque plastic to keep the surgical team blinded to treatment."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded"
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	"All outcomes of interest were reported."
Other bias	Unclear Risk	
Crisp et al, 2017	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"Randomization was created using block randomization, with block sizes of 10 and a final block of 14 to randomly assign participants to either intravenous acetaminophen or placebo in a 1:1 ratio."
Allocation concealment (selection bias)	Low Risk	"Randomization was created using block randomization, with block sizes of 10 and a final block of 14 to randomly assign participants to either intravenous acetaminophen or placebo in a 1:1 ratio."
Blinding of participants and personnel (performance bias)	Low Risk	"Either placebo or acetaminophen, depending on the subject's allocation, was mixed by the pharmacy and placed in an identical 100-mL saline bag ensuring blinding of physicians, nurses, and subjects."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Abdulla et al, 2012	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"After informed consent, 120 patients were assigned to one of four groups, based on a computer-generated randomization table."
Allocation concealment (selection bias)	Low Risk	"After informed consent, 120 patients were assigned to one of four groups, based on a computer-generated randomization table."

Figure 3b. Quality assessment of included trials.

Blinding of participants and personnel (performance bias)	Low Risk	"The study solutions were prepared by one of the researchers who was not involved in the intraoperative and postoperative treatment of these patients, whereas postoperative data were collected by anesthesiologists who were blinded as to the treatment used."
Blinding of outcome assessment (detection bias)	Low Risk	"The study solutions were prepared by one of the researchers who was not involved in the intraoperative and postoperative treatment of these patients, whereas postoperative data were collected by anesthesiologists who were blinded as to the treatment used."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Moon et al, 2011	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"The hospital pharmacy performed the randomization using a computer-generated random number table."
Allocation concealment (selection bias)	Low Risk	"The hospital pharmacy performed the randomization using a computer-generated random number table."
Blinding of participants and personnel (performance bias)	Low Risk	"They also masked the study medication bottles by packing and sealing in opaque plastic bags labeled with the randomization numbers. Each consenting patient received a consecutive randomization number. No person was aware of group assignment until all patients had been included and assessments were completed."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Kvalsvik et al, 2003	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"Randomization and blinding were performed by the Hospital Pharmacy at St. Olavs University Hospital, Trondheim. Randomization was carried out on an individual basis by computer random-number generation."
Allocation concealment (selection bias)	Low Risk	"Randomization was carried out on an individual basis by computer random-number generation."
Blinding of participants and personnel (performance bias)	Low Risk	"Randomization and blinding were performed by the Hospital Pharmacy at St. Olavs University Hospital, Trondheim. Blinding was performed by preparation of identical suppositories for placebo and active treatment, respectively."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Gunusen et al, 2012	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	" The women were randomly allocated into one of three groups; according to a computer-generated randomization table."
Allocation concealment (selection bias)	Low Risk	" The women were randomly allocated into one of three groups; according to a computer-generated randomization table."
Blinding of participants and personnel (performance bias)	Low Risk	"The study drugs as previously randomized were prepared by an anesthetic nurse who was not otherwise involved in the care of the patient and were administered by the same anesthetist not involved in the study follow-up."

Figure 3b. Continued.

