Improved Outcomes Associated With the Use of Intravenous Acetaminophen for Management of Acute Post-Surgical Pain in Cesarean Sections and Hysterectomies

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Abstract

Background: Post-surgical pain impacts many patient outcomes. Effective pain management increasingly relies on multimodal analgesia regimens in which acetaminophen (APAP) is a key component. The aim of our study was to examine the impact of oral APAP versus intravenous (IV) APAP as a component of post-surgical pain management after Cesarean sections and hysterectomies.

Methods: A retrospective analysis of the Cerner HealthFacts® database (from January, 2011 to December, 2015) was conducted to compare outcomes of Cesarean section and hysterectomy surgery patients who received oral APAP to those who received IV APAP post-surgically. Length of stay (LOS), daily morphine milligram equivalent (MME) consumption, the presence of potential opioid-related adverse events (ORADEs), and total pharmacy costs were assessed. Adjusted results were derived using inverse probability weighted regression adjustment (IPW-RA) estimators based on covariates that included demographics, comorbidities, patient clinical characteristics, and hospital characteristics.

Results: The study identified 29,124 Cesarean section patients (24,612 oral APAP; 4,512 IV APAP) and 9,767 hysterectomy surgery patients (5,586 oral APAP; 4,181 IV APAP). Compared to the oral APAP group, the IV APAP group had reductions in adjusted LOS (Cesarean section: -11.7% days (P < 0.001), hysterectomy: -11.8% days (P = 0.005)), lowered adjusted daily MME consumption from day 0 to day 3 (Cesarean section: -1.6 mg (P < 0.001), hysterectomy: -1.7 mg (P = 0.014)), and reduced risk of ORADEs for Cesarean sections (relative risk of 0.45, P < 0.001). Total pharmacy costs were not significantly different between the two APAP groups.

Conclusions: Post-surgical pain managed with IV APAP in patients undergoing Cesarean section or hysterectomy was associated with shorter LOS, reduced risk of ORADEs, and lower opioid consumption compared to patients managed with oral APAP, without adversely impacting total pharmacy costs.

Keywords: IV acetaminophen; Multimodal analgesia; Cesarean section; Hysterectomy; Opioid; Post-surgical pain; Acute pain; Health outcomes

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Introduction

Post-surgical pain management is the key to successful surgical recovery [1]. Acute pain impacts short-term and long-term post-surgical outcomes since inadequate pain management can result in extended hospital length of stay (LOS) and increased risk of developing chronic pain [2, 3]. Population-based studies suggest that women may be more likely to experience chronic pain syndromes, and obstetric and gynecologic surgeries are among the most common surgeries in women [4-6].

The most commonly used analgesics for post-surgical pain are intravenous (IV) and oral opioids. While effective for pain relief, opioids are associated with a variety of costly opioid-related adverse events (ORADEs) [7, 8]. Opioid use can lead to addiction and abuse [9], and the overprescribing of opioids post-surgery is a contributor to the opioid epidemic in the United States [10]. Differences in opioid efficacy have also been reported between women and men [11, 12], and following Cesarean deliveries, additional concerns for postoperative pain management arise. For example, although breastfeeding while receiving opioid medications is generally permitted [13, 14], sedation associated with opioid-based analgesia following Cesarean sections can disrupt breastfeeding, infant care, and mother-infant bonding [15]; while suboptimal pain manage-

ment or increased sedation may impair the mother's ambulation, which increases the risk of thromboembolic disease [16].

New guidelines from the American Pain Society (APS), the American Society of Anesthesiologists (ASA), and the American Society of Regional Anesthesia and Pain Medicine (ASRA), as well as other professional societies, strongly recommend the use of multimodal therapies, incorporating non-opioid analgesics as foundational therapies to treat postoperative pain [17]. The American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), and the Academy of Breastfeeding Medicine (ABM) have specific guidelines and recommendations for breastfeeding mothers that include maximizing the use of multi-modal non-opioid analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (APAP) if feasible and as appropriate [18]. Multimodal analgesia (MMA) regimens can generally reduce the use of opioids and consequent ORADEs [17]. Since most pain is multi-factorial in nature, owing to the physiology of pain transmission, the use of combinations of analgesics with differing mechanisms of action may also have additive or synergistic effects to reduce pain [19-22].

MMA regimens are well-established in guidelines for both Cesarean section and hysterectomy surgeries. In both surgical types, MMA has been associated with reduced hospital LOS and decreased opioid use [23-26]. A plethora of medications are utilized in MMA regimens, including NSAIDs, non-NSAIDs (e.g. APAP) and GABA analogs (gabapentin, pregabalin) [20, 21]. However, NSAIDS may be contra-indicated when certain comorbidities are present [27].

Oral APAP has been widely used for over 50 years. An intravenous (IV) APAP formulation appropriate for post-surgical patients who cannot take oral drugs due to sedation, nausea, vomiting, or slow gastrointestinal (GI) recovery became available in 2010. Use of IV APAP has expanded in several surgery types, including orthopedic and spine surgeries, but the overall impact of IV APAP on post-surgical pain remains relatively unstudied in non-clinical trials, real-world conditions, and especially in obstetric or gynecologic surgeries [2, 28, 29]. The primary objective for this retrospective analysis of electronic health records (EHR) was to evaluate the clinical and administrative outcomes associated with the utilization of oral APAP versus IV APAP in women undergoing a Cesarean section or hysterectomy.

Methods

Study design

This retrospective cohort study was conducted using data from the Cerner HealthFacts® dataset (Cerner HealthFacts®; Kansas City, MO) from January 1, 2011 to December 31, 2015. Cerner HealthFacts® is a large US electronic health database, based on patient records across the United States from over 600 hospitals. Patients receiving oral APAP versus IV APAP (verified through the selected National Drug Codes; NDC) and medication administration route in a post-surgical setting were evaluated. The study was granted an Institutional Review Board exemption from Western IRB.
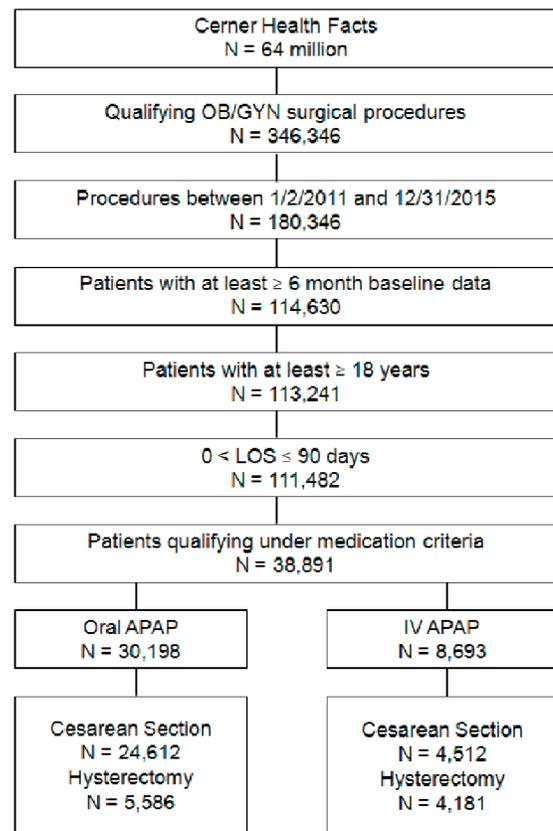

Figure 1. Patient selection in OB/GYN patients treated with oral vs. IV APAP. The study identified 30,198 unique Cesarean section and hysterectomy patients who were treated with oral APAP and 8,693 Cesarean section and hysterectomy patients who were treated with IV APAP. IV: intravenous; APAP: acetaminophen; OB/GYN: obstetrics and gynecology.

Patients and selection

The patient population was selected using International Classification of Diseases (ICD)-9-CM and ICD-10-CM codes for Cesarean section and hysterectomy surgeries (Fig. 1). Inclusion criteria selected adult patients ($\geq$ 18 years) undergoing a qualifying Cesarean or hysterectomy procedure (see Supplementary Table 1, www.jocmr.org), with admission between January 1, 2011 and December 31, 2015, and administration of either oral APAP or IV APAP during the first 24 h post-surgery (day 0) (see medication criteria schematic in Supplementary Figure 1, www.jocmr.org). Oral APAP was defined as tablet or capsule formulations of APAP. Other formulations, such as liquid taken orally or suppositories, were not considered for inclusion. Combination APAP medications (e.g. acetaminophen/dextromethorphan/doxylamine succinate/pseudoephedrine HCl) were not regarded as oral APAP for inclusion purposes. Exclusion criteria included patients with < 6 months of history captured in the database prior to the index visit, missing information for age or gender, and in-hospital LOS > 90 days. The oral APAP and IV APAP cohorts were mutually exclusive. Patients in the oral APAP cohort could not have received IV

Table 1. Demographics and Baseline Characteristics for Cesarean Section Surgery Patients

Variable	IV APAP (N = 4,512)	%	Oral APAP (N= 24,612)	%
Age (mean, SD)	30.9 (6.0)		29.6 (5.9)	
Imputed BMI (mean, SD)	33.3 (6.8)		33.8 (7.0)	
Race				
Caucasian	2,181	48.3%	17,180	69.8%
African American	1,656	36.7%	3,127	12.7%
Asian/other	465	10.3%	3,006	12.2%
Hispanic	54	1.2%	960	3.9%
Missing/unknown	156	3.5%	339	1.4%
Admission source				
Emergency	1,717	38.1%	109	0.4%
Healthcare facility	844	18.7%	137	0.6%
Non-healthcare facility	1,559	34.6%	20,245	82.3%
Other	56	1.2%	2,170	8.8%
Unknown	336	7.5%	1,951	7.9%
Admission type				
Emergency	1,785	39.6%	415	1.79%
Urgent	520	11.5%	3,806	15.5%
Elective	1,980	43.9%	18,430	74.9%
Other	4	0.1%	677	2.8%
Unknown	223	4.9%	1,284	5.2%
Hospital characteristics				
Urban	1,497	33.2%	18,716	76.0%
Teaching hospital (missing 111 patients)	3,793	84.2%	14,651	59.8%
Bed size				
< 200	345	7.7%	7,282	29.6%
200 to 299	618	13.7%	2,991	12.2%
300 to 499	831	18.4%	7,540	30.6%
500+	2,718	60.2%	6,799	27.6%
Census region				
Midwest	490	10.9%	6,977	28.4%
Northeast	2,852	63.2%	8,448	34.3%
South	739	16.4%	5,970	24.3%
West	431	9.6%	3,217	13.1%

A total of 29,124 Cesarean section surgery patients were analyzed. IV: intravenous; APAP: acetaminophen; SD: standard deviation; BMI: body mass index.

APAP on days 0 - 3 and *vice versa*. Patients were excluded if they had received either oral or IV APAP on day 4 or after (see medication criteria schematic in Supplementary Figure 1, www.jocmr.org).

Patient characteristics

Baseline characteristics (e.g. age, gender, race, year of admission) and chronic comorbidities (based on the definitions of Elixhauser) at index admission and study outcomes were collected [30]. The Elixhauser comorbidities were calculated using the approach from Healthcare Cost and Utilization Project (HCUP), Elixhauser Comorbidity Software, Version 3.7 [30]. Hospital characteristics (e.g. bed size, urban/rural status, census region) at index admission and payer type were collected as reported. Additional information about procedure type for hysterectomies were incorporated into analytical models as open, laparoscopic, total vaginal hysterectomy, and total abdominal hysterectomy.

Study outcomes

Study outcomes included length of hospital stay, presence of ORADEs, total daily opioid consumption (i.e. morphine (mg) equivalent; MME) and total pharmacy cost. Opioid consumption was calculated using the amounts administered to the patient, while taking into account any doses that were returned to the hospital pharmacy unused. The conversion to MME was performed as previously described [31, 32]. For outpatients, total, per patient, pharmacy cost was calculated by summing unit costs for all medications that were dispensed (unit cost represent cost per medication package), and for inpatients, it was calculated by summing unit cost of the medication multiplied by the number of medication units that were charged to the pharmacy (unit cost represents cost per unit). Missing body mass index (BMI) values were imputed with a univariate imputation sampling method from a regression model of known covariates [33]. To minimize the effect of outliers, total pharmacy costs were Winsorized at the 2.5% level, which means that values above the 97.5th percentile were set to the 97.5th percentile value and values below the 2.5th percentile were set to the 2.5th percentile value. Total morphine equivalent dosing had the following constraints to be deemed valid: No 4-day total from Day 0 to Day 3 could exceed 800 mg MME and each day after Day 0 could have no more than 200 mg MME.

Statistical analysis

The Cesarean and hysterectomy patients were analyzed separately using multivariable methods. The primary method to estimate the impact of IV APAP on the study outcomes (e.g. hospital LOS) was inverse probability weighted regression adjustment (IPW-RA) with covariates that included patient demographics, comorbidities, patient admission type (e.g. emergency admission), relevant surgical characteristics (e.g. a laparoscopic hysterectomy), and prior drug history up to the day of surgery [34, 35]. See Supplementary Tables 2, 3 (www.jocmr.org) for all variables used for multivariable adjustment. Hospital characteristics (e.g. the number of beds, teaching status, geographic location) were also used for adjustment.

As a sensitivity analysis, generalized linear models (GLM) estimated the effect of IV APAP on the outcomes and were used with the same covariates that were used to estimate the propensities in the IPW-RA model. For continuous outcomes (e.g. LOS) a logarithmic link and a gamma distribution were used in the regression models. When the outcomes were binary, logistic regression models were utilized. Odds ratios (ORs) were converted to risk ratios (relative risks (RRs)) [36]. All GLM models used robust, Huber-White standard error estimators, clustered at the hospital level to account for potential serial correlation of patient outcomes among patients treated in the same hospital.

Results

We identified 38,891 patients, with 9,767 (25.1%) undergoing hysterectomies and 29,124 (74.9%) patients undergoing Cesar-

ean section surgery (Tables 1, 2). Overall, 8,693 (22.4%) of all Cesarean section and hysterectomy surgical patients received IV APAP (Tables 1, 2). However, the proportion varied by surgical type, with 15.5% of the Cesarean patients and 42.8% of hysterectomy patients receiving IV APAP (P < 0.001).

Mean ages within surgical categories were similar between the oral and IV APAP groups (Cesarean mean age = 29.6 vs. 30.9 years; hysterectomy mean age = 47.1 vs. 47.4 years) (Tables 1, 2). The majority of hysterectomy patients (90.5% of oral APAP and 64.3% of IV APAP) were treated at urban facilities. In contrast, 76.0% of Cesarean section patients in the oral APAP cohorts were treated at urban facilities and only 33.2% of the IV APAP cohorts were treated at urban facilities. Regardless of procedure type (Cesarean section or hysterectomy) or APAP cohort (oral or IV), the majority of patients were treated at teaching hospitals, with a greater percentage of IV APAP cohorts treated at a teaching hospital versus the oral APAP cohorts.

Adjusted results (see (Supplementary Table 4, www.jocmr. org) for unadjusted outcomes) were derived using IPW-RA estimators based on covariates that included demographics, comorbidities, patient clinical characteristics, and hospital characteristics. In the IPW-RA analyses (Table 3), Cesarean section patients receiving IV APAP (versus oral APAP) showed an 11.7% shorter LOS. In the IV APAP cohort, the total (marginal) mean adjusted LOS was 3.40 days (95% CI 3.29, 3.51) for IV APAP versus 3.85 days (95% CI 3.60, 4.10) for oral APAP. This 0.45 day shorter LOS for IV APAP patients (95% CI -0.72, -0.17) was statistically significant (P < 0.001). Similarly, in patients undergoing hysterectomies, IV APAP was associated with an 11.8% shorter LOS, with a total adjusted 2.01 days (95% CI 1.89, 2.13) for IV APAP versus LOS of 2.28 days (95% CI 1.14, 2.43) for oral APAP. This 0.27 day shorter LOS for IV APAP patients (95% CI -0.46, -0.08) was also statistically significant (P < 0.001). The results in the GLM sensitivity analyses (Table 3) showed similar reductions in LOS associated with the receipt of IV APAP.

Total MME consumption per day observed from Day 0 to Day 3 was statistically significantly lower for IV APAP patients in both Cesarean section and hysterectomy surgeries (-1.6 mg; 95% CI -2.5, -0.8; P < 0.001 for Cesarean section and -1.7 mg; 95% CI -3.1, -0.3; P < 0.014 for hysterectomy) (Table 3). However, these differences in total MME consumption per day were not significantly different by APAP route in the GLM sensitivity analysis for either surgery type.

IV APAP was associated with fewer potential ORADEs [37] than oral APAP in Cesarean section surgeries (relative risk = 0.45; 95% CI 0.26, 0.78; P < 0.001). However, there was no significant association between the route of APAP administration and the adjusted risk of potential ORADEs in hysterectomy surgeries (relative risk = 1.09; 95% