Title: IV Acetaminophen (Ofirmev)

SBAR: Situation-Background-Assessment-Recommendation

Initiation and Feedback Phase

Situation:

IV acetaminophen (Ofirmev) was added to Trinity Health formulary in 2011. It was removed from formulary in 2014 when there was a price increase from $12 per vial to $35 per vial. While IV acetaminophen was non formulary, last year there was utilization of $1.8 million dollars. It was requested to re-evaluate the formulary status of IV acetaminophen (Ofirmev) in Trinity Health. The formulary monograph of IV acetaminophen (Ofirmev) was developed in collaboration with the Surgery Multimodal Project. The objective of the formulary evaluation was to identify the role of this medication for as an opiate sparing medication compared to currently available formulary alternatives as well as alternative formulations of acetaminophen.

Background:

Acetaminophen (paracetamol) is recognized as one of the most commonly used synthetic, nonopioid, centrally acting analgesic agents. It represents a key part of pain management in patients with cancer, and is used preoperatively, intraoperatively, and postoperatively in a wide range of surgical settings, offering effective and fast pain relief. Acetaminophen has a well-established efficacy profile, favourable adverse drug reaction profile, and very low potential for harmful drug–drug interactions.

Acetaminophen has been available in oral and rectal formulations for decades. However, controversy exists regarding the suitability of these formulations for use in some settings, such as postoperative or acute care. Intravenous (IV) acetaminophen was first commercialized in Europe, in 2002. Later, in 2010, the US Food and Drug Administration approved an IV formulation of acetaminophen for management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever in adults and children 2 years and older. Since then, acetaminophen has become one of very few nonopioid analgesics available in oral, rectal, and IV formulations.

Assessment:

Guidelines on the Management of Postoperative Pain Management of Postoperative Pain recommends that " that clinicians provide adults and children with acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)". Further stated that "research indicates no clear differences between IV versus oral administration of acetaminophen or NSAIDs in reducing postoperative pain, although onset of action might be faster with IV administration. Further studies evaluating IV acetaminophen to an active comparator did not demonstrate a clinical advantage for pain scores, although onset of action might be faster with i.v. administration."

Studies comparing IV acetaminophen to placebo demonstrated some small advantages in pain management and decreasing opioids. That impact seemed to be diminished when IV acetaminophen was included as part of a multimodal pain management strategy.

Studies comparing IV acetaminophen to an active comparator (including PO and PR acetaminophen) did not demonstrate an advantage for IV acetaminophen related to pain management, opioid use, patient satisfaction, length of stay, or diminishing adverse effects related to opioids.

Without a significant difference in outcomes, use of either oral or IV acetaminophen should be based on other patient and cost factors.

Trinity Health

FEEDBACK PROCESS:

Group	Initial Presentation	Formalized Council Feedback
Orthopedic Clinical Excellence Council	November 15, 2018	January 17, 2019
Cardiovascular Clinical Excellence Council	November 6, 2018	December 5, 2018
Perinatal Patient Safety	November 14, 2018	December 13, 2018
Surgery Clinical Excellence Council	November 1, 2018	December 6, 2018

Voting at CEC:

Surgical CEC (12/6/18):

Support Recommendations – 7, Support Recommendations with suggestions – 6, do not support recommendations - 1

Perinatal Patient Safety (12/9/18):

Support recommendations – 47, do not support recommendations -6

Cardiovascular CEC (1/17/19) surgeons only:

- Support recommendations-2
- Do not support recommendations -0

Comments:

Unanimously Supported

At times opioid dependent patients are given in OR, but felt that able to give oral acetaminophen prior to surgery

Orthopedic Clinical Excellence Council:

- Support recommendations -9
- Do not support recommendations – 4

Comments:

Majority supported.

Those that did not support: Lumbar spine surgery patients are often NPO and not able to turn to administer rectal, would support use of IV acetaminophen in special case consideration

Recommendation:

- Maintain non-formulary status for IV acetaminophen (Ofirmev)
- Establish IV acetaminophen (Ofirmev) as non-formulary, not available
- For perioperative analgesia, the recommendation is to give acetaminophen PO prior to surgery.
- For pain management outside of PACU, the recommendation is to give acetaminophen as part of a multimodal pain management approach using either PO tablets or liquid or PR dosage forms.
- If a clinician identifies new clinical evidence (e.g. new trials) or clinical evidence that was not evaluated in the monograph that demonstrates significant safety or clinical advantage of the IV acetaminophen (Ofirmev), the clinician should submit the request in addition to the clinical evidence providing the significant safety or significant clinical advantage for formulary re-review, the P&T steering committee (in collaboration with expert panels) could determine to recommend a re-evaluation of the decision of the P&T committee.

References/Citations:

See Complete monograph

Submitted by:	Rachael Lu, PharmD, BCPS
CEC/CLG/CSG:	Pharmacy CLG – Trinity Health Pharmacy and Therapeutics Committee
Date	2-20-19

Trinity Health

Title: IV Acetaminophen (Ofirmev)

Final Decision and Action Planning Phase

CEC Decision for Implementation

1. **What were final decisions? Would include any changes to the recommendations out for feedback**

- Pharmacy and Therapeutics Committee (1-29-19) supported recommendation to:
    - Maintain non-formulary status for IV acetaminophen (Ofirmev)
    - Establish IV acetaminophen (Ofirmev) as non-formulary, not available
    - For perioperative analgesia, the recommendation is to give acetaminophen PO prior to surgery.
    - For pain management outside of PACU, the recommendation is to give acetaminophen as part of a multimodal pain management approach using either PO tablets or liquid or PR dosage forms.
    - If a clinician identifies new clinical evidence (e.g. new trials) or clinical evidence that was not evaluated in the monograph that demonstrates significant safety or clinical advantage of the IV acetaminophen (Ofirmev), the clinician should submit the request in addition to the clinical evidence providing the significant safety or significant clinical advantage for formulary re-review, the P&T steering committee (in collaboration with expert panels) could determine to recommend a re-evaluation of the decision of the P&T committee.

2. **Who owns the next steps**?

- ICS team in collaboration with TIS

3. **Estimated timeframe…**

- Target implementation by 5-1-19.

4. **Which functional groups will be involved in the implementation?**

- Nursing, Prescribers, Pharmacists

5. **Regional ICLT to communicate to functional leads and areas.**

Teams	Actions	When
CMO	Share background and decision with medical staff for support, awareness and understanding.	Upon receipt of information
CNO	Share background and decision with nursing staff for support, awareness, and understanding.	Upon receipt of information
Pharmacy	Share background and decision with staff and coordinate efforts with ICS team to update electronic medical records to remove IV acetaminophen (Ofirmev) from order sets and formulary and stock alternatives where appropriate.	By 5-1-19
Informatics	Coordinate efforts with ICS team to manage change toward removal of IV acetaminophen (Ofirmev) from formulary	By 5-1-19

Trinity Health

Finalized by:	Rachael Lu, PharmD, BCPS
CEC/CLG/CSG:	Pharmacy CLG – Trinity Health Pharmacy and Therapeutics Committee Trinity Health
Date	2-20-19

Trinity Health

PHARMACY & THERAPEUTICS COMMITTEE
Trinity Health Formulary Review

ACETAMINOPHEN INTRAVENOUS (OFIRMEV)

November 2018

Recommendations approved 1-29-19 Trinity Health P&T Committee

Recommendation to Committee:

- Maintain non-formulary status for IV acetaminophen (Ofirmev)
- Establish IV acetaminophen (Ofirmev) as non-formulary, not available
- For perioperative analgesia, the recommendation is to give acetaminophen PO prior to surgery.
- For pain management outside of PACU, the recommendation is to give acetaminophen as part of a multimodal pain management approach using either PO tablets or liquid or PR dosage forms.
- If a clinician identifies new clinical evidence (e.g. new trials) or clinical evidence that was not evaluated in the monograph that demonstrates significant safety or clinical advantage of the IV acetaminophen (Ofirmev), the clinician should submit the request in addition to the clinical evidence providing the significant safety or significant clinical advantage for formulary re-review, the P&T steering committee (in collaboration with expert panels) could determine to recommend a re-evaluation of the decision of the P&T committee.

FORMULARY STATUS	*MO IMPLICATIONS*	*RESTRICTIONS REQUIRED*
Non-formulary	**Do not add**	**None**

Key Findings Summary:

It was determined that IV acetaminophen (Ofirmev) was non-formulary in May 2014 at Trinity Health Pharmacy and Therapeutics Committee. Since removal from formulary, there has been extensive use of "non-formulary" IV acetaminophen. Additionally, there has been extensive studies published in the literature evaluating impact of IV acetaminophen. Further, there is currently pressure to reduce the utilization of opioids that are used for patients.

Guidelines on the Management of Postoperative Pain Management of Postoperative Pain recommends that " that clinicians provide adults and children with acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)". Further stated that "research indicates no clear differences between IV versus oral administration of acetaminophen or NSAIDs in reducing postoperative pain, although onset of action might be faster with IV administration. Further studies evaluating IV acetaminophen to an active comparator did not demonstrate a clinical advantage for pain scores, although onset of action might be faster with i.v. administration."

Studies comparing IV acetaminophen to placebo demonstrated some small advantages in pain management and decreasing opioids. That impact seemed to be diminished when IV acetaminophen was included as part of a multimodal pain management strategy.

Studies comparing IV acetaminophen to an active comparator (including PO and PR acetaminophen) did not demonstrate an advantage for IV acetaminophen related to pain management, opioid use, patient satisfaction, length of stay, or diminishing adverse effects related to opioids.

Without a significant difference in outcomes, use of either oral or IV acetaminophen should be based on other patient and cost factors.

Key RHM Feedback:

Draft_Review_Comments (2) ofirmev 1-29-1

Clinical Excellence Council Feedback and/or Decisions:

Group	Initial Presentation	Formalized Council feedback
Orthopedic Clinical Excellence Council	November 15, 2018	January 17, 2019
Cardiovascular Clinical Excellence Council	November 6, 2018	December 5, 2018
Perinatal Patient Safety Group	November 14, 2018	December 13, 2018
Surgery Clinical Excellence Council	November 1, 2018	December 6, 2018

Recommendations:

- Maintain non-formulary status for IV acetaminophen (Ofirmev)
- Establish IV acetaminophen (Ofirmev) as non-formulary, not available
- For perioperative analgesia, the recommendation is to give acetaminophen PO prior to surgery.
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- If a clinician identifies new clinical evidence (e.g. new trials) or clinical evidence that was not evaluated in the monograph that demonstrates significant safety or clinical advantage of the IV acetaminophen (Ofirmev), the clinician should submit the request in addition to the clinical evidence providing the significant safety or significant clinical advantage for formulary re-review, the P&T steering committee (in collaboration with expert panels) could determine to recommend a re-evaluation of the decision of the P&T committee.

Surgical CEC (12/6/18): **Support Recommendations – 6, Support Recommendations with suggestions – 6, do not support recommendations - 1**

Perinatal Patient Safety (12/9/18): **Support recommendations – 47, do not support recommendations -6**

Cardiovascular CEC (1/17/19) surgeons only:

- Support recommendations-2
- Do not support recommendations -0

Comments:
Unanimously Supported
At times opioid dependent patients are given in OR, but felt that able to give oral acetaminophen prior to surgery

Orthopedic Clinical Excellence Council:

- **Support recommendations -9**
- **Do not support recommendations – 4**

Comments:
Majority supported.
Those that did not support: Lumbar spine surgery patients are often NPO and not able to turn to administer rectal, would support use of IV acetaminophen in special case consideration

THERAPEUTIC CLASS

Analgesics; Antipyretics

SIMILAR DRUGS

Acetaminophen Oral, Acetaminophen Rectal, Ketorolac, Ibuprofen

INDICATIONS

Intravenous (IV) acetaminophen is indicated for: management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. [1]

CLINICAL PHARMACOLOGY

Acetaminophen exerts analgesic and antipyretic effects following systemic administration. The mechanism for these pharmacologic effects has not been established, but involves both central and peripheral actions. [23] It has been available in the United States for years in various oral formulations and rectal suppositories. [2] An injectable formulation has not been available because of the drug's poor stability in aqueous solutions and inadequate solubility. [4] An injectable prodrug of acetaminophen, propacetamol, was developed as a means to overcome the limitations associated with the IV formulation, but was poorly tolerated. [5]

Following initiation of an IV infusion of acetaminophen, the onset of pain relief is 5 to 10 minutes. Peak analgesic effects occur within 1 hour, and the duration of analgesic effect is usually 4 to 6 hours.[3] Fever is reduced within 30 minutes after the start of the infusion, and the duration of antipyretic effect is at least 6 hours.[3]

PHARMACOKINETICS

Following IV administration, peak concentration (Cmax) is observed at the end of the infusion.Ref16 The mean plasma Cmax is 29.9 mcg/mL after an infusion of 1 g. [5] Pharmacokinetics are dose-proportional in adults following single doses of 500, 650, and 1,000 mg.[1] Higher Cmax and overall exposure were observed with IV administration of a 1 g dose compared with the same dose administered as a rectal suppository or oral tablets.[57]

The mean volume of distribution reported in several studies has ranged from 69.2 to 85 L. Acetaminophen is not extensively plasma protein–bound (10% to 25%).[15]

The mean elimination half-life is 2.4 hours in adults, 2.9 hours in adolescents, 1.5 to 3 hours in children, 4.2 hours in infants, and 3.5 to 7 hours in neonates.Ref1358 Clearance is lower in neonates than in infants, children, and adolescents, but increases quickly and plateaus at approximately 2 years of age.[8] Acetaminophen is metabolized in the liver by glucuronidation and sulfation. At higher doses, it is metabolized by CYP2E1 to form the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). NAPQI rapidly forms conjugates with glutathione to generate nontoxic thiol metabolites. If glutathione stores are depleted, the toxic NAPQI metabolite may accumulate and result in hepatotoxicity. [5]

Less than 5% of the dose is excreted unchanged in the urine.Ref15 In patients with severe renal impairment (creatinine clearance [CrCl] 10 to 30 mL/min), the half-life is increased to 2 to 5.3 hours.[5]

The pharmacokinetic parameters of IV acetaminophen after a 2 g loading dose and 1 g every 6 hours for 5 doses were assessed in 26 healthy volunteers following 5 doses. The 2 g IV loading dose was administered over 15 minutes; the plasma concentration at the end of the loading dose was 67.9 mcg/mL (Cmax), and the plasma concentration just prior to the next dose (trough concentration [Cmin]) was 6.2 mcg/mL. The plasma Cmax and Cmin at steady state were approximately 35% lower than those observed with the 2 g dose. The mean elimination half-life after the fifth dose was 7 hours.[6]

Acetaminophen readily penetrates into the cerebrospinal fluid (CSF) following IV administration. Levels are detectable within the CSF as early as 5 minutes after IV administration, and they peak within 1 hour. CSF levels following a single dose of 15 mg/kg infused over 10 minutes in 32 children 3 months to 12 years of age ranged from 1.3 to 18 mg/L, while plasma concentrations ranged from 2.4 to 33 mg/L. CSF concentrations did not vary by age, height, or weight; however, CSF levels were higher in girls than boys (P = 0.001). [9]

The pharmacokinetics of IV acetaminophen were evaluated in 50 neonates. The dose used was based on the following postmenstrual ages: 28 through 31 weeks of age received 10 mg/kg, 32 through 35 weeks of age received 12.5 mg/kg, and 36 weeks of age and older received 15 mg/kg. The median age of the neonates was 38.6 weeks. The mean number of doses administered over a median 4-day period was 15. The estimated clearance was 5.24 L/h per 70 kg and the volume of distribution was 76 L per 70 kg. Clearance increased with postmenstrual age from 4.4 L/h/kg at 34 weeks of age to 6.3 L/h per 70 kg at 46 weeks of age. Unconjugated hyperbilirubinemia was associated with reduced clearance. Acetaminophen concentrations between 10 and 23 mg/L at steady state are predicted after a dose of 15 mg/kg every 6 hours for a neonate at 40 weeks of postmenstrual age. [10]

COMPARATIVE EFFICACY

The new drug application contained data from one study for the treatment of acute pain in patients following orthopedic surgery, 1 study for the treatment of endotoxin-induced fever, 9 placebo-controlled clinical trials, 4 active-controlled clinical trials, and several other safety or pharmacokinetic studies. Not all of these studies have been published; most of the published studies have had small patient populations.

A. Ear, nose, and throat surgeries

IV acetaminophen was assessed in a randomized, double-blind, placebo-controlled study enrolling 76 adult patients undergoing tonsillectomy. The tonsillectomy was conducted under general anesthesia and the patients were given IV acetaminophen 1 g (38 patients) or IV isotonic sodium chloride 0.9% solution (38 patients) at 6-hour intervals during their postoperative care. The primary outcome was the need for rescue analgesia during the first postoperative 24-hour period. The permitted rescue analgesic was meperidine, which was provided for patients with a resting pain score greater than 30 on a 100 mm visual analog scale (VAS). No other analgesic medication was permitted during the study. Rescue medication was needed in 29% of patients in the acetaminophen group compared with 100% in the placebo group during this postoperative period, and the placebo group had higher pain scores at rest and upon swallowing. Patients in the placebo group requested a mean of 2.2 doses of meperidine, while the acetaminophen group used a mean of 0.5 doses (P < 0.001). The mean accumulative amount of meperidine used as a rescue analgesic was 18 mg in the acetaminophen group and 82 mg in the placebo group. [11]

IV acetaminophen was also assessed in a randomized, double-blind, placebo-controlled study enrolling 74 patients undergoing endoscopic sinus surgery. Patients received IV acetaminophen (36 patients) or isotonic sodium chloride 0.9% solution (38 patients) at the completion of the surgery performed under local anesthesia. Need for rescue analgesic (IV oxycodone) during the first 4 hours after the procedure was the primary outcome. No other analgesics were permitted. Rescue analgesics were required in 27 (71%) of 38 patients in the placebo group compared with 9 (25%) of 36 in the acetaminophen group (difference, 46%; 95%

confidence interval [CI], 26% to 66%; P = 0.001). The total number of oxycodone doses was 57 in the placebo group (mean, 1.5) compared with 18 in the acetaminophen group (mean, 0.5; P = 0.001). The time to first dose of rescue medication was 70 minutes in the placebo group compared with 126 minutes in the acetaminophen group (mean difference, 55 minutes; 95% CI, 14 to 93 minutes; P = 0.009). Worst pain after surgery on a 0 to 10 scale was 4.4 in the placebo group compared with 2.9 in the acetaminophen group (P = 0.026). [12]

Another study compared the duration of analgesia following IV and rectal acetaminophen in 50 children 2 to 5 years of age undergoing adenotonsillectomy. Patients received acetaminophen 15 mg/kg IV or 40 mg/kg rectally intraoperatively. During the procedure, patients received standardized anesthetic, including fentanyl. The primary outcome measure was time to first rescue analgesia. Rescue analgesia was provided for scores of four or more on the Children and Infants Postoperative Pain Scale. Study medication was administered to 46 children; 45 of them required a dose of rescue medication. The median time to first rescue analgesia was 10 hours for those receiving rectal acetaminophen (interquartile range [IQR], 9 to 11 hours) and 7 hours in those receiving IV acetaminophen (IQR, 6 to 10 hours; P = 0.01). [22]

IV acetaminophen was compared with intramuscular (IM) meperidine in a randomized, double-blind study enrolling 80 children undergoing tonsillectomy. Patients received IV acetaminophen 15 mg/kg or IM meperidine 1 mg/kg intraoperatively. On admission to the recovery room, objective pain scale scores were 3.1 in the acetaminophen group and 2.1 in the meperidine group (P = 0.147). Seven (17.5%) patients in the acetaminophen group required a rescue morphine dose compared with none in the meperidine group (P < 0.01). Sedation was greater in the meperidine group; the Ramsay sedation scores were 3 in the acetaminophen group and 4 in the meperidine group (P < 0.05). Median time to readiness for discharge from the postanesthesia care unit was 15 minutes in the acetaminophen group (IQR, 0 to 20 minutes) and 25 minutes in the meperidine group (IQR, 15 to 30 minutes; P = 0.005). Nurses were more satisfied with patients' analgesia in the meperidine group; however, after adjusting for the effect of morphine administration, overall nursing satisfaction scores were similar in the 2 groups.[30]

B. Spinal surgery

IV acetaminophen was assessed in a randomized, double-blind, placebo-controlled study enrolling 40 patients undergoing lumbar laminectomy and discectomy. Patients received IV acetaminophen 1 g or isotonic sodium chloride 0.9% solution at the end of the operation and at 6-hour intervals over the next 24 hours. The rescue medication in this study was IV patient-controlled analgesic (PCA) morphine. Pain scores at rest and upon movement were reduced at 12, 18, and 24 hours in the acetaminophen group (P < 0.001), but the morphine consumption did not differ between the groups. More patients in the acetaminophen group rated their pain management as excellent (45% vs 5%).[13]

A large retrospective study using national data assessed current utilization and whether it reduces inpatient opioid prescription and opioid-related side effects in a patients undergoing a lumbar/lumbosacral spinal fusion (n = 117,269; 2011–2014). The study could not demonstration that perioperative IV APAP reduces inpatient opioid prescription with subsequent reduced odds for adverse outcomes. The authors concluded that it remains to be determined if and under what circumstances IV APAP has a meaningful clinical role in everyday practice.[43]

A prospective, randomized placebo controlled study evaluated the effects of IV acetaminophen 1 gram every 6 hours for 24 hours versus placebo in craniotomy patients. After controlling for VAS pain score at time 0, no statistically significant difference of VAS pain score was observed between two treatment groups. There was no significant difference in morphine equivalents consumed between the two group. There were no differences in secondary outcomes with regard to time to extubation, time for patient to meet PACU discharge, and opioid related side effects.[44]

IV acetaminophen was also compared with IV parecoxib and IV metamizole (dipyrone) in a randomized, double-blind, placebo-controlled study enrolling 80 patients undergoing lumbar microdiscectomy. Patients received IV parecoxib 40 mg, IV acetaminophen 1 g, IV metamizole 1 g, or IV placebo 45 minutes before the end of surgery. All patients received PCA with the opioid piritramide. Pain scores at arrival to the postanesthesia care unit were lower in the metamizole group than in the acetaminophen, parecoxib, or placebo groups. Fewer patients in the metamizole group required additional PCA. Time to request for PCA and total PCA consumption did not differ among the groups.[29]

C. Ob/Gyn or urologic surgery

IV acetaminophen was compared with oral ibuprofen in a randomized, double-dummy study enrolling 45 term patients scheduled for cesarean delivery. Patients received IV acetaminophen 1 g every 6 hours plus oral placebo or ibuprofen 400 mg orally every 6 hours plus IV placebo, with the first dose given 30 minutes preoperatively and therapy continuing for 48 hours. Spinal anesthesia was used in all patients. Intraoperative pain was treated with fentanyl as needed. Postoperatively, all patients received a bolus morphine dose of 0.05 mg/kg and PCA with morphine for 48 hours using a morphine bolus dose of 2 mg IV, a lockout interval of 10 minutes, and no basal infusion. VAS scores decreased similarly in both groups, with no difference between groups at any time. Cumulative doses of postoperative morphine were 98 mg in the acetaminophen group and 93 mg in the ibuprofen group (P = 0.628). The median number of PCA attempts made was similar in the two groups. Patient satisfaction 48 hours postoperatively, on a scale from 1 to 10, was 9 in both groups. [28]

IV acetaminophen was no more effective than placebo in a randomized, double-blind study enrolling 70 women undergoing fractional curettage. Patients received IV acetaminophen 1 g (36 patients) or sodium chloride 0.9% (34 patients) prior to the procedure. Pain scoring, using a 10 cm VAS, was conducted prior to, during, and 30 minutes after the procedure. No other analgesic or anesthesia was provided; cervical dilation was not performed. Pain scores were higher during and after the procedure than before the procedure in both groups; there was no difference between treatment groups.[19]

IV acetaminophen reduced parent-/nurse-controlled fentanyl use compared with placebo in a randomized, double-blind study enrolling 63 children (6 to 24 months of age) undergoing elective ureteroneocystostomies. Postoperatively, patients in both groups received fentanyl 0.25 mcg/kg/h as a basal infusion with 0.25 mcg/kg boluses and a 0.5 mcg/kg loading dose. Patients in the acetaminophen group also received an acetaminophen 1.5 mg/kg/h infusion with 1.5 mg/kg boluses and a 15 mg/kg loading dose. Patients in the placebo group received saline in place of acetaminophen. Postoperative pain scores did not differ between groups. The total dose of fentanyl was lower in the acetaminophen group at day 1 (8.3 vs 18.1 mcg/kg/day, P = 0.021) and day 2 (7 vs 16.6 mcg/kg/day, P = 0.042). Rates of vomiting and sedation were also substantially lower in the acetaminophen group.[20]

Stoudenmire evaluated the impact of adding scheduled IV acetaminophen to postoperative analgesic regimens following gynecologic procedures in one hundred and thirty-seven patients. In the first 24 hours postoperatively, there were no differences in opioid requirements between groups. The average pain score or average incident of adverse events was not different between groups. [55]

D. Cardiac surgery

The impact of IV acetaminophen on opioid consumption was assessed in a randomized study enrolling 80 patients undergoing coronary artery bypass grafting. Patients received acetaminophen 1 g every 6 hours during the postoperative period, as either tablets or IV, in conjunction with ketobemidone, an opioid,

infusion. The amount of ketobemidone administered during the study period was measured from the first dose of acetaminophen until 9:00 the following morning. Pain was assessed using a VAS from 0 to 10. Ketobemidone consumption was lower in the IV group (17.4 vs 22.1 mg, P = 0.016). Postoperative nausea and vomiting and VAS scores did not differ between groups.[21]

IV acetaminophen was assessed as an adjunct agent used with tramadol background analgesia in a randomized, double-blind, placebo-controlled study enrolling 113 patients undergoing nonemergent cardiac surgery. Patients received IV acetaminophen 15 minutes before the end of surgery and every 6 hours for 72 hours (56 patients) or placebo (57 patients). Tramadol IV and ondansetron were available to both patient groups. A rescue dose of morphine 2 to 5 mg IV was administered whenever the VAS score was more than 3. At 12, 18, and 24 hours after the end of the operation, patients treated with acetaminophen had less pain at rest (P = 0.0041, P = 0.0039, and P = 0.0044, respectively); during a deep breath, the patients receiving acetaminophen also had less pain, but only at the 12-hour assessment (P = 0.004). Median VAS scores were generally two or less at each time point. After 24 hours, the groups did not differ. For amount of morphine required, the difference was not significant (48 vs 97 mg, P = 0.274).[23]

Ratliff et al evaluated retrospectively IV acetaminophen (at least 4 doses) plus opioids versus opioids alone in patients recovering from CABG. The study found the primary end point of morphine equivalents was greater in the IV acetaminophen group. There were no differences between groups in pain control, length of stay or length of ICU stay.[49]

E. Orthopedic surgery

Oral versus intravenous acetaminophen was evaluated in a single center prospective, placebo controlled study of 486 patients of total knee or total arthroplasty. There were no significant differences in preoperative and intraoperative use of pain medications between groups. Postoperative use of morphine equivalents between groups, postoperative pain scores, nausea vomiting, length of PACU stay and length of hospital stay were the same between groups.[58]

IV acetaminophen was also compared with IV propacetamol and placebo in a randomized, double-blind study enrolling 151 patients (mean age, 60.1 years) with moderate to severe pain following orthopedic surgery. Patients received IV acetaminophen 1 g, propacetamol 2 g, or placebo at 6-hour intervals over 24 hours. Rescue PCA with IV morphine was permitted. Pain relief from 15 minutes to 6 hours was greater with both active treatments compared with placebo (P < 0.05), as was median time to morphine rescue (acetaminophen, 3 hours; propacetamol, 2.6 hours; placebo, 0.8 hours; P < 0.0001). Morphine consumption during the first 24 hours was reduced in both active-treatment groups. Total morphine doses received over 24 hours were 38.3 mg with acetaminophen, 40.3 mg with propacetamol, and 57.4 mg with placebo (a 33% reduction from placebo). Maximal pain relief scores were similar in the 2 active-drug groups and were greater than those observed in the placebo group.[25]

Small reductions in morphine consumption were also observed with IV acetaminophen in a randomized, double-blind study comparing IV acetaminophen, metamizol, and lornoxicam following lumbar disc surgery. Seventy-seven patients received morphine PCA plus IV acetaminophen 1 g, metamizol 1 g, lornoxicam 8 mg, or saline placebo. During the first 24 hours postoperatively, pain was reduced to a greater extent with acetaminophen (P = 0.04) and metamizol (P = 0.001) than placebo, but not with lornoxicam. Morphine consumption was reduced with acetaminophen (P < 0.001); however, total morphine consumption did not differ between groups, possibly because of the small sample size. Morphine-related adverse events also did not differ between groups. [26]

IV acetaminophen was evaluated compared to placebo in both a preventative (given prior to skin closure) and preemptive (given prior to surgery) manner in seventy-give patients undergoing lower extremity surgery. There was a decrease in the pain scores in both groups versus placebo. There was not a statistical

difference in the amount of meperidine consumption between the preemptive group. There were no difference in nausea and vomiting, hypotension, bradycardia, or hypoxemia between groups. The authors concluded it makes no difference in acetaminophen is given preoperatively or before skin-closure.[47]

Gupta compared IV acetaminophen plus IV ibuprofen versus IV ibuprofen alone in patients undergoing hip and knee arthroplasty. Primary outcomes of VAS pain scores demonstrated only a statistically significant difference on day 3. There was no difference between groups on day 0-2 in VAS. There were no statistical differences between groups in opioid consumption, antiemetic consumtion, quality of recovery scale. The group that did not receive IV acetaminophen had more instances of adverse events, but types were not reported.[50]

Murata-Ooiwa investigated the impact of intravenous acetaminophen at six hour interveals compared to placebo as part of a multimodal pain management protocol (including periartcular cocktail of ropivacaine, methylprednisolone and scheduled NSAIDs). No narcotic pain medications were used. Primary outcomes of pain score on visual analogue scale was similar at all intervals except for post-operative day 2. The rates of complications between groups were not similar. Further, the mean number of rescue medications were similar for all outcomes except on POD 2 (NSAID suppository was used for rescue medication).[51]

The efficacy of intravenous acetaminophen was compared with oral acetaminophen as part of a multimodal regimen. The study enrolled 174 patients in a placebo controlled study randomizing to IV acetaminophen 1 gram IV and oral placebo before anesthesia, oral 1 gram acetaminophen and placebo IV or only placebo. Primary outcomes were average pain scores, maximum pain scores. Secondary outcomes were total opiate consumption, time to analgesia, and time to breakthrough pain. There were no significant differences between groups for any outcome. Intraoperatively patients received a pericapsular injection (ropivacaine, ketorolac, clonidine, and epinephrine).[52]

A retrospective cohort study evaluated adult patients who underwent elective total knee arthroplasty (TKA) and was stratified into patients that had received at least one dose of IV acetaminophen versus patients who did not. There were 161 patients in the study. The use of the IV acetaminophen was not associated with a decrease in opiate use, opiate related side effects or any secondary outcomes in patients who underwent TKA in the retrospective study. [56]

Gallipani compared patients treated with IV acetaminophen with patients who did not receive IV acetaminophen in a retrospective study of total hip and knee arthroplasty patients. A total of 609 patients were included in the study. The primary safety endpoints included any adverse events. Secondary outcomes were changes in laboratory values, vital signs and pain scores. More patients in the intravenous acetaminophen group experienced adverse events compared to patients who did not received IV acetaminophen (91.63% versus 84.73% p=0.012). Mean cumulative acetaminophen exposure was similar between groups. Mean opioid use was similar between groups. Higher mean pain scores were found in the intravenous acetaminophen group versus the group that did not receive IV acetaminophen.

F. Surgery – Multiple procedure types

IV acetaminophen was also compared with dipyrone and parecoxib for postoperative pain management in a randomized, double-blind, placebo-controlled study enrolling 196 patients undergoing plastic surgery, oral and maxillofacial surgery, gynecologic or urologic surgery, or orthopedic surgery under general anesthesia. Patients were randomized to receive IV acetaminophen 1 g every 6 hours, dipyrone 1 g every 6 hours, parecoxib 40 mg every 12 hours, or placebo for 48 hours in

conjunction with piritramide PCA. Postoperative pain did not differ significantly between the groups receiving nonopioid analgesics; all 3 agents were more effective than placebo. None of the agents resulted in a reduction in piritramide use compared with placebo.[32]

IV acetaminophen reduced meperidine use compared with placebo in a randomized study enrolling 40 patients admitted to an intensive care unit (ICU) following major abdominal or orthopedic surgery. Patients received IV saline and IV meperidine, or IV acetaminophen 1 g every 6 hours and IV meperidine for 24 hours. Meperidine 1 mg/kg IV was administered when behavioral pain scale and VAS scores exceeded 4. Behavioral pain scale and VAS scores were lower in the acetaminophen group at 24 hours ($P < 0.05$). Meperidine use was 76.75 mg in the acetaminophen group compared with 198 mg in the placebo group ($P < 0.01$). Time to extubation was also reduced with acetaminophen (64.3 minutes) compared with placebo (204.5 minutes, $P < 0.01$). Postoperative nausea, vomiting, and sedation were also reduced with acetaminophen ($P < 0.05$). Time spent in the ICU did not differ.[16]

Morphine consumption was also reduced with IV acetaminophen in a randomized, double-blind study enrolling 40 patients undergoing laparoscopic cholecystectomy under general anesthesia. Patients received IV acetaminophen 1 g or saline intraoperatively, and morphine PCA postoperatively. Pain scores were lower in the acetaminophen group ($P < 0.05$). Time to first morphine dose was prolonged (15 vs 5 minutes, $P < 0.05$) and total morphine consumption was reduced with acetaminophen (2.3 vs 6.1 mg, $P < 0.05$). Nausea and vomiting were less frequent with acetaminophen. [17]

A retrospective study of patients that received at least four doses of IV acetaminophen plus opioids versus opioids alone evaluated bariatric patients and opioid requirements. The study found the patients in the opioid/IV acetaminophen group required more oral morphine equivalents (primary end point) than the opioid alone group. There were not any significant differences in median change in pain score between each group. [48]

Gonzalez evaluated the effect of IV acetaminophen in bariatric patients using a retrospective study. The retrospective study found that patients that received IV acetaminophen received less opioids in 24 hours compared to patients that did not. Intravenous acetaminophen was given intraoperatively and then every 6 hours post-operatively. Hydromorphone was used as a rescue medication. [56]

IV acetaminophen and IM meperidine were also compared in a randomized, double-blind, double-dummy study enrolling 40 children 3 to 16 years of age undergoing dental restoration. Patients received IV acetaminophen 15 mg/kg or IM meperidine 1 mg/kg after anesthesia induction and before surgery; patients also received fentanyl at that time. The acetaminophen group had higher pain scores upon arrival to the recovery room (mean, 3 vs 2; $P = 0.012$). Rescue morphine administration was required in 3 (15%) patients in the acetaminophen group compared with 1 (5%) patient in the meperidine group ($P = 0.342$). Sedation scores were higher in the meperidine group (mean, 4 vs 2; $P = 0.013$). Scores indicating readiness for discharge from the recovery room were achieved sooner in the acetaminophen group (5 vs 16 minutes, $P = 0.009$); however, actual discharge times did not differ (32 vs 34 minutes, $P = 0.519$). [31]

Neurocritical subarachnoid hemorrhage patients were evaluated in a retrospective study to identify the impact of patients that received IV acetaminophen to patients that received oral acetaminophen. The pain score, pain intensity, as well as need for rescue medications were evaluated. There was no difference between groups in any outcomes. The authors concluded there was a trend to better pain control, but did not reach statistical significance. [54]

G. Pain — other types of studies

IV acetaminophen was compared with IV morphine and placebo in a randomized, double-blind study enrolling 165 patients presenting to an emergency department with suspected renal colic. Patients received IV acetaminophen 1 g, IV morphine 0.1 mg/kg, or isotonic sodium chloride solution placebo. Subjects

with inadequate pain relief at 30 minutes received rescue fentanyl. The mean reduction in VAS score at 30 minutes was 43 mm with acetaminophen (95% CI, 35 to 41 mm), 40 mm with morphine (95% CI, 29 to 52 mm), and 27 mm with placebo (95% CI, 19 to 34). Pain reductions were significant with acetaminophen (reduction of 16; 95% CI, 5 to 27; P = 0.005) and morphine (reduction of 14; 95% CI, 0.4 to 27; P = 0.05), with no difference between treatments. Rescue analgesics were required in 45% of patients treated with acetaminophen, 49% receiving morphine, and 67% receiving placebo (P = 0.08).Ref33 IV acetaminophen was also compared with piroxicam in the treatment of acute renal colic pain in a randomized study enrolling 100 patients. Patients received IV acetaminophen 1 g or IM piroxicam 20 mg upon presenting to an emergency department with signs and symptoms consistent with renal colic. The primary end point of pain relief, defined as a reduction of at least 50% in the VAS score at 90 minutes, was achieved in 40 (80%) patients who received acetaminophen and 24 (48%) who received piroxicam (P = 0.002).Ref34

The effect of IV acetaminophen on morphine consumption was also assessed in an under-powered, randomized, placebo-controlled study enrolling 43 patients with chronic cancer pain receiving step 2 treatment according to the World Health Organization analgesic ladder. Patients received IV acetaminophen or IV saline placebo in addition to morphine therapy. VAS and Patient Rating Index (PRI) scores improved in both groups; however, no differences between acetaminophen and placebo were observed for VAS or PRI scores or morphine consumption.Ref35

Another study compared IV acetaminophen 50 mg with IV lidocaine 40 mg with venous occlusion for the prevention of propofol injection pain in 150 patients undergoing general anesthesia. The incidence of pain on injection of propofol was 64% in the isotonic sodium chloride solution control group, 22% in the acetaminophen group, and 8% in the lidocaine group (P < 0.05 for both active groups vs control).Ref36

Data were also presented from an open-label, noncomparative study of IV acetaminophen administered to 590 patients undergoing minor knee surgery (71.4%), minor gynecologic procedures (19%), or varicose vein surgery (9.6%). Mean age was 46.7 years; 58.7% of patients were women. Patients received an IV infusion of acetaminophen 1 g 30 minutes before the planned end of their surgery. Analgesics were coadministered in 57% of patients, primarily piritramide (44.4%), metamizole (16.6%), other acetaminophen formulations (13.6%), and diclofenac (8.8%). Concomitant pain medications were provided after a mean period of 40 minutes. Mean self-reported pain intensity on a 100 mm VAS was 33.2 at 15 minutes after the end of surgery and was reduced to 19.2 at patient discharge (results were truncated at 120 minutes because most patients had been discharged by that time). Acetaminophen therapy was rated as very good or good by 80.5% of physicians and 81.6% of patients. Satisfaction was greatest in patients undergoing varicose vein or gynecologic procedures.Ref37

H. Fever

IV acetaminophen was compared with IV propacetamol in the treatment of acute fever caused by infection in a randomized, double-blind, noninferiority study enrolling 67 children 1 month to 12 years of age with a rectal body temperature of 38.5° to 41°C (101.3° to 105.8°F). Patients received single-dose IV acetaminophen 15 mg/kg (35 patients) or IV propacetamol 30 mg/kg (32 patients). The primary end point was the maximum body temperature reduction over the 6-hour monitoring period. Noninferiority was demonstrated by a median body temperature reduction of 1.9°C (35.4°F) in the acetaminophen group and 2.05°C (35.7°F) in the propacetamol group. There was no difference in the percentage of patients who achieved a normal body temperature (79% with acetaminophen vs 75% with propacetamol). The median time to reach normal body temperature was 2 hours in both groups. Therapy was rated good or excellent by the investigators in 73% of patients in the acetaminophen group and 65% in the propacetamol group. Local adverse events occurred more frequently in the propacetamol group (28.1% vs 5.7%).Ref538

The labeling also describes a randomized, double-blind, placebo-controlled study evaluating single-dose IV acetaminophen 1 g in the treatment of endotoxin-induced fever in 60 healthy men. Antipyretic effect was observed through 6 hours compared with placebo.Ref1

Only studies evaluating IV acetaminophen versus an active comparator were presented in the table below.

Table 1: IV ACETAMINOPHEN VERSUS ORAL OR PR ACETAMINOPHEN OR ACTIVE COMPARATOR

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
ENT						
Capici[22] N=50 IV APAP v. PR APAP Randomized observer blind controlled in children after adenoidectomy w/ or w/out tonsillectomy	IV APAP 15 mg/kg versus 40 mg/kg APAP PR	Time to first analgesic request was longer in children receiving rectal APAP (median 10 h, inter-quartile range 9–11 h) compared with those receiving i.v. acetaminophen (7, 6–10 h)	NA	NA	NA	NA
Alhashemi[30] N=80 Randomized, DB prospective study Children undergoing tonsillectomy IM meperidine versus IV APAP **	IV APAP 15 mg/kg or IM meperidine 1 mg/kg	No difference pain scores on admission to recovery room	Seven (17.5%) patients in the APAP group required a rescue morphine dose compared with none in the meperidine group (P < 0.01).	Median time to readiness for discharge from the postanesthesia care unit was 15 minutes in the APAP group (IQR, 0 to 20 minutes) and 25 minutes in the meperidine group (IQR, 15 to 30 minutes; P = 0.005).		Sedation was greater in the meperidine group; the Ramsay sedation scores were 3 in the APAP group and 4 in the meperidine group (P < 0.05).
Grundmann [29] N=80	4 treatment groups to receive either	At arrival in the PACU	The metamizol group significantly fewer patients	NA	NA	No difference between groups

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
prospective, DB, randomized, PC lumbar microdiscectomy. 4 treatment groups Paracoxib, (*n*=20 each) to receive either parecoxib 40 mg, paracetamol 1 g, metamizol 1 g, or placebo IV 45 min before the end of surgery	parecoxib 40 mg, paracetamol 1 g, metamizol 1 g, or placebo IV 45 min before the end of surgery	postoperative VAS pain scores were significantly lower in the metamizol group compared with the paracetamol, parecoxib, and placebo groups.	required additional PCA compared with the other groups. Patients requiring additional pain therapy: there was no significant difference in time to first request for piritramide and cumulative consumption of piritramide			
OB/GYN/UROLOGICAL						
Alhashemi[28] N=45 Cesarean section patients IV APAP versus IBU oral Prospective randomized, double dummy	IV APAP 1 gram Q6 h plus oral placebo or IBU 400 mg PO Q6H Spinal anesthesia Morphine PCA bolus PRN (first dose 30 minutes pre-op) continued for 48 hours		No difference in morphine administered between groups		Patient satisfaction: no differences between groups	No difference between groups. There were no episodes of desaturation or respiratory depression in either group, and no major adverse events were observed in the study
CARDIAC SURGERY						
Pettersson [21] N=80 Prospective, randomized study CABG patients IV APAP v. PO APAP	1 g of APAP PO vs 1 g of APAP IV every sixth hour after surgery. All patients received the first dose of APAP after	There were no differences in VAS scores between the 2 groups, neither during the early study	The amount of opioid administered during the postoperative	NA	NA	The incidence of PONV did not differ between the 2 groups

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
	extubation when they were awake, responding, and able to swallow tablets. Study protocol began with the first dose of acetaminophen and ended at 9 o'clock the following morning.	period, from acetaminophen administration until 120 minutes, (Table 2, Fig 2) nor during the rest of the stay in the ICU (data not shown).	study period, from the first APAP administered until the next morning in the ICU, was lower in the IV than in the PO group (5 mg morphine in 15 hours) p=0.016			
HERNIA REPAIR						
Murat [24] Single dose of IV APAP v. single dose PO APAP Pediatric Hernia repair N=183 Randomized DB	Patients ASA I or II in-patients, 1–12 yo, either IV paracetamol 15 $mg \cdot kg^{-1}$ ($n = 95$) or propacetamol 30 $mg \cdot kg^{-1}$ ($n = 88$) for postoperative pain as soon as pain intensity was greater than 30 on a 100 mm visual analog scale.	No significant difference between treatments on pain relief (PR), pain intensity difference (PAID) from baseline, and objective pain scale intensity difference (OPSD).	NA	NA	NA	NA
ORTHOPEDIC						
Hickman[58] N=486 Oral versus IV acetaminophen single dose Randomized, placebo controlled study Prospective	1000 mg PO APAP before surgery or 1000 mg IV APAP during surgery	No difference between groups over 24 hours	No difference between groups	No difference in length of stay or length of PACU stay	No difference in time to ambulation	No difference in postoperative nausea and vomiting

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
Total hip and knee patients						
O'Neal [52] N=174 Randomized, single-center, double-blinded placebo controlled study	randomized to one of the 3 groups: IV APAP group (IV group, n ¼ 57) received 1 g IV APAP and PO placebo before PACU admission; PO APAP eceived 1 g PO APAP and IV placebo; placebo group received PO placebo and IV placebo Standard preoperative pain medication regimen included doses of Celecoxib and OxyContin Intraoperatively, all patients received a pericapsular injection of 300 mg ropivacaine, 30 mg ketorolac, 0.08 mg clonidine, and 1 mg epinephrine in a total volume of 100 cc of 0.9% sodium chloride 0.9% into the knee joint In addition, a majority of patients	No difference between all groups	No difference between all groups	No difference between all groups: time to PACU discharge	Not assessed	Not assessed

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
	received IV dexamethasone (4-10 mg)					
Sinatra [25] N=151 repeated-dose, randomized, double-blind, placebo-controlled, three–parallel group study was performed to evaluate the analgesic efficacy and safety of IV APAP as compared with its prodrug (propacetamol) and placebo major orthopedic surgery	After orthopedic surgery, patients reporting moderate to severe pain received either 1 g intravenous acetaminophen, 2 g propacetamol, or placebo at 6-h intervals over 24 h. Patients were allowed "rescue" intravenous patient-controlled Analgesia morphine.	For both active groups, IV APAP and propacetamol, pain relief scores were significantly higher than those of the placebo group from 15 min to 6 h (*P* _ 0.05), with no significant difference between the two active groups Maximal pain relief scores were similar in the two active groups (2.0 _ 1.4) and significantly higher than that observed in the placebo group (0.9 _ 1.1). The median time to peak effect for pain relief was 30 min in both active groups.	Morphine consumption over the 6 h after the first dose was significantly (*P* _ 0.01) lower for both active groups (9.7 _ 10 and 9.3 _ 8.9 mg for intravenous acetaminophen and propacetamol, respectively) than for the placebo group (17.8 _ 16.7 mg). This reduction was maintained over 24 h (repeated doses), with total doses of 38.3 _ 35.1, 40.8 _ 30.2, and 57.4 _ 52.3 mg for intravenous acetaminophen, propacetamol, and placebo, respectively			There was no significant difference between treatment groups regarding the number of patients experiencing AEs.
SURGICAL PATIENTS						
Brodner [32] N=196 DB, placebo-controlled study was	Patients undergoing minor-to-intermediate surgery	Postoperative surgical pain did not differ	The number of piritramide administrations in			The incidence of side effects did not differ among groups

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
designed to compare the efficacy of IV paracetamol with other IV non-opioids	under general anesthesia were randomly assigned to receive infusions of paracetamol (1 g every 6 h), dipyrone (1 g every 6 h), parecoxib (40 mg every 12 h) separated by infusions of physiological saline 0.9%, or placebo (0.9% saline every 6 h), respectively, for at least 48 h	significantly among the groups receiving a non-opioid analgesic. From themorning after surgery, these groups reported less surgical pain than those receiving placebo. Additionally, the administration of dipyrone decreased associated pain compared to placebo There was no significant difference in time to first piritramide bolus and the total number administered or demanded	the recovery room did not differ among groups: group 1 paracetamol 7.6 (8.3), group 2 dipyrone 5.9 (7.3), group 3 parecoxib 7.8 (9.2) and group 4 placebo 6.4 [(7.3); P¼0.6].			Nausea and vomiting were frequent
Bayrlee [54] N=157 Retrospective Patients that received IV APAP versus PO APAP SAH patients		No difference between pain scores at any time (0-6 hours) between any group	There were no differences between use of rescue medications for any group	Not assessed	Not assessed	Not assessed

CONTRAINDICATIONS

IV acetaminophen is contraindicated in patients with hypersensitivity to acetaminophen or any of the product ingredients and in patients with severe hepatic impairment or severe active liver disease.Ref1

WARNINGS AND PRECAUTIONS

The warnings and precautions associated with injectable acetaminophen are similar to those associated with oral and rectal acetaminophen, and include cautions in patients with regular alcohol consumption or liver disease, and cautions about the risk of hepatotoxicity.Ref12

Administration at doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. The maximum recommended total acetaminophen dose must not be exceeded. Caution is advised in patients with hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (CrCl 30 mL/min or less).Ref1

Hypersensitivity and anaphylaxis have been reported in association with the use of acetaminophen. Clinical signs have included respiratory distress, urticaria, rash, pruritus, and swelling of the face, mouth, and throat. Acetaminophen should be immediately discontinued if symptoms associated with allergy or hypersensitivity occur.Ref1

IV acetaminophen is approved for use in patients 2 years of age and older.Ref1 Limited safety and efficacy data are available in neonates.Ref39 In a retrospective safety assessment of 189 neonates exposed to a total of 2,360 doses of IV acetaminophen, hepatotoxicity was not observed.Ref40

IV acetaminophen is in Pregnancy Category C. The IV formulation should be used only if clearly needed.Ref1 Oral forms have routinely been used in all stages of pregnancy and are categorized in Pregnancy Category B.Ref2

Acetaminophen is excreted in breast milk in low concentrations. The American Academy of Pediatrics regards acetaminophen as compatible with breast-feeding.Ref2 The labeling for the IV formulation advises caution with use in breast-feeding women.Ref1

ADVERSE REACTIONS

Acetaminophen has been well tolerated when administered as a 15-minute IV infusion. The adverse event profile has been very similar to placebo.Ref5 The most common adverse reactions in patients treated with IV acetaminophen in placebo-controlled, repeat-dose studies were nausea, vomiting, pyrexia, headache, and insomnia in at least 5% of adults (Table 2); and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in at least 5% of children. [1]

Table 2. Treatment-Emergent Adverse Reactions (>5%) Associated With the IV Administration of Acetaminophen in Adults in the Placebo-Controlled, Repeated-Dose StudiesRef1

	IV Acetaminophen (n = 402)	Placebo (n = 379)
Nausea	34%	31%

Table 2. Treatment-Emergent Adverse Reactions (>5%) Associated With the IV Administration of Acetaminophen in Adults in the Placebo-Controlled, Repeated-Dose StudiesRef1		
	IV Acetaminophen (n = 402)	Placebo (n = 379)
Vomiting	15%	11%
Headache	10%	9%
Insomnia	7%	5%

In a pooled analysis of clinical trials, hepatotoxicity has not been associated with the use of IV acetaminophen at recommended doses. Transaminase enzyme levels were elevated in 3.1% of acetaminophen recipients and 6.3% of placebo recipients. [5]

DRUG INTERACTIONS

The potential drug interactions with IV acetaminophen are the same as those observed with the oral and rectal formulations (eg, lamotrigine, probenecid, warfarin). Additive risk of hepatotoxicity may also be observed with concomitant therapy with other hepatotoxic medications. [241]

Agents that induce or regulate hepatic CYP2E1 enzyme (eg, ethanol, ethotoin, fosphenytoin, mephenytoin, phenytoin, sulfinpyrazone, amobarbital, barbiturates, primidone) may alter the metabolism of acetaminophen and increase its hepatotoxic potential. [141]

Chronic oral acetaminophen at a dosage of 4 g/day has been shown to increase the international normalized ratio in some patients stabilized on warfarin.Ref1

RECOMMENDED MONITORING

Patients should be monitored for total acetaminophen dose, including acetaminophen included in coadministered oral and rectal products.

DOSING

The recommended dosage of IV acetaminophen is 1 g every 6 hours or 650 mg every 4 hours in adults and adolescents weighing 50 kg or more (maximum, 4 g/day). In adults and adolescents weighing less than 50 kg and children 2 to 12 years of age, the recommended dosage is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours (maximum, 75 mg/kg/day). No dosage adjustment is necessary when converting between oral and IV acetaminophen in adults and adolescents. The minimum duration between doses is 4 to 6 hours. It may be administered as a single or repeated dose. [1]

Acetaminophen injection is administered as a 15-minute infusion. The solution can be administered without further dilution. The 1 g doses can be administered by inserting a vented IV set through the septum of the 100 mL vial. For doses less than 1 g, the dose must be withdrawn from the vial and placed into a separate container prior to administration. Small-volume pediatric doses should be placed in a syringe and administered using a syringe pump. [1]

In patients with severe renal impairment, dosing intervals should be lengthened and the total daily dose should be reduced. IV acetaminophen is contraindicated in patients with severe liver impairment or severe active liver disease. Dosage adjustments have not been recommended for elderly patients or patients with liver disease. [15]

The approved labeling does not include dosing for children younger than 2 years of age.Ref1 In other sources, a dose of 15 mg/kg in children weighing at least 10 kg and less than 33 kg (maximum, 2 g/day) and 7.5 mg/kg for full-term newborns, infants, toddlers, and children weighing less than 10 kg (maximum, 30 mg/kg/day) has been recommended.Ref35 Pharmacokinetic studies suggest that dose reductions of 33% in infants 1 month to younger than 2 years of age and 50% in neonates 28 days of age and younger, with a minimum dosing interval of 6 hours, will produce exposure similar to that observed in children 2 years of age and older. [1]

PRODUCT AVAILABILITY AND STORAGE

Acetaminophen has been available in the United States since 1955. IV acetaminophen (Perfalgan, Bristol-Myers Squibb) has been marketed in Europe since 2002, and approximately 90 million vials of IV acetaminophen were sold in Europe in 2008. IV acetaminophen is available in approximately 80 countries. Cadence Pharmaceuticals in-licensed rights to the Bristol-Myers Squibb product in the United States and Canada, and received Food and Drug Administration approval on November 2, 2010. [3442]

Ofirmev is available as a preservative-free injection for IV infusion supplied in 100 mL single-use glass vials containing acetaminophen 1,000 mg (10 mg/mL). It should be stored at 20° to 25°C (68° to 77°F).Ref1 Each 100 mL contains acetaminophen 1,000 mg; mannitol 3,850 mg; cysteine hydrochloride, monohydrate 25 mg; and dibasic sodium phosphate, anhydrous 10.4 mg. The pH is adjusted with hydrochloric acid and/or sodium hydroxide. [1]

COST:

TABLE 3:COSTS OF VARIOUS ACETAMINPOPHEN FORMULATIONS	
IV Acetaminophen (Ofirmev) 1000 mg	$36.94
PO Acetaminophen (Tylenol) 500 mg tablet	$0.02
PO Acetaminophen liquid 650 mg/20 ml unit dose	$1.51
PR Acetaminophen 650 mg	$0.33

PURCHASES:

During July 2017-June 2018, there were 2238 cases of IV acetaminophen purchased by Trinity Health for $1,821,706.

CONCLUSIONS/RECOMMENDATION:

It was determined that IV acetaminophen (Ofirmev) was non-formulary in May 2014 at Trinity Health Pharmacy and Therapeutics Committee. Since removal from formulary, there has been extensive use of "non-formulary" IV acetaminophen. Additionally, there has been extensive studies published in the literature evaluating impact of IV acetaminophen. Further, there is currently pressure to reduce the utilization of opioids that are used for patients.

Guidelines on the Management of Postoperative Pain Management of Postoperative Pain recommends that " that clinicians provide adults and children with acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)". Further stated that "research indicates no clear differences between IV versus oral administration of acetaminophen or NSAIDs in reducing postoperative pain, although onset of action might be faster with IV administration. Further studies evaluating IV acetaminophen to an active comparator did not demonstrate a clinical advantage for pain scores, although onset of action might be faster with i.v. administration."

Studies comparing IV acetaminophen to placebo demonstrated some small advantages in pain management and decreasing opioids. That impact seemed to be diminished when IV acetaminophen was included as part of a multimodal pain management strategy.

Studies comparing IV acetaminophen to an active comparator (including PO and PR acetaminophen) did not demonstrate an advantage for IV acetaminophen related to pain management, opioid use, patient satisfaction, length of stay, or diminishing adverse effects related to opioids.

Without a significant difference in outcomes, use of either oral or IV acetaminophen should be based on other patient and cost factors.

Recommendations:

- Maintain non-formulary status for IV acetaminophen (Ofirmev)
- Establish IV acetaminophen (Ofirmev) as non-formulary, not available
- For perioperative analgesia, the recommendation is to give acetaminophen PO prior to surgery.
- For pain management outside of PACU, the recommendation is to give acetaminophen as part of a multimodal pain management approach using either PO tablets or liquid or PR dosage forms.
- If a clinician identifies new clinical evidence (e.g. new trials) or clinical evidence that was not evaluated in the monograph that demonstrates significant safety or clinical advantage of the IV acetaminophen (Ofirmev), the clinician should submit the request in addition to the clinical evidence providing the significant safety or significant clinical advantage for formulary re-review, the P&T steering committee (in collaboration with expert panels) could determine to recommend a re-evaluation of the decision of the P&T committee.

* (11-17) Meperidine is not used for pain in Trinity Health. Based on the availability of safer alternatives for most indications, recommend restricting meperidine to indications that there are not alternatives available.

1. Meperidine oral tablets will be designated as *non-formulary*.
2. Meperidine for injection will be designated as *formulary with restrictions:*
    a. to prevent and treat drug induced or blood product induced rigors
    b. treatment of postoperative shivering
    c. Treatment for targeted temperature management-related shivering

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Appendix A: Bariatric Surgery

Attached are several published articles that support the successful use of oral acetaminophen as part of an ERAS protocol for bariatric surgery.

There was a concern about absorption of oral APAP after bariatric surgery, there is a PK study in this population that states that its absorption is not affected by the surgery.

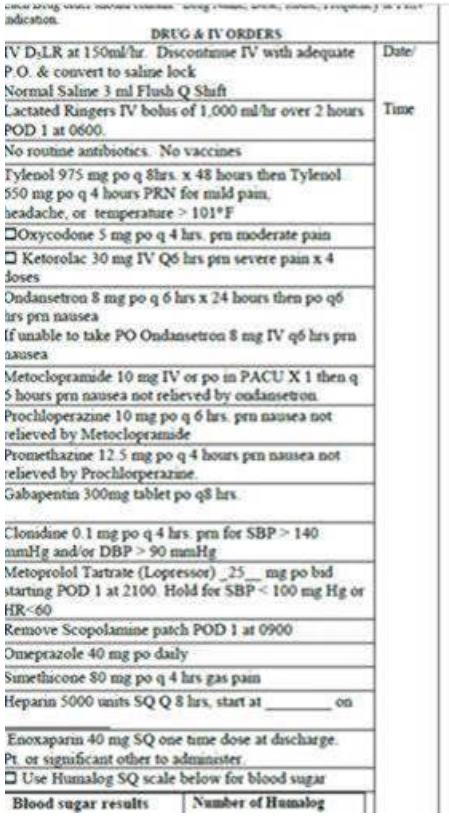
Table 2 Controlled comparisons

Study	Type of surgery	Mean preop wt (kg)	Mean time since operation (mo)	Design (*n*)	Drug and dose	Evidence favours decreased drug absorption?	Outcome and findings (SD)
Analgesics							
Andreasen *et al.* (13)	JIB	133	35	Surgical cases (17) Normal weight controls (11)	Phenazone 15 mg kg^{-1} single dose as oral solution	No	Urinary excretion of phenazone (mg 24 h^{-1}): Cases 24.6 (8.4); controls 20.7 (14.1); difference 3.9; 95% CI −4.8 to 12.6; $P = 0.37$ Urinary excretion of 4-hydroxyphenazone (mg 24 h^{-1}): Cases 299 (243); controls 228 (186); difference 371; 95% CI −106 to 248; $P = 0.42$
Terry *et al.* (41)	JIB	132	3	Pre-post surgery (3)	Acetaminophen 1.5 g single oral dose	No	Serum AUC (μg mL^{-1}·h): Pre 43.0 (7.0); post 43.0 (14.9); difference 0; 95% CI −26 to 26; $P = 1.0$*

Livonia – a center of excellence for bariatric surgery: The one consistent process is that they administer acetaminophen elixir 975 mg preop.

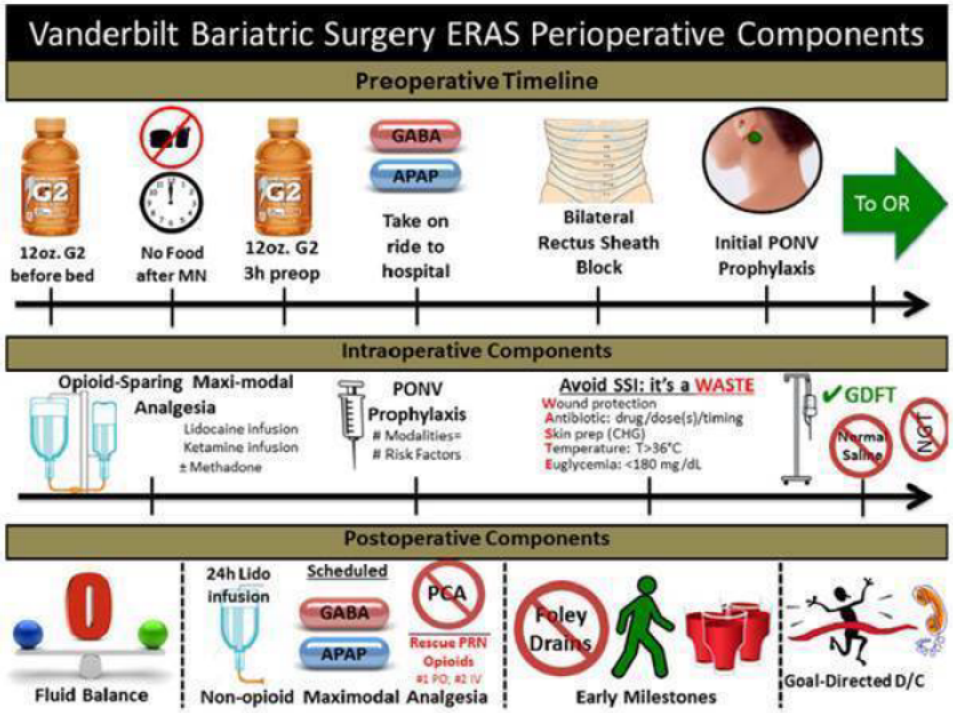
Post-op I will see them use acetaminophen elixir as scheduled, as PRN, or use acetaminophen suppository. This practice is less standardized [between our site physicians]

St Joseph Syracuse – a center of excellence for bariatric surgery



indication.	
DRUG & IV ORDERS	
IV D_5LR at 150ml/hr. Discontinue IV wyth adequate P.O. & convert to saline lock Normal Saline 3 ml Flush Q Shift	Date/
Lactated Ringers IV bolus of 1,000 ml/hr over 2 hours POD 1 at 0600.	Time
No routine antibiotics. No vaccines	
Tylenol 975 mg po q 8hrs. x 48 hours then Tylenol 550 mg po q 4 hours PRN for mild pain, headache, or temperature > 101°F	
☐Oxycodone 5 mg po q 4 hrs. prn moderate pain	
☐ Ketorolac 30 mg IV Q6 hrs prn severe pain x 4 doses	
Ondansetron 8 mg po q 6 hrs x 24 hours then po q6 hrs prn nausea If unable to take PO Ondansetron 8 mg IV q6 hrs prn nausea	
Metoclopramide 10 mg IV or po in PACU X 1 then q 8 hours prn nausea not relieved by ondansetron.	
Prochloperazine 10 mg po q 6 hrs. prn nausea not relieved by Metoclopramide	
Promethazine 12.5 mg po q 4 hours prn nausea not relieved by Prochlorperazine.	
Gabapentin 300mg tablet po q8 hrs.	
Clonidine 0.1 mg po q 4 hrs. prn for SBP > 140 mmHg and/or DBP > 90 mmHg	
Metoprolol Tartrate (Lopressor) _25__ mg po bid starting POD 1 at 2100. Hold for SBP < 100 mg Hg or HR<60	
Remove Scopolamine patch POD 1 at 0900	
Omeprazole 40 mg po daily	
Sumethicone 80 mg po q 4 hrs gas pain	
Heparin 5000 units SQ Q 8 hrs, start at _____ on	
Enoxaparin 40 mg SQ one time dose at discharge. Pt. or significant other to administer.	
☐ Use Humalog SQ scale below for blood sugar	
Blood sugar results	**Number of Humalog**

Vanderbilt – a center of excellence for baratric surgery uses the following protocol (see published trial attached)



Also, I took a look at the studies sent (no active comparator for retrospective or placebo controlled for prospective) and broke down the outcomes, similar to the table that was completed in the monograph.

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
Wang **N=96** **IV APAP + Opiates versus Opiates alone (at least 4 doses)** **Retrospective chart review study**	IV morphine (2 mg or 4 mg every four hours) or IV hydromorphone (1 mg	No difference After opioid treatment, patients in both groups had a median	The median OME was significantly greater among the patients who received IV acetaminophen	Both groups had a median LOS of two days ($P = 0.704$),		

Bariatric surgery	or 2 mg every three hours), plus ketorolac (30 mg IV every six hours) as needed. Once patients tolerated oral medications, oxycodone tablets were started.	pain score of 3 (P = 0.173), and in both groups the median change in the pain score was 4 (P = 0.162)	(1 g) with opioids than among those who received opioids alone (93.5 mg [IQR, 51.5–121.5] versus 63.0 mg [IQR, 36–90], respectively; P = 0.017).			
Chaar **IV apap versus placebo** **Randomized, DB, PC study** **N=100** Patients underwent laparoscopic Roux-en-Y gastric bypass (LRYGB) or laparoscopic sleeve gastrectomy (SG). Conflict of Interest Dr. El Chaar, Dr. Stoltzfus, and Ms. Wasylik received study funding from Cadence Pharmaceuticals (now a part of Mallinckrodt Pharmaceuticals), including fees for Principal Investigator costs (Dr. El Chaar), statistician services (Dr. Stoltzfus), and research coordinator services (Ms. Wasylik).	Group 1 (treatment) received IV acetaminophen plus IV narcotics 30 min before surgery, then medication plus IV narcotics/PO narcotics for the remaining 18 h. Group 2 (control) received IV normal saline plus IV/PO narcotics.	pain scores were not significantly different between groups (p > 0.05), indicating that the IV acetaminophen group's pain scores did not differ from the normal saline's pain scores across the entire range of time points from 2–22 h.	there were no statistically significant differences in dosage amounts for either treatment group or surgery type.	no statistically significant association between treatment group (IV acetaminophen versus normal saline) and length of stay (p> 0.05) after adjusting for type of surgery (LRYGB or SG).	There were no statistically significant differences in the distribution of pain scores based on treatment group (IVacetaminophen versus normal saline)	**No difference in readmissions 30 days, 30 day reoperation, 30 day mortality or 30 day ER visits** **Less ER visits with reported abdominal pain in IV apap group**

Gonzalez **REtrospecitve study** **N=92** **Bariatric surgery patients** Anthony Michael Gonzalez report payment for lectures as a speaker bureau for Cadence Pharmaceuticals Inc and also as speaker and proctor for Intuitive Surgical Inc.	patients who received IVA, and group B, which included 50 patients and did not receive IVA.	**Not assessed**	Those that received IVA (group A) had a mean 24-h total opioid dose of 99.5 mg, whereas those that did not receive IVA (group B) had a mean 24-h total opioid dose of 164.6 mg.	**Not assessed**	**Not assessed**	**Not assessed**
Lange **N=89** **IV apap versus placebo** prospective, double-blind, randomized controlled trial laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery This study was funded by Mallinckrodt Pharmaceuticals, Inc., the distributor of Ofirmev (IV acetaminophen).		The difference was not statistically significant (p = 0.29).	total narcotic use was similar between the two groups (p = 0.64).	The LOS ranged from 2 to 7 days with a median of 3 (variance = 1.5) days in the control group and a median LOS of 3 days (variance =0.39) in the treatment group with a range of 2–4 days. The Median Test for two Independent Samples showed a significant difference (p = 0.035) with the distribution of the treatment group being significantly fewer days than control	return of bowel function with an average time of 1.87 days versus 2.24 days in the control group (p = 0.04)44	**No statistics reported**

Appendix B: Acetaminophen and Colorectal Surgery

Situation

Reducing opioids and their adverse effects is a goal for colorectal, and all, surgery patients. The role of IV acetaminophen in achieving this goal should be examined.

Background

Objective:

Evaluate the role of IV acetaminophen (Ofirmev) as an opiate sparing medication identifying clinical trials comparing IV acetaminophen to an active comparator.

Methods:

A comprehensive review of all available evidence was performed for patients undergoing abdominal surgery. The methodology used for this review is listed below.

Guiding Principles - Gathering the Evidence and Structuring the Information

- Question: Is there a demonstrated efficacy benefit of IV acetaminophen over comparators (oral or rectal) acetaminophen for relieving pain, reducing opiate consumption, and decreasing opiate related adverse events?
- Multiple sources were used to identify studies – PubMed, guidelines, Meta-analysis and Systematic Reviews of articles, Google scholar
- What type of studies were included and why?
    - Active comparator studies
    - Evaluating role of these medications for as an opiate sparing medication
    - From FDA consultant: If you are going to talk about opiate-sparring, you are not going to want to compare that to the placebo," Gregory Terman, MD, PhD, professor, department of anesthesiology and pain medicine at the University of Washington and temporary voting member of the committee, said. "I am not sure too many people would think placebo causes a lot of opiate-sparring. There you really do need an active comparator and the fact that, despite recommendations for active comparators, that has not been what the sponsor has done except with investigator-initiated studies. I am not sure that opioid-sparring was the plan at all."
    -

Assessment

Practice guideline Recommendations

1. **The American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) Joint Consensus Statement on Optimal Analgesia within an Enhanced Recovery Pathway for Colorectal Surgery: Part 1—from the preoperative period to PACU 2017; doi: 10.1186/s13741-017-0064-5**

    Oral analgesia

"Major non-opioid oral analgesic agents include non-steroidal anti-inflammatory agents (NSAIDs), acetaminophen (paracetamol), gabapentinoids (gabapentin and pregabalin), and tramadol. All except oral tramadol have been examined within the setting of intra-abdominal surgery and have been found to have significant effect on reducing the opioid burden postoperatively. As such, routine, scheduled use of these agents should be considered as part of a plan to achieve optimal analgesia after colorectal surgery."

Acetaminophen

"Most studies including pharmacokinetic outcomes reported higher postoperative plasma concentrations

and larger proportions of patients achieving target plasma concentrations after IV dosing compared

with oral dosing (Jibril et al. 2015). However, for patients who can take oral medications preoperatively, *there does not appear to be evidence of a clear benefit of the intravenous formulation*. Decision making should take into account of convenience and cost (Jibril et al. 2015)."

American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) Joint Consensus Statement on Optimal Analgesia within an Enhanced Recovery Pathway for Colorectal Surgery: Part 2—From PACU to the Transition Home; doi: 10.1186/s13741-017-0064-5

Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

"Acetaminophen and NSAIDs have been reported as the backbone of multimodal analgesia in the postoperative period of ERPs. There is evidence that they can reduce the need for opioids by 15–50% (Elia et al. 2005; Jibril et al. 2015; O'Neal 2013; Smith 2011; Toms et al. 2008). It is reasonable, barring any contraindications, to provide scheduled *oral or IV doses of acetaminophen* and NSAIDs in the postoperative period."

2. **Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery From the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons 2017;** DOI: 10.1097/DCR.0000000000000883

B. Pain Control

"A multimodal, opioid-sparing, pain management plan should be used and implemented before the induction of anesthesia. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B

Multiple prospective studies have demonstrated that minimizing opioids is associated with earlier return of bowel function and shorter length of stay. *One of the simplest techniques to limit opioid intake is to schedule narcotic alternatives, such as oral acetaminophen,* nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentin, rather than giving them on an as-needed basis. The scheduled use of nonselective or selective NSAIDs (and cyclooxygenase 2

inhibitors), when not contraindicated, and of *acetaminophen (by mouth or intravenously)* have been shown to improve postoperative analgesia and reduce systemic opioid consumption and some of their dose-dependent adverse effects that have been shown to delay surgical recovery"

3. **Guidelines on the Management of Postoperative Pain Management of Postoperative Pain 2016** http://dx.doi.org/10.1016/j.jpain.2015.12.008

Recommendation 15
"The panel recommends that clinicians provide adults and children with acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)…. *Most research indicates no clear differences between i.v. versus oral administration of acetaminophen or NSAIDs in reducing postoperative pain, although onset of action might be faster with i.v. administration."*

Meta-Analyses:

1. **The impact of intravenous acetaminophen on pain after abdominal surgery: a meta-analysis.** https://doi.org/10.1016/j.jss.2018.02.032

Acetaminophen versus other types of medications
"Eight studies included a comparator group of a nonactive placebo. This included 331 patients in the acetaminophen group and 282 patients in the placebo group. *There was no difference in between acetaminophen or nonactive placebo in either 24-h pain scores or 24-h narcotic consumption*….Seven studies included comparator groups of various NSAID involving 178 patients in the acetaminophen group and 207 patients in the NSAID group. There was no difference in 24-h pain scores; however, *24-h narcotic consumption was significantly lower in the NSAID group* compared with the acetaminophen group."

Colorectal Surgery Data

IV acetaminophen v oral acetaminophen or other comparator

There is one large retrospective cohort evaluating the impact of IV compared to oral acetaminophen for colorectal surgeries (chart) which does not support the routine use of intravenous acetaminophen. There are numerous other head to head trials in other types of surgeries (see full monograph) that consistently identify no difference between IV acetaminophen and PO acetaminophen in regards to pain levels, amount of opioids administered to patients, length of stay, or other complications (ie.nausea, vomiting, constipation, falls).

STUDY	INTERVENTION	PAIN	OPIOID USE	LOS	FUNCTION	COMPLICATIONS
Colorectal Surgery						

Wasserman N= 181, 640 Retrospective Cohort Of colectomy patients at 602 hospitals 25.1% of patients received IV acetaminophen DOI: 10.1097/ALN.0000000000002227	Comparison of route (oral v IV) of acetaminophen and number of doses at 3 intervals: day of surgery (DOS), POD 1, and POD 2 and later. A clinically significant reduction in opioid use was prespecified as a minimum reduction of 25%.	N/A	• No clinically significant difference in MME for any group • Most (48%) of IV patients received only one dose on DOS; Median MME 543 IV v 563 PO • >1 IV dose on DOS: MME (-8%) 499 IV v (-8.7%) 445 PO • POD 1: 2 or more doses reduced MME by 12.4 and 22.4% (IV and PO, respectively)	Not a primary or secondary outcome: Unadjusted LOS not different; Lower with IV adjusted for covariates	N/A	Opioid related adverse effects were comparable

Oral acetaminophen is a demonstrated effective part of a comprehensive colorectal ERAS protocol in the literature

A selection of successful published colorectal ERAS protocols using oral acetaminophen:

- **Outcomes after implementation of a multimodal standard care pathway for laparoscopic colorectal surgery (Mayo Protocol)** *BJS* 2014; **101**: 1023–1030 **https://doi.org/10.1002/bjs.9534**
- **Enhanced recovery after surgery in colorectal surgery: Impact of protocol adherence on patient outcomes** Journal of Clinical Anesthesia, 2019-08-01, Volume 55, Pages 7-12 https://doi.org/10.1016/j.jclinane.2018.12.034
- **Enhanced Recovery After Surgery (ERAS) Eliminates Racial Disparities in Postoperative Length of Stay After Colorectal Surgery** Ann Surg. 2018 Dec;268(6):1026-1035 DOI: 10.1097/SLA.0000000000002307
- **Implementation of an enhanced recovery protocol in pediatric colorectal surgery** Journal of Pediatric Surgery 53 (2018) 688–692 http://dx.doi.org/10.1016/j.jpedsurg.2017.05.004

IV acetaminophen v placebo *(trials not included in monograph due to lack of comparator)*

1. Aryaie AH, Lalezari S, Sergent WK, et al. Decreased opioid consumption and enhance recovery with the addition of IV Acetaminophen in colorectal patients: a prospective, multi-institutional, randomized, double-blinded, placebo-controlled study (DOCIVA study). Surg Endosc. 2018;1(0930-2794):1-7. Result: Opioid consumption 41% lower, LOS 1.5 days reduced, Ileus 22% to 2%
   - Patients randomized to receive either IV acetaminophen or placebo in addition to opioid PCA. No active comparator was used.
   - During this entire study, an enhanced recovery pathway was not yet adopted; therefore the trial does not assess whether IV acetaminophen provides benefit in hospitals with ERAS protocols or compared to oral use.

Trials comparing multiple interventions including IV acetaminophen *(ERAS Protocols with IV acetaminophen compared to historical protocols, not included in monograph)*

1. Brandal D, Keller MS, Lee C, et al. Impact of Enhanced Recovery after Surgery and Opioid-Free Anesthesia on Opioid Prescriptions at Discharge from the Hospital: A Historical-Prospective Study. *Anesth Analg*. 2017;125(5):1784-1792.Colorectal surgery . **Result: Postop PCA was reduced 21% to 1%**
   - **Multiple interventions were used as part of the ERAS protocol including use of neuroaxial analgesia (77% pre-ERAS v 92% post-ERAS) , ketamine (9% v 57%) , and preoperative celecoxib (0% v 40%) were implemented**
   - IV acetaminophen given to the majority of both groups (IV acetaminophen use was 72% pre-ERAS and 87% post-ERAS)

2. Omar SH, Radwan KG, Youssif MA, et al. A non opioid fast track anesthetic regimen for colonic resection. J Egypt Soc Parasitol. 2009;39(3):849-64.Colorectal Results: IV ACETAMINOPHEN with epidural - Less N/V, Less morphine, LOS 1 day less
   - **The intervention group received many new interventions versus control including combined light general anesthesia and epidural techniques as well as IV acetaminophen and IV ketorolac**

3. Beck DE, Margolin DA, Babin SF, Russo CT. Original research benefits of a multimodal regimen for postsurgical pain management in colorectal surgery. *Ochsner Journal*. 2015;15(4):408-412. Result: LOS 2 days less, less opioids
   - Patients in the intervention group received both tap blocks and IV **acetaminophen**

4. Keller DS, Stulberg JJ, Lawrence JK, Delaney CP. Process control to measure process improvement in colorectal surgery: modifications to an established enhanced recovery pathway. *Dis Colon Rectum*. 2014;57(2):194-200. Result: Lower LOS, cost same, but margin improved, fewer complications
   - **Patients in the intervention group received both TAP block and IV acetaminophen**

5. Thiele RH, Rea KM, Turrentine FE, et al. Standardization of care: impact of an enhanced recovery protocol on length of stay, complications, and direct costs after colorectal surgery. *J Am Coll Surg*. 2015;220(4):430-43. Results: Combined epidural and IV acetaminophen reduced opioids, pain and LOS
   - **Patients in the intervention group received both TAP block and an epidural**

6. Zafar N, Davies R, Greenslade GL, Dixon AR. The evolution of analgesia in an "accelerated" recovery programme for resectional laparoscopic colorectal surgery with anastomosis. *Colorectal Dis*. 2010;12(2):119-
   - **Patients in the intervention group received m**ultiple interventions including change in anesthesia, use of TAP blocks, pre-op oral IBU, lidocaine, celecoxib and gabapentin – postop IV acetaminophen

Summary and Conclusion:

There is no data demonstrating an efficacy benefit of IV acetaminophen over comparators (oral or rectal) acetaminophen for relieving pain, reducing opiate consumption, and decreasing opiate related adverse events for colorectal surgery patients. Studies comparing IV acetaminophen to placebo demonstrated some small advantages in pain management and decreasing opioids. That impact was diminished when IV acetaminophen was included as part of a multimodal pain management strategy.

Practice guidelines from several surgical and pain professional societies do not recommend the use of IV acetaminophen over oral for colorectal ERAS protocols. There are numerous published colorectal surgery ERAS protocols that administer oral acetaminophen and demonstrate reduced opioid consumption and length of stay.

There is no demonstrated benefit of IV acetaminophen compared to oral or rectal acetaminophen for relieving pain, reducing opiate consumption, and decreasing opiate related adverse events for colorectal surgery patients.