Blinding of outcome assessment (detection bias)	Low Risk	"The study drugs as previously randomized were prepared by an anesthetic nurse who was not otherwise involved in the care of the patient and were administered by the same anesthetist not involved in the study follow-up."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Arici et al, 2009	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"Patients undergoing an elective total abdominal hysterectomy by laparotomy in an operating room and under general anesthesia were included into the prospective, randomized, planned study. Patients were allocated into three groups."
Allocation concealment (selection bias)	Low Risk	"Patients undergoing an elective total abdominal hysterectomy by laparotomy in an operating room and under general anesthesia were included into the
		prospective, randomized, planned study. Patients were allocated into three groups."
Blinding of participants and personnel (performance bias)	Unclear risk	"Not described."
Blinding of outcome assessment (detection bias)	Unclear risk	"Not described."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Ünal et al, 2013	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	" Randomization was performed using a sealed opaque envelope with a computer generated block random allocation."
Allocation concealment (selection bias)	Low Risk	" Randomization was performed using a sealed opaque envelope with a computer generated block random allocation."
Blinding of participants and personnel (performance bias)	Low Risk	"double blinded. The researcher who knows the group of the patient prepared the test drug was blind to the evaluation of pain relief, whereas the person evaluating the analgesic effects was blind to the treatment drug."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded. The researcher who knows the group of the patient prepared the test drug was blind to the evaluation of pain relief, whereas the person evaluating the analgesic effects was blind to the treatment drug."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Yalcin et al, 2012	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	" Patients of ASA physical sta-tus I–II scheduled for elective total abdominal hys-terectomy by using a computer-generated random number system."
Allocation concealment (selection bias)	Low Risk	" Patients of ASA physical sta-tus I–II scheduled for elective total abdominal hys-terectomy by using a computer-generated random number system."
Blinding of participants and personnel	Unclear risk	"Not described."

Figure 3b. Continued.

Blinding of outcome assessment (detection bias)	Unclear risk	"Not described."
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Cobby et al, 1999	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	" Patients were allocated randomly to one of three equal groups."
Allocation concealment (selection bias)	Low Risk	" Patients were allocated randomly to one of three equal groups."
Blinding of participants and personnel (performance bias)	Low Risk	"double blinded."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	"All outcomes of interest were reported."
Other bias	Unclear Risk	
Jokela et al, 2010	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"The hospital pharmacy performed the randomization using a computer- generated random number table."
Allocation concealment (selection bias)	Low Risk	"The hospital pharmacy performed the randomization using a computer- generated random number table."
Blinding of participants and personnel (performance bias)	Low Risk	"double blinded."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	
Dahl et al, 1997	**Risk of Bias**	**Quotations**
Random sequence generation (selection bias)	Low Risk	"patients were allocated at random to one of three groups."
Allocation concealment (selection bias)	Low Risk	"patients were allocated at random to one of three groups."
Blinding of participants and personnel (performance bias)	Low Risk	"double blinded."
Blinding of outcome assessment (detection bias)	Low Risk	"double blinded."
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	All outcomes of interest were reported.
Other bias	Unclear Risk	

Figure 3b. Continued.

Public Health, and R software 30.6 with the installed "metafor" package. Fixed or random-effects models were applied according to data heterogeneity with the Der-Simonian Liard method. Data was pooled as standardized mean differences (SMD). The missing SD was calculated from the standard error or 95% CI or range, according to Wan et al.[17] To test for statistical heterogeneity between trials, χ^2 and I2 tests were employed; values of 0–40%,

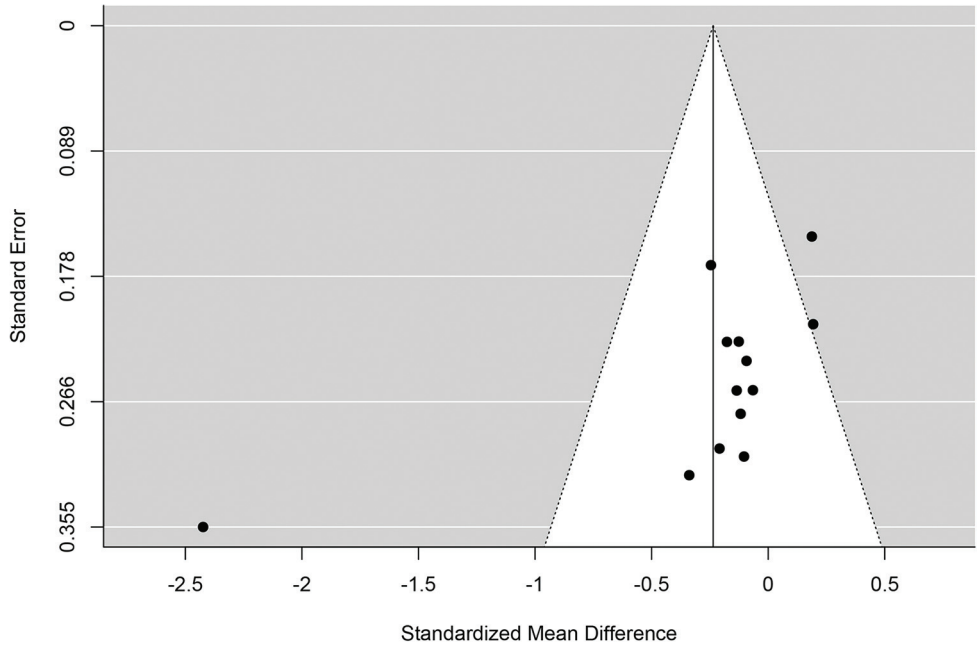

Figure 3c. Funnel plot of sources of bias.

30–60%, 50–90%, and 75–100% represented low, moderate, substantial, and considerable heterogeneity, respectively. $P < 0.1$ was set as a level of significant heterogeneity. When significant heterogeneity was detected, we performed a further sensitivity analysis to find the source of heterogeneity by excluding one study at a time. Publication bias was assessed by the funnel plot, Egger's Regression, and Fail-Safe N methods.[18]

RESULTS

Search Results and Characteristics of Included Studies

Our search retrieved 423 unique citations from searching electronic databases. Following title and abstract screening, 25 full-text articles were retrieved and screened for eligibility. Of them, 12 articles were excluded, and 13 RCTs (n = 495 patients) were reviewed in detail and included in this meta-analysis (PRISMA flow diagram; **Figure 2**).[19–31] All of the included studies were conducted between 1997 and 2019, five studies in Turkey, two studies in the United States, two studies in Norway, and a study in the United Kingdom, Germany, Finland, and South Korea. Eleven studies administered acetaminophen through the intravenous route and two studies through the rectal route. The follow-up period ranged from 1 h to 24 h after the operation. Both sexes were represented approximately equally in each study. **Table 1** summarizes the characteristics of included patients and studies.

Potential Sources of Bias

Applying the Cochrane ROB tool, the quality of the included studies ranged from moderate to high. The main concern was incomplete outcome data (loss of follow-up), which was identified in all studies. A summary of quality assessment domains is shown in **Figure 3a**, while authors' judgments with justifications are shown in **Figure 3b**. The funnel plot (**Figure 3c**) showed asymmetrical representation, and further Egger's Regression and Fail-Safe N analyses revealed significant publication bias ($P = .005$).

Outcomes

Pain Score SMD after 2 h

The overall effect size showed no significant difference between the two groups' pain scores after 2 h (SMD = −0.020, 95% CI (−0.216; 0.176)) (**Figure 4a**). Pooled analyses were heterogeneous; therefore, a sensitivity analysis was applied (**Figure 4b**), yielding homogenous results.

Pain score SMD after 6 h

The overall effect size showed no significant difference between the two groups' pain scores after 6 h (SMD = −0.115, 95% CI (−0.312; 0.083)) (**Figure 4a**). Pooled

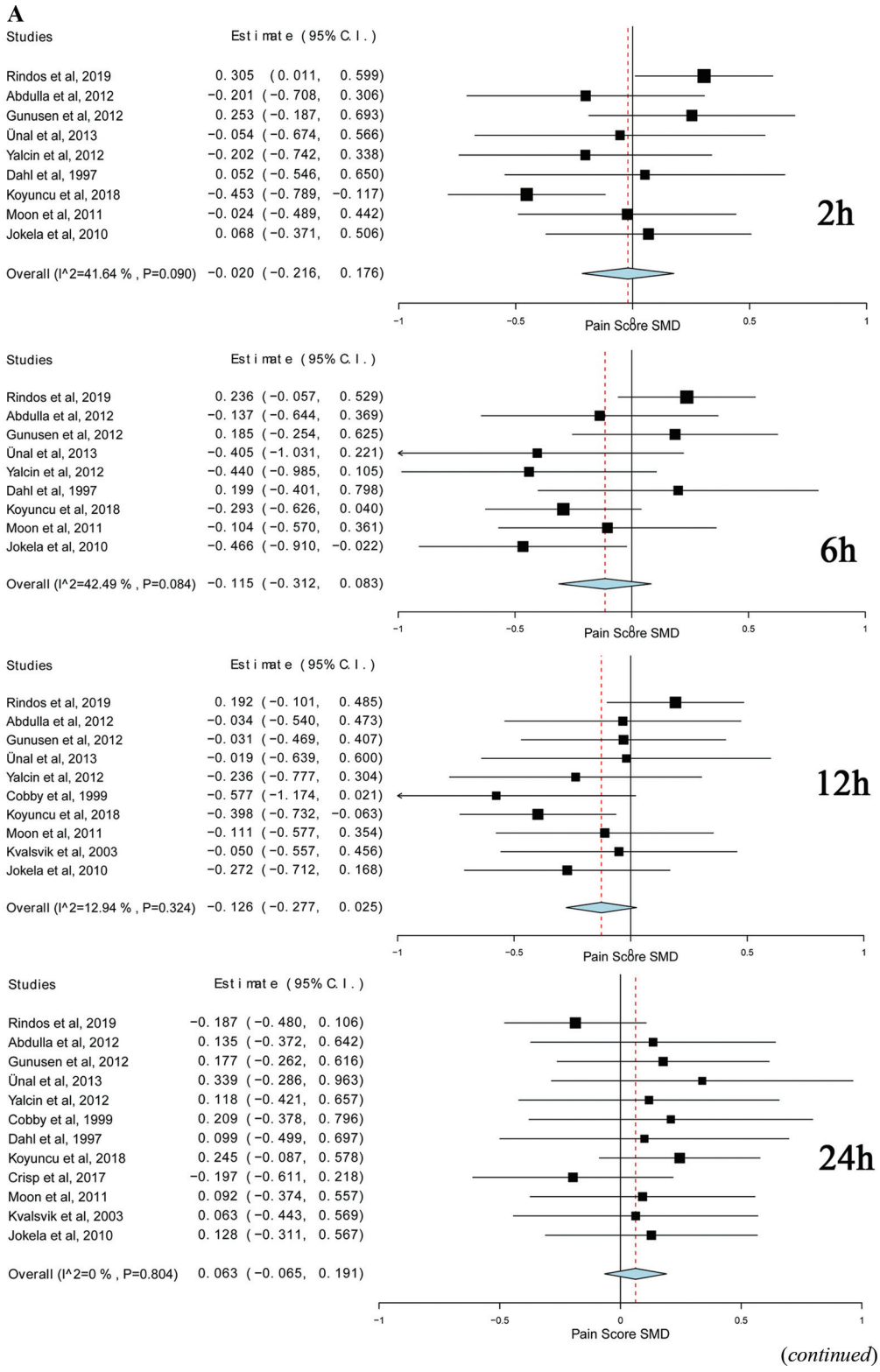

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Figure 4a. Pain Score SMD - pooled analysis.

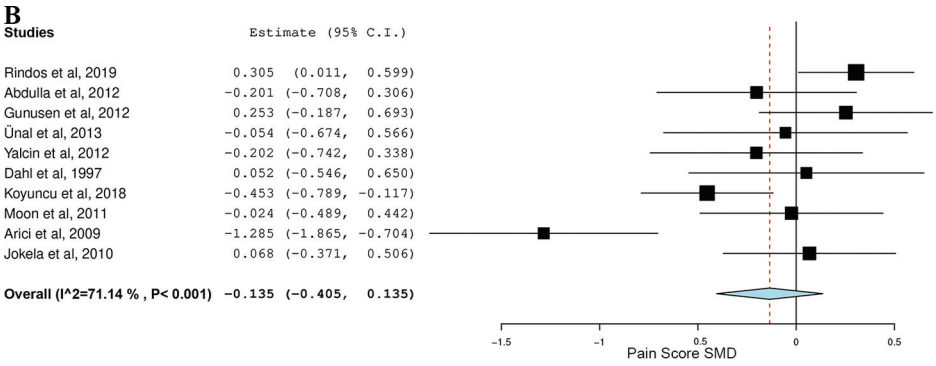

Figure 4b. Pain score SMD sensitivity analysis -2 hours.

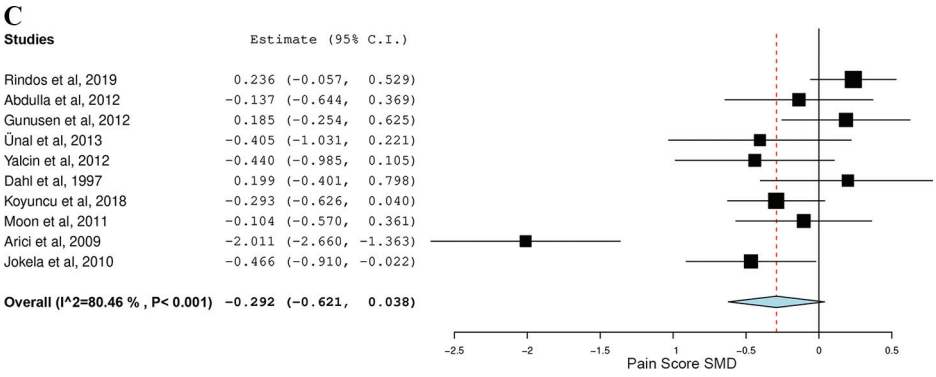

Figure 4c. Pain score SMD sensitivity analysis - 6 hours.

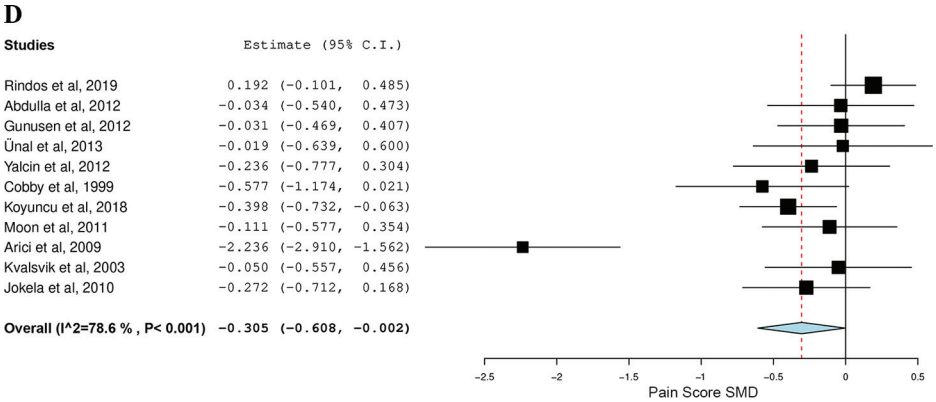

Figure 4d. Pain score SMD sensitivity analysis - 12 hours.

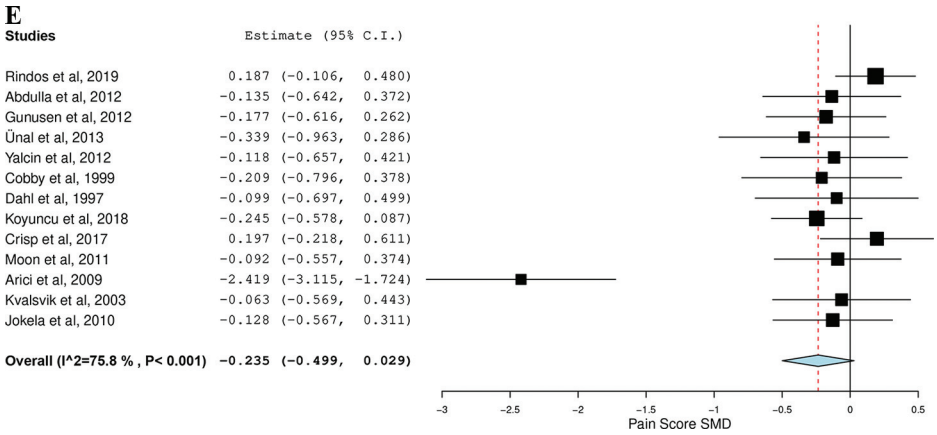

Figure 4e. Pain score SMD sensitivity analysis -24 hours.

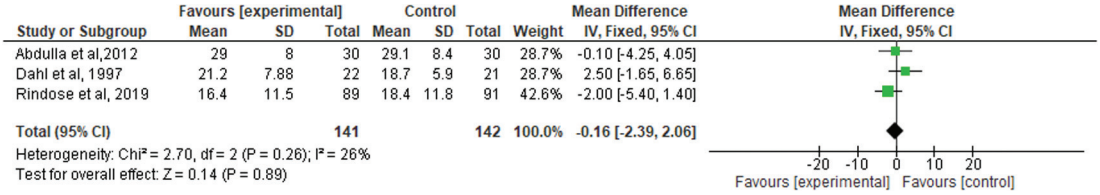

Figure 5. Morphine consumption after 24 hours.

analyses were heterogeneous; therefore, a sensitivity analysis was employed (**Figure 4c**), yielding homogenous results.

Pain score SMD after 12 h

The overall effect size showed no significant difference between the two groups' pain scores after 12 h (SMD = −0.126, 95% CI (−0.277; 0.025)) (**Figure 4a**). Pooled analyses were heterogeneous; therefore, a sensitivity analysis was applied (**Figure 4d**), yielding homogenous results.

Pain score SMD after 24 h

The overall effect size showed no significant difference between the two groups' pain scores after 24 h (SMD = 0.063, 95% CI (−0.065; 0.191]) (**Figure 4a**). Pooled analyses were heterogeneous; therefore, a sensitivity analysis was employed (**Figure 4e**), yielding homogenous results.

Morphine consumption after 24 H

The overall effect size showed no significant difference between the two groups' pain scores after 24 h (MD = –0.16, 95% CI (–2.39, 2.06), P = .89) (**Figure 5**). Pooled data were homogeneous (I^2 = 26%, P = .26).

DISCUSSION

This systematic review and meta-analysis compared the efficacy of acetaminophen in controlling postoperative pain after laparoscopic hysterectomy with placebo. We found that acetaminophen did not show a significant difference in reducing pain scores SMD at different time intervals (2, 6, 12, and 24 h) following administration, either IV or rectally.

We conducted our review upon acetaminophen, particularly as it is endorsed by the the World Health Organization as the first line of pain management in general.[32] It is the most commonly used analgesic worldwide.[33] This wide endorsement of acetaminophen is attributed to its minimal side effects compared with other treatment options.[34] It also has a comparable efficacy with nonsteroidal anti-inflammatory drugs, and is not generally considered abusable.[35]

By reviewing the previously published studies that were concerned with the efficacy of acetaminophen for pain management, we found a great deal of evidence for acetaminophen's usefulness in acute pain management.[36] For example, Derry et al.[37] confirmed its efficacy in the treatment of acute migraines. Specifically for postoperative

pain control, McNicole et al.[38] and Tzortzopoulou A et al.[39] validated the efficacy of single-dose intravenous acetaminophen, whereas Toms et al.[40] and Barden et al.[41] validated the efficacy of the single dose of its oral form. None of these studies specifically noted on efficacy of acetaminophen in hysterectomy. Acetaminophen is administered in many different surgeries in different specialties. For example, Ghaffarpasand et al.[42] showed efficacy in the treatment of post craniotomy pain with acetaminophen, whereas Lee et al.[43] proved its efficacy in bariatric surgery in reducing both pain scores after 24 h and reducing postoperative opioid doses. Moreover, Liang et al.[44] stated that intravenous acetaminophen was efficacious for reducing postoperative pain and reducing opioid consumption in arthroplasty surgeries. In obstetrics and gynecology, acetaminophen proved its efficacy in the management of perineal pain in the early postpartum period according to Chou et al.[45], but in pelvic organ prolapse repair it did not reduce pain scores or opioid use and had no effect on patient satisfaction or QOL according to Turner et al.[46] Regarding pain management after laparoscopic hysterectomy, which was the focus of this review, the data extracted from the studies included in our meta-analysis revealed that adding acetaminophen to a multimodal pain relief protocol at the time of hysterectomy does not reduce VAS scores and does not have opioid-sparing benefits.[27,47,48] As none of the compared regimens across all studies showed statistical significance, we feel that we can assume that no acetaminophen regiment in any dosage or duration would be likely to be efficacious. Of course, without the data to review there is no way for us to extrapolate this information, and no guarantee that a regiment of different duration, dosage or both might be more efficacious than those reviewed here. One possible explanation for the lack of efficacy is that the pain of the laparoscopic hysterectomy simply does not reach a severe enough level for there to be a significant change brought on by acetaminophen administration.[47] Several of our authors agree with the likelihood of this proposed possibility. Another hypothesis proposed by our authors is resistance from surgeons in decreasing narcotic doses secondary to their own fears of poor patient satisfaction. This phenomenon would not necessarily be a detectible or describable form of bias. Our results, however, do contradict the results of the previous meta-analysis by Unal et al.[48] That study suggested that the baseline analgesic regimen for laparoscopic hysterectomy should include acetaminophen and dexamethasone. That study, although recent, did not include a direct comparison of acetaminophen against placebo, but rather compared multiple regimens for analgesic efficacy.

As for the ideal regiment for pain control following laparoscopic hysterectomy, this falls well outside the scope of our investigation. Over the course of our literature search we found compelling, although not definitive literature describing the utility of oxycodone, dexamethasone, pregabalin, and ibuprofen in postoperative pain control regimens.[49–52] As there are essentially unlimited combinations of medications that could be administered, the authors are very interested in future research on this topic and plan to watch upcoming clinical trials closely. It is fair to say that the discovery of a regiment that routinely keeps patient's pain scores very low would be of interest to many in the specialty.

Strengths

The strength of our systematic review and meta-analysis comes from our inclusion of only randomized placebo-controlled trials, and all included studies are of low risk of bias. The interpretation of each piece of the study was made by several independent reviewers. The number of the included studies is relatively large[13] with a considerable sample size (495 patients).

Limitations

Although this research has reached its aims, there were some unavoidable limitations. Some included studies provided insufficient information, and others had a high risk of bias. Other studies were abandoned prior to reaching their stated goals, lowering the quality of the reported data. The marked inconsistency among our results represents a major limitation that some could see as interfering with the correct interpretation of our results. Although we managed to solve the heterogeneity by performing sensitivity analyses, care must always be taken during the interpretation of results.

Conclusion

Regarding pain management after laparoscopic hysterectomy, acetaminophen has no significant efficacy. It also failed to reduce the dependency on opioids. Caution should be given to the inclusion of acetaminophen in ERAS protocols designed for laparoscopic hysterectomy, especially as a single agent or to reduce opioid consumption.

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