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Research Article

JOURNAL OF SURGERY AND RESEARCH

ISSN: 2640-1002

Effect of IV Acetaminophen Administration in the Perioperative Period on the Quality of Postoperative Pain Relief and Adverse Side Effects

Ofelia Loani Elvir-Lazo[1]*, Alicia L. Romero-Navarro[2], Pravjit Bhatti[3], Sana Zubair[3], Roya Yumul,[1,4], Paul F. White[5]

Abstract

Background: The administration of intravenous (IV) acetaminophen during the perioperative period has been studied to evaluate its impact on postoperative pain management, opioid-sparing effects, rescue opioid analgesic use, and side effects [e.g., postoperative nausea and vomiting (PONV)]. However, the reports on the impact of the timing of IV acetaminophen administration during the perioperative period have yielded conflicting results. This review synthesizes findings from various studies to provide an understanding of the optimal timing and effectiveness of IV acetaminophen in different surgical settings.

Methods: A literature review was conducted to evaluate studies related to IV acetaminophen administration, timing, dosing, and its effects on pain scores, opioid consumption, and common side effects (e.g., PONV). Specifically, the effect of the timing of IV acetaminophen administration (pre-, intra-postoperative, or perioperative) on clinical outcomes was studied.

Results: Preemptive administration of IV acetaminophen before the surgical incision can significantly reduce opioid consumption and postoperative pain scores after abdominal and laparoscopic hysterectomy, cesarean surgeries, hip and knee arthroplasty, and endoscopic thyroidectomy. Intraoperative administration of IV acetaminophen during surgery has demonstrated reductions in opioid use and enhanced recovery metrics (e.g., earlier ability to discontinue PCA and advancement to solid food). Postoperative administration in the recovery room has been effective in reducing opioid consumption and improving pain scores, particularly in total knee arthroplasty. However, despite these benefits, some studies reported no significant differences in pain relief or opioid consumption. Comparisons with oral acetaminophen highlight its cost-benefit because even though it is more expensive, the IV formulation is faster-acting. IV administration shows advantages in specific settings like orthopedic surgeries (total knee and hip arthroplasty), major abdominal surgery, abdominal & laparoscopic hysterectomy, endoscopic thyroidectomy, cesarean deliveries, cardiac surgery, and spine fusion. IV acetaminophen achieves peak plasma concentrations rapidly, providing rapid analgesic effects with the recommended dose of 1g, and a maximum daily dose of 4g/day. Some studies suggest that an initial loading dose of 2 g may offer better analgesia.

Conclusions: IV acetaminophen administration significantly influences its effectiveness in managing postoperative pain and reducing opioid use. Its most significant impact likely lies in reducing opioid requirements. Opioids carry a substantial risk of adverse events, especially in the postoperative setting. Reducing opioid dependence is a crucial public health goal. Clinicians should consider incorporating IV acetaminophen into multimodal analgesia regimens, emphasizing its benefits in pain control and opioid reduction.

Affiliation:

[1]Department of Anesthesiology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

[2]No affiliation

[3]Georgetown University School of Medicine, Washington, DC, USA

[4]Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, Australia

[5]David Geffen School of Medicine-UCLA, Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA

[6]White Mountain Institute, The Sea Ranch, CA, USA (a not-for-profit private foundation)

***Corresponding author:**

Ofelia Loani Elvir Lazo, Department of Anesthesiology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Citation: Ofelia Loani Elvir-Lazo, Alicia L. Romero-Navarro, Pravjit Bhatti, Sana Zubair, Roya Yumul, Paul F. White. Effect of IV Acetaminophen Administration in the Perioperative period on the Quality of Postoperative Pain Relief and Adverse Side Effects. Journal of Surgery and Research. 8 (2025): 145-157.

Received: November 14, 2024
Accepted: November 27, 2024
Published: February 28, 2025

Elvir-Lazo OL, et al., J Surg Res 2025
DOI:10.26502/jsr.10020431

Keywords: Intravenous (IV) acetaminophen; Postoperative pain management; Postoperative nausea and vomiting (PONV); Side effects; Perioperative outcomes

Introduction

Postoperative pain management remains a significant challenge. Acetaminophen, a commonly used analgesic, is often administered in the perioperative period to manage acute pain. Its mechanism of action involves reversible inhibition of cyclooxygenase (COX), primarily in the central nervous system (CNS) as it is inactivated peripherally, resulting in analgesic and antipyretic effects without the anti-inflammatory properties seen with nonsteroidal anti-inflammatory drugs (NSAIDs) [1]. It may also enhance analgesia by stimulating descending serotonin pathways that inhibit nociceptive signal transmission in the spinal cord, and by interfering with the delivery of peripheral β-endorphins to their receptors [2].

The manufacturer of IV acetaminophen, Ofirmev®, recommends a maximum daily dose of 4 g per day for adults and children ≥ 13 years of age and weighing ≥ 50 kg. However, they advise not exceeding 1 g (1000 mg) every 6 hours or 650 mg every 4 hours, with dosing intervals of at least 4 hours between doses, and a single dose should not exceed 1 g [3]. The major concern with acetaminophen use is hepatic toxicity [3], particularly in cases of overdose (ingestion of more than 10 to 15 g in adults and 150 mg/kg in children), necessitating cautious administration in patients with existing liver disease [4]. With the rise of multimodal analgesic regimens designed to reduce opioid use in response to the opioid epidemic, non-opioid analgesics like acetaminophen have become more prominent in the perioperative period. It is widely acknowledged that incorporating acetaminophen into opioid-sparing multimodal analgesic strategies can also lessen opioid-related side effects, such as postoperative nausea and vomiting (PONV), urinary retention, and ileus [5]. Although there is debate, some trials have reported that the intravenous administration of acetaminophen reduces pain more effectively than oral [6]. Intravenous acetaminophen offers a faster onset of analgesia and may impact opioid requirements differently compared to oral acetaminophen, which is affected by opioid-induced gastrointestinal inhibition [7].

In recent years, preemptive pain control has emerged as an area of focus. Preemptive analgesia focuses on administering analgesics before the surgical procedure begins to prevent the establishment of central sensitization. This approach aims to block pain signals and reduce the overall pain experience by addressing pain before the nociceptive stimuli are introduced [8]. Otherwise, preventive analgesia is a broader approach that involves administering medications not only before but also during, and after surgery by reducing peripheral and central sensitization throughout the perioperative period [6,9]. By attenuating the impact of noxious stimuli at multiple stages, preventive analgesia aims to reduce postoperative pain intensity and analgesic requirements. In the perioperative setting, intravenous acetaminophen is suggested to have a more predictable pharmacokinetic and pharmacodynamic behavior compared to an equivalent oral dosage. Typically, clinicians administer the oral dose in the preoperative holding area, while the IV dose is administered just before anesthesia induction or during surgery [5]. This review explores the timing of IV acetaminophen administration and its impact on postoperative analgesic efficacy, opioid-sparing effects, side effects, and PONV, comparing various dosing regimens to placebo, NSAIDs, local anesthetics and oral acetaminophen in patients undergoing major surgeries (orthopedic, abdominal, or gynecological).

Methods

A comprehensive literature review was conducted on PubMed, Ovid Medline, Web of Science, and Google Scholar to identify articles relevant to the timing of intravenous acetaminophen administration and postoperative outcomes in patients undergoing major orthopedic, abdominal, or gynecological surgical procedures. The search strategy included keywords such as “Acetaminophen”, “Intravenous”, “Injections”, and terms related to surgical procedures like “Knee Arthroplasty”, “Hip Arthroplasty”, “Obstetrics”, “Gynecology”, “Abdomen”, “Laparoscopy”, and “Spine” surgery. Inclusion criteria were studies that considered postoperative outcomes with IV acetaminophen administration in the perioperative setting. Exclusion criteria were any studies that were not written in the English language and studies that failed to include IV administration of acetaminophen in their protocol. There were no limitations on the year of publication. The review process involved an independent assessment by one author, who screened titles and abstracts for relevance, removed duplicates, and filtered by studies meeting the inclusion criteria. Data extracted from each study included the year of publication, number of samples, dosage of acetaminophen, route of administration, timing of administration, other modifiers, postoperative pain scores, PONV, and opioid consumption.

Results

Preoperative Administration

The preemptive approach, involving the use of IV acetaminophen before a surgical incision or prior to noxious stimulus, has been explored in various surgical contexts. Moon YE et al. [10] observed that preemptive administration (30 min before surgery) of a single 2g dose of IV acetaminophen resulted in a 30% reduction in hydromorphone consumption over 24 h in patients undergoing abdominal hysterectomy. Jokela et al. [11] found periodic doses (1g every 6 h) of IV acetaminophen starting at anesthesia induction reduced the total dosage of oxycodone required in laparoscopic hysterectomy patients. Similarly, Hong et al. [12] found

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DOI:10.26502/jsr.10020431

that preemptive IV acetaminophen (1 h before induction of anesthesia and then at 6-h intervals following 24 h) demonstrated a significant reduction in postoperative pain scores, rescue analgesia, and adverse effects such as nausea and vomiting compared to placebo in patients undergoing endoscopic thyroidectomy. Hassan et al. [13] further reported improved hemodynamic stability, reduced opioid consumption, and fewer postoperative side effects when preemptive IV acetaminophen was used in cesarean deliveries compared to a preventive approach. Wang et al. [14] also found that preemptive administration of IV acetaminophen (1g within 15 min after anesthesia induction and before incision) reduced hospital LOS by 32% without significantly affecting pain scores or opioid use. Meta-analyses, such as those by Xuan et al. [15], reinforce these findings by showing modest pain relief and delayed rescue analgesia compared to placebo. Khalili et al. [9] demonstrated that both preemptive and preventive administration of IV acetaminophen effectively reduced pain and opioid consumption in lower extremity orthopedic surgeries, with the preemptive approach requiring less rescue analgesia.

Additional studies highlight the varying effects of preemptive IV acetaminophen. Evidence suggests that its administration can reduce postoperative opioid consumption, improve analgesia, and lower associated side effects (e.g., constipation), and reduce hospitalization costs, particularly in procedures such as abdominal hysterectomy and orthopedic surgeries [16-18]. Beyond its analgesic benefits, preemptive IV acetaminophen has been associated with improved hemodynamic stability during cesarean sections and a reduction in severe postoperative shivering, likely due to its influence on thermoregulation [13,19-20]. However, other studies present contrasting results. Towers et al. [21] and Rindos et al. [22] found no significant reductions in pain scores or opioid consumption with preincisional administration of IV acetaminophen in cesarean delivery and laparoscopic hysterectomy, respectively. Similarly, Politi et al. [23] and Cain et al. [24] observed no notable advantages of IV acetaminophen over oral formulations in reducing opioid consumption or improving pain scores in hip and knee arthroplasty and open gynecologic surgeries, respectively. While Turner et al. [25] also found no significant differences in pain scores, opioid use, or satisfaction when administering IV acetaminophen preemptively (10-30 min prior to incision) in patients undergoing pelvic organ prolapse repair, Sacha et al. [18] found no benefit on pain scores or time to discharge, but it did reduce opioid use and constipation in patients undergoing oocyte retrieval, highlighting the variability in outcomes on specific surgical and clinical context. Apfel et al. [26] in a systematic review of randomized controlled trials that included 30 studies with 2364 patients undergoing general surgery found that IV acetaminophen compared to placebo reduced nausea (mainly mediated through superior pain control) when given prophylactically either before surgery or before arrival in the postanesthesia care unit, but not when given after the onset of pain.

Perioperative Administration (Preventative Combination)

Preventive administration of IV acetaminophen, delivered after the noxious stimulus, has been shown to reduce opioid use and enhance recovery. Altenau et al. [27] demonstrated that preventive administration of IV acetaminophen (within 60 min of skin incision) significantly reduced postoperative oral narcotic consumption, without impacting pain scores in cesarean patients. In a similar context, Kiliçaslan et al. [28] reported a reduction in tramadol use and pain scores following intraoperative administration of IV acetaminophen (15 min before the end of surgery) in cesarean deliveries, compared to placebo. Cattabriga et al. [29] also observed reduced morphine consumption and improved pain control in cardiac surgery when IV acetaminophen was administered intraoperatively (at skin closure) as part of a multimodal approach. Other benefits of preventive administration include faster recovery timelines. Rizkalla et al. [30] found that preventive administration (at skin closure) was associated with faster PCA discontinuation and advancement to solid food in posterior spinal fusion (PSF) patients, while also reducing postoperative opioid consumption. In pediatric and adolescent PSF patients, Kim et al. [31] similarly found that IV acetaminophen reduced opioid use without significant drug-induced adverse effects. Mamoun et al. [32] found intraoperative administration of IV acetaminophen (15 min before the end of surgery) reduced pain intensity after cardiac surgery, although opioid consumption remained unchanged. Subramaniam et al. [33] reported that preventive administration of IV acetaminophen reduced antiemetic requirements in major abdominal surgery, though pain relief and opioid use were similar to placebo. On the other hand, Deng et al. [34] reported that a single intraoperative dose (1g) of IV acetaminophen administered at skin closure during spine surgery did not produce an opioid-sparing effect or reduce opioid-related adverse effects. Hickman et al. [35] found no equivalent outcomes between preoperative oral and intraoperative IV acetaminophen in hip and knee arthroplasty, emphasizing the limited advantage of IV administration in these contexts. Sacha et al.18 investigated the efficacy of preoperative IV acetaminophen (1g) compared to oral (1g) and placebo in women undergoing oocyte retrieval and no significant differences were found in postoperative pain scores, time to discharge, or embryology outcomes between the groups. While not statistically significant, women who received IV acetaminophen had lower opioid requirements and reported less constipation. These findings suggest that routine preoperative IV acetaminophen may not be warranted for pain management after oocyte retrieval. Using a retrospective cohort study Miler et at. [36] investigated the impact of a multidisciplinary initiative to prioritize

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DOI:10.26502/jsr.10020431

oral IV acetaminophen in adult patients undergoing non-cardiac surgery. Data was analyzed from before and after the initiative and showed increased oral acetaminophen use and decreased IV use, no significant differences in perioperative narcotic consumption, pain scores, time to PACU discharge, or the incidence of PONV.

Postoperative administration of IV acetaminophen, initiated in the recovery room or shortly after surgery, plays a critical role in multimodal pain management. Huang et al. [37] demonstrated significant reductions in opioid consumption and improved pain scores within 24 h following total knee arthroplasty. Similarly, Aksoy et al. [38] found that IV acetaminophen was as effective as subcutaneous bupivacaine in reducing pain and opioid consumption compared to placebo, although bupivacaine provided superior immediate pain relief. Comparisons between IV and oral acetaminophen highlight the cost-effectiveness of oral formulations. Wilson et al. [39] reported no significant differences in pain scores or opioid use between IV and oral acetaminophen in cesarean patients. Takeda et al. [40] observed significant reductions in fentanyl use and pain scores after total hip arthroplasty.

Dosing Considerations for IV Acetaminophen

The dosing strategy for acetaminophen in the perioperative setting can be influenced by its route of administration. IV acetaminophen achieves peak plasma concentrations within 15 min, providing rapid analgesic effect within 5 min and lasting up to 4 h. This is notably faster compared to oral and rectal forms, which reach peak levels in 45-60 min and 4 h, respectively [41]. The recommended dose for IV acetaminophen in adults is 1g, with a maximum daily dose of 4g/day. However, it has been suggested that better analgesia could be obtained with a 2-g starting dose. Piguet et al. [42] demonstrated a significant, dose-dependent correlation between acetaminophen's plasma levels and its analgesic effects in healthy volunteers, suggesting a dose-dependent central antinociceptive effect.

Some authors have reported a significant reduction in opioid consumption with IV acetaminophen, others have found no such effect. This inconsistency has been accredited to variations in dosing and administration duration, which ranged from 24 to 48 h in their study, potentially due to financial considerations [43]. Remy et al. [2] reported the standard dose of 1g of IV acetaminophen every six h generally results in less than 10 mg reduction in opioid use over 24 h. In contrast, Juhl et al. [44] found that a 2 g starting dose of IV acetaminophen was more effective than 1 g every six h for postoperative pain following third molar surgery, with no significant difference in safety. However, these findings should be interpreted cautiously, as additional research is needed to determine the applicability of this dosing regimen to major surgical procedures [44]. Gregoire et al. [45] evaluated the efficacy of IV paracetamol with a 2 g starting dose up to a total of 5 g dose administered in the first 24 h. It was found that plasma concentrations following repeated 1-g doses were approximately 35% lower than those measured after 2-g dose, with no evidence of drug accumulation [45]. Acetaminophen's pharmacokinetics remained stable, with concentrations far below the toxic threshold, demonstrating both clinical and biological safety in healthy subjects. To assess the risk of liver damage, researchers measured peak and 4-h post-dose paracetamol levels. The highest level recorded after a 2-g infusion in healthy subjects was 115 mg/ml, with no adverse effects reported. The average levels at 4 h were: 11.4 mg/ml (after the first 2-g infusion), 7.3 mg/ml (after the second 1-g infusion), and 6.4 mg/ml (after the fifth 1-g infusion). All these levels were well below the 150 mg/ml threshold for potential liver toxicity [45]. This suggests that a more consistent or higher dose of IV acetaminophen may be needed to achieve significant opioid-sparing effects. Further research is required to explore the potential of new IV acetaminophen dosing regimens for enhancing analgesia and reducing opioid use [2]. Table 1 include the effect of timing of perioperative administration of IV acetaminophen.

Table 1: Studies on effect of timing (pre-post incisional) of intravenous acetaminophen administration on analgesic efficacy (opioid-sparing), side effects and recovery

Author(s) and Year	Study Design	Type of Surgery	Timing of Administration	Dose and Duration	Comparison Group(s)	Main Outcomes (Postoperative Pain Relief)	Adverse Effects/ Side Effects	Study Conclusions
Khalili et al. (2013) [9]	Randomized, double-blind clinical trial	Lower extremity orthopedic surgery	Preemptive: 30 min before surgery. Preventive: During skin closure	IV acetaminophen 15 mg/kg (both preemptive and preventive); Placebo: IV saline 100 mL	Placebo	Significantly reduced pain scores at 6 h post-surgery ($P < 0.001$) compared to placebo. Preemptive group required less rescue analgesia within 24 h ($P < 0.01$). No significant difference in pain scores after 6 h between preemptive and preventive groups.	Not reported.	IV acetaminophen reduce pain and analgesic consumption in lower extremity surgery, with the preemptive group requiring less rescue analgesia within 24 h.

Citation: Ofelia Loani Elvir-Lazo, Alicia L. Romero-Navarro, Pravjit Bhatti, Sana Zubair, Roya Yumul, Paul F. White. Effect of IV Acetaminophen Administration in the Perioperative period on the Quality of Postoperative Pain Relief and Adverse Side Effects. Journal of Surgery and Research. 8 (2025): 145-157.

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DOI:10.26502/jsr.10020431

Moon et al. (2011) [10]	Randomized, double-blind, placebo-controlled trial	Abdominal hysterectomy	Preemptive: 30 min before incision.	2 g IV acetaminophen (single dose)	Placebo	Significant reduction in hydromorphone consumption (30% reduction over 24 h; P= 0.013). No significant difference in pain scores.	Lower incidence of PONV in acetaminophen group. (P < 0.05).	Preoperative acetaminophen reduced hydromorphone consumption and opioid-related side effects in patients undergoing abdominal hysterectomy but did not significantly reduce pain intensity.
Jokela et al. (2010) [11]	Randomized controlled trial	Laparoscopic hysterectomy	Preemptive: before induction and incision. Preventive: then every 6 h.	1 g IV acetaminophen, every 6 h for 24 h; Ondansetron 4mg at the end of surgery	Acetaminophen + placebo (AP), Acetaminophen + ondansetron (AO), Placebo + placebo (PP)	Preemptive IV acetaminophen significantly reduced the total oxycodone dosage required over 24 h (P = 0.031). Ondansetron at the end of surgery had no effect on acetaminophen's analgesic effect (P = 0.723).	Not reported.	IV acetaminophen, compared to placebo, reduces total oxycodone requirements postoperatively in women undergoing laparoscopic hysterectomy. Ondansetron does not affect acetaminophen's analgesic effect.
Hong et al. (2010) [12]	RCT, double-blinded, placebo-controlled	Endoscopic thyroidectomy (robot-assisted)	Preemptive: 1 h before induction. Preventative: then every 6-h for 24 h.	1 g IV 1 h before induction then acetaminophen every 6 h for 24 h	Placebo	Significant reduction in postoperative pain scores at 1, 3, 6 and 24 h post-surgery; Significant reduction in rescue analgesia use (9.5% vs. 65.6% for placebo).	Fewer cases of postoperative nausea (44.3% vs. 22.2%) and vomiting (21.3% vs. 6.3%) in the acetaminophen group compared to placebo.	IV acetaminophen effectively reduced postoperative pain and analgesic rescue use. It was well-tolerated and had fewer adverse effects compared to placebo after gasless robot-assisted endoscopic thyroidectomy.
Hassan et al. (2014) [13]	RCT, randomized, double-blinded, placebo-controlled	Elective cesarean section (CS)	Preemptive: 30 min before induction. Preventative: 30 min before end of surgery.	1 g IV acetaminophen (100 ml)	Preemptive (before induction) vs preventive (at the end of surgery)	Preemptive group showed improved hemodynamic stability; required longer time for next analgesia; fewer postoperative side effects; lower opioid consumption. Preventive group had higher postoperative pain scores at 4 and 8 h.	Fewer postoperative side effects were observed in the preemptive group compared to the preventive group.	IV acetaminophen was more effective in managing pain and reducing opioid use compared to preventive administration during cesarean sections.
Wang et al. (2018) [14]	Randomized, double-blind, placebo-controlled trial	Robotic-assisted laparoscopic prostatectomy (RALP)	Preemptive: 15 min before surgical incision. Preventative: then every 6-h for 24 h.	1 g IV acetaminophen before induction, then every 6 h for 4 doses; Placebo: IV saline 100 mL	Placebo	Median pain scores were not statistically significant slightly lower in the acetaminophen group compared to placebo (P= .055 for the first 24h; P= .13 for the second 24h). Opioid use was similar between groups (P= .64 ntraoperatively; P= .16 postoperatively.	Not reported.	IV acetaminophen significantly reduced hospital length of stay by 32% without significantly affecting pain scores or opioid consumption.

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DOI:10.26502/jsr.10020431

Xuan C et al. (2022) [15]	Network meta-analysis of 188 RCTs including 13,769 participants. Data were synthesized from multiple studies evaluating 19 preemptive analgesia regimens.	General surgery (non-specific)	Preemptive	Acetaminophen IV: not specified, duration up to 12 h.	Placebo, NSAIDs (e.g., ibuprofen, lornoxicam), gabapentinoids (e.g., gabapentin, pregabalin), epidural analgesia, etc.	Preemptive IV acetaminophen reduced pain scores, but not significantly more than placebo in some cases. VAS 6h: -11.57, VAS 12h: -10.52. Opioid consumption: Reduced opioid consumption by -0.48 mg IMME (95% CI: -0.89 to -0.08) at 12 h and delayed rescue analgesia slightly compared to placebo.	No significant reduction in PONV incidence compared with placebo.	Preemptive IV acetaminophen significantly reduced opioid consumption and delayed rescue analgesia compared to placebo. Pain reduction was significant but modest, showing less efficacy than NSAIDs like lornoxicam.
Hansen et al. (2016) [16]	Retrospective analysis, Premier Database (2009–2015)	Orthopedic surgery	Preemptive: before induction. Preventative: continued for 2 days post-op.	IV acetaminophen in combination with IV opioids	IV opioids alone	IV acetaminophen combined with opioids led to a significantly shorter length of stay (LOS) and lower hospitalization costs compared to opioid monotherapy.	Not reported.	Compared to opioids alone, managing post-orthopedic surgery pain with the addition of IV acetaminophen administered preemptively is associated with shorter LOS and decreased hospitalization costs.
Arici et al. (2009) [17]	Randomized, placebo-controlled trial	Total Abdominal Hysterectomy	Group I: Preemptive: 30 min before induction. Group II: Preventative: before skin closure.	Single dose of 1,000 mg IV paracetamol administered to Groups I and II Group III: saline.	Placebo (saline)	Preemptive and preventive groups showed lower pain scores at rest and with movement compared to placebo. Group I (preemptive) had significantly lower morphine consumption compared to Group II (preventive).	Intravenous paracetamol intraoperatively and postoperatively did not result in any hemodynamic effects.	Preemptive IV paracetamol 1 g, provides better postoperative analgesia, reduces morphine consumption compared to intraoperative administration or placebo in total abdominal hysterectomy.
Sacha et al. (2022) [18]	Randomized, double-blind, placebo-controlled trial	Oocyte retrieval	Preemptive: 1 h -30 min before surgery.	IV acetaminophen 1 g preoperatively	PO acetaminophen and placebo	No significant difference in postoperative pain scores or time to discharge between groups.	Lower opioid dose requirement in the IV acetaminophen group (0.24 mg IV morphine equivalents vs. 0.59 mg in the other groups). Less constipation in the acetaminophen group (19% vs. 33% and 40%).	Preoperative IV acetaminophen did not reduce postoperative pain scores or time to discharge, but it did reduce opioid use and constipation.
Kinjo et al. (2020) [19]	Randomized, triple-blind, placebo-controlled trial	Gynecological laparotomy	Preemptive: after induction of anesthesia and before surgery. Preventive: another dose if surgery extended after 4h	IV acetaminophen 15 mg/kg administered over 15 min	Placebo: IV saline	Incidence of severe postoperative shivering significantly lower in the acetaminophen group (22.2%) compared to placebo (73.7%; P = .005).	Core body temperature at 1-h post-observation was slightly lower in the acetaminophen group (P < .001).	Perioperative administration of IV acetaminophen reduced severe postoperative shivering, likely by suppressing the postoperative increase in the body temperature set point.

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Ayatollahi et al. (2014) [20]	Randomized, double-blind, placebo-controlled trial	Cesarean Delivery	Preemptive: 20 min prior to incision	1 g IV acetaminophen (single dose); control: saline	Placebo (saline)	IV paracetamol significantly reduced postoperative VAS pain scores, delayed the first analgesic request, and decreased analgesic consumption compared to placebo.	The SBP, DBP, MAP and HR were controlled significantly better in paracetamol group than in placebo group.	Preemptive administration of IV paracetamol effectively decreases hemodynamic responses to tracheal intubation and improved postoperative pain management without neonatal complications in cesarean section.
Towers et al. (2018) [21]	Prospective double-blinded randomized placebo-controlled trial	Cesarean Delivery	Preemptive: 15 min prior to incision	1 g IV acetaminophen (single dose); control: saline	Placebo	No significant difference in pain scores, postoperative opioid consumption (94.2 mg vs. 90.7 mg morphine equivalents) nor length of stay.	Not mentioned	Preincisional administration of IV acetaminophen did not reduce opioid use, pain scores, or length of stay post cesarean. Acetaminophen cord blood levels were subtherapeutic.
Rindos et al. (2019) [22]	Prospective double-blind randomized study	Laparoscopic Hysterectomy	Preemptive: at the time of induction of anesthesia and before incision. Preventive: another dose 6 h later	1 g IV acetaminophen and 6 h later	Placebo	No significant differences in generalized abdominal pain at any time point postoperatively that included 2 h (placebo 3.6±2.5 vs acetaminophen 4.4±2.5; P=.07) and up to 24 h (placebo 3.3±2.4 vs acetaminophen 3.6±2.5; P=.28).	No significant difference in postoperative nausea, satisfaction, or opioid consumption (placebo 1.4±2.0 vs acetaminophen 1.6±2.1; P=.61).	IV acetaminophen showed no benefit in pain relief, high cost; oral alternatives available.
Politi et al. (2017) [23]	Randomized controlled trial	Hip and knee arthroplasty	Preemptive: before surgery Preventive: after surgery every 6 h for 24 h	1 g IV or PO acetaminophen	Oral acetaminophen	No significant difference in narcotic use or pain scores between IV and oral groups, except for the first 4 h postoperatively (IV: 3.00 vs PO: 3.40, P = .03).	Not mentioned	IV acetaminophen administered preoperatively may reduce immediate postoperative pain but does not provide significant benefit in reducing pain or narcotic use compared to the much less expensive oral form.
Cain et al. (2020) [24]	Retrospective observational study	Open Gynecologic Oncology Surgery	Preemptive: at the time of induction of anesthesia or 1 h before surgery. Preventive: after surgery (oral) 1 g every 6 h	1 g IV acetaminophen	1 g Oral Acetaminophen	No significant difference in opioid consumption on POD 0 and POD 1; Pain scores in PACU not reported as significantly different.	Not mentioned	IV acetaminophen showed no advantage over oral acetaminophen in reducing postoperative opioid consumption within an ERAS program for patients undergoing open gynecologic oncology surgery.

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Turner et al. (2019) [25]	Double-blind, placebo-controlled, multicenter trial	Pelvic organ prolapse repair	Preemptive: 10 -30 min before incision	1 g IV acetaminophen	Placebo (saline)	No significant difference in pain scores at 24 h post-surgery, opioid use, or patient satisfaction.	Increased urinary retention in the acetaminophen group, potentially due to mannitol suspension. No significant difference in other side effects like nausea.	Preemptive IV acetaminophen did not reduce pain or opioid use and had no effect on satisfaction or quality of life in women undergoing prolapse repair.
Apfel et al. (2013) [26]	Systematic review of RCTs	General Surgery	Preemptive: before surgery Preventative: after surgery, administered before moving to PACU	1 g IV acetaminophen (prophylactic use)	Placebo	Reduced postoperative nausea and vomiting when administered prophylactically, either before surgery or before arrival in the PACU, but not after the onset of pain.	The reduction of nausea correlated with the reduction of pain (OR = 0.66, 95% CI: 0.47-0.93), but not with reduction in postoperative opioids (OR = 0.89, 95% CI: 0.64-1.22).	Perioperative IV acetaminophen reduces postoperative nausea and vomiting, primarily through enhanced pain control, without a significant effect on opioid consumption.
Altenau et al., 2020 [27]	Double-blind, placebo-controlled, randomized trial	Cesarean Delivery	Preemptive: 30 min before incision Preventative: Then another dose every 8 h for 48 h	1 g IV acetaminophen every 8 h for 48 h (6 doses total)	Placebo	Reduced oral narcotic consumption (47 mg vs 65 mg of oxycodone; P = .034) No difference in pain scores between groups before and after study drug administration.	No significant impact on opioid side effects (nausea/emesis, respiratory depression, constipation)	Perioperative IV acetaminophen significantly reduced oral narcotic consumption postoperatively without impacting pain scores.
Kiliçaslan et al. (2010) [28]	Randomized, double-blind, placebo-controlled trial	Cesarean Delivery	Preventative: 15 min before the end surgery and every 6 h for 24 h	1 g IV acetaminophen administered 15 min before surgery ends and every 6 h for 24 h	IV acetaminophen vs. placebo (saline)	IV acetaminophen reduced pain scores, and cumulative tramadol consumption compared to placebo.	No significant difference in sedation or nausea/vomiting scores between groups	Preventive administration of IV acetaminophen effectively reduced post-cesarean pain and tramadol consumption.
Cattabriga et al. (2007) [29]	Single-center, double-blind, randomized, placebo-controlled trial	Cardiac surgery	Preventative: at skin closure and then 6, 12, 18, and 24 h postoperative	1 g IV acetaminophen	IV acetaminophen vs. placebo	Pain at rest and movement lower in IV acetaminophen group at 12,18, and 24 h compared to placebo; IV acetaminophen required less cumulative morphine compared to the placebo group (48 mg vs. 97 mg).	Not reported.	Preventive administration of IV acetaminophen as part of a multimodal approach in combination with tramadol provides effective pain control in patients undergoing cardiac surgery.
Rizkalla et al. (2018) [30]	Randomized, double-blind study	Posterior spine fusion surgery	Preventative: at skin closure, then every 6 h for 42 h.	15 mg/kg IV acetaminophen every 6 h for 42 h	IV acetaminophen vs placebo	Lower opioid use in the first 24 h compared to placebo; shorter time to PCA discontinuation (73 h vs. 90 h in the placebo group).	Faster advancement to solid food intake (49 h vs. 69 h in the placebo group).	Preventive administration of IV acetaminophen was associated with reduced postoperative opioid consumption, faster PCA discontinuation, and earlier time to diet advancement.

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Kim et al. (2024) [31]	RCT, triple-blinded, placebo-controlled	Posterior spinal fusion (PSF)	Preemptive: after induction of anesthesia and before surgery. Preventative: at the end of surgery just before skin closure.	15 mg/kg IV acetaminophen for preemptive or preventive groups	Placebo	No significant differences in pain scores between preemptive and preventive groups; preventive group had significantly lower opioid consumption than placebo (P = 0.013)	No increase in drug-related adverse effects was observed with preventive administration.	Perioperative IV acetaminophen reduces opioid consumption in pediatric and adolescent patients undergoing PSF without adding significant drug-induced adverse effects.
Mamoun et al. (2016) [32]	Randomized, double-blind, placebo-controlled trial	Cardiac Surgery via Median Sternotomy	Preventive: Intraoperative (after sternal closure) then every 6 h	Four doses of IV acetaminophen (1 g) every 6 h	Placebo	Reduced pain scores by about 1 point compared to placebo, with an estimated difference of -0.90 on a 0-10 Numeric Rating Scale; it did not significantly reduce opioid consumption.	No significant effect on duration of mechanical ventilation, ICU, or hospital LOS.	Intraoperative administration of IV acetaminophen reduced pain intensity but did not reduce opioid consumption, providing insufficient analgesia alone for patients recovering from median sternotomy.
Subramaniam et al. (2022) [33]	Randomized, double-blind clinical trial	Major abdominal surgery	Preventive: after incision (before wound closure), then every 6 h for 48 h	1 g IV acetaminophen every 6 h for 48 h; Placebo: IV saline 100 mL	Placebo	No significant difference in pain relief between acetaminophen and placebo groups (P = 0.20). Opioid consumption was comparable between groups.	Fewer rescue antiemetics in acetaminophen group (41% vs. 58%, P = 0.02). No major adverse effects reported.	Perioperative administration of IV acetaminophen did not improve postoperative pain relief or characteristics of postoperative recovery in patients undergoing major abdominal surgery within an ERP (enhanced recovery protocol) but reduced the need for rescue antiemetics.
Deng et al. (2017) [34]	Retrospective comparative cohort study	Spine surgery	Preventative: after incision (at skin closure)	1 g IV acetaminophen (single dose)	IV acetaminophen group vs no IV acetaminophen group	IV acetaminophen group had lower VAS scores shortly after surgery at 60 min. However, no consistent VAS differences across all procedures or timepoints.	No difference was found for other secondary outcomes between groups.	Intraoperative administration of IV acetaminophen did not consistently improve pain scores or exhibit opioid-sparing effects.
Hickman et al. (2018) [35]	Randomized, placebo-controlled, equivalence trial	Total Hip/Knee Arthroplasty (THA/TK)	Group 1 (oral) Preemptive Acetaminophen. Group 2 (IV) Preventative: After incision:	1 g PO acetaminophen, preoperatively; 1 g IV acetaminophen, intraoperatively	PO vs IV acetaminophen	No significant differences in postoperative opioid use (MMEs) or pain scores over 24 h between oral and IV acetaminophen groups.	No significant differences in postoperative nausea/vomiting, ambulation time, PACU length of stay, or hospital length of stay.	Timing (preoperative vs. intraoperative) did not impact outcomes in THA/TKA. Preoperative PO acetaminophen and intraoperative IV acetaminophen. provided equivalent pain control; IV acetaminophen was not superior to oral acetaminophen.

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Huang et al. (2018) [36]	Retrospective review	Primary Total Knee Arthroplasty (TKA)	Preventative: After surgery then every 6 h for 24 h	1 g IV acetaminophen every 6 h for 24 h	IV acetaminophen group vs. no additional intervention group	Significantly reduced overall opioid consumption (37.6 vs 18.6 morphine milligram equivalents). Reduced VAS pain scores between 16 and 24 h postoperatively; no significant difference in LOS (at 3.3 days in the control group and 2.9 days in the intervention group).	Not reported.	Postoperative administration of IV acetaminophen significantly reduced opioid consumption and improved pain scores in the first 24 h following primary TKA.
Aksoy et al. (2023) [37]	Prospective, double-blind, placebo-controlled, randomized trial	Cesarean Delivery	Preventative: After surgery then every 6 h for 24 h	1 g IV acetaminophen every 6 h for 24 h; SC bupivacaine	IV acetaminophen vs. SC bupivacaine vs. placebo	IV acetaminophen and SC bupivacaine both significantly reduced VAS pain scores (at rest and during coughing) and decreased opioid consumption compared to placebo.	Not reported.	Postoperative administration of IV acetaminophen is as effective as SC bupivacaine in reducing pain and opioid consumption compared to placebo; bupivacaine is superior to IV acetaminophen at 15 min.
Wilson et al. (2019) [38]	Prospective, three-arm, randomized clinical trial	Cesarean Delivery	Preventative: First dose at PACU then every 8 hs for 3 doses	IV acetaminophen: 1 g every 8 h for 3 doses; oral acetaminophen: 1 g every 8 h for 3 doses	IV acetaminophen vs. PO acetaminophen vs. no acetaminophen	Reduced opioid consumption and pain scores compared to no acetaminophen. However, there was no significant difference between IV and oral acetaminophen in opioid consumption or pain scores.	Not reported	IV acetaminophen administered postoperatively Postoperative IV or oral acetaminophen decreased opioid consumption and pain scores compared to no acetaminophen but did not outperform oral acetaminophen.
Takeda et al. (2019) [39]	Prospective, open-label randomized control study	Total Hip Arthroplasty (THA)	Preventative: After surgery, then every 6 h for 24 h	1 g IV acetaminophen every 6 h for 24 h; Control: standard pain control	IV acetaminophen vs. control group	IV acetaminophen significantly reduced pain scores at rest 24 h after surgery and decreased total fentanyl citrate consumption.	Not reported.	Postoperative administration of IV acetaminophen as part of multimodal significantly reduced pain scores and opioid use after THA.

Discussion

The timing of intravenous (IV) acetaminophen administration during the perioperative period has been studied extensively to evaluate its effects on postoperative pain scores, postoperative nausea and vomiting (PONV), and rescue opioid analgesic use.

The timing of IV acetaminophen administration during the perioperative period has shown the following: (1) Preemptive administration, given before surgical incision or anesthesia induction, demonstrated to reduce opioid consumption, better postoperative pain control, reduce side adverse effects like postoperative nausea and vomiting (PONV) and improve hemodynamic stability and reduce severe postoperative shivering in cesarean section [10-13] Despite the positive findings, some studies have shown that the benefits of preemptive administration may not be as pronounced for all surgical procedures [23,24]. Intraoperative and preventive administration has been shown to reduce opioid consumption, improve recovery outcomes, and faster mobilization [30,31]. However, in some studies, intraoperative administration did not reduce opioid use or pain scores. Postoperative administration, often shows comparable outcomes to oral acetaminophen, suggesting

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that oral routes may offer comparable benefits at lower costs for certain patient populations [39]. Despite this, IV acetaminophen has been associated with faster onset of analgesia [40]. Dosing considerations indicate that standard doses of IV acetaminophen (1 g every six h) are effective, but higher doses (2 g) may enhance analgesia and opioid-sparing effects [44,45]. Some studies [2,44,45] show stable pharmacokinetics and safety, but further research on higher doses and financial factors is needed.

In conclusion, the administration of IV acetaminophen during the perioperative period has been studied for its impact on postoperative pain management, opioid-sparing effects, and side effects such as PONV. Evidence supports its effectiveness compared to placebo, oral acetaminophen, NSAIDs, and local anesthetics in reducing pain scores and opioid consumption, particularly in orthopedic surgeries like total knee and hip arthroplasty. The timing of administration, whether preincisional or postincisional, significantly influences its efficacy. Preincisional administration is particularly effective in reducing opioid requirements and mitigating adverse effects in cesarean surgeries, while intraoperative use enhances recovery metrics. Postoperative administration remains crucial in multimodal analgesia, especially when oral alternatives are not viable. Clinicians should consider incorporating IV acetaminophen into multimodal analgesia regimens, with further research needed to establish standardized guidelines and explore its role in various surgical contexts and timings. Overall, IV acetaminophen is a valuable component of multimodal analgesia, contributing to improved patient outcomes and potentially reducing opioid dependence in the postoperative period. Future prospective research on studies on timing of IV administration still need to be specifically conducted in order to reach a clear conclusion on its optimal use.

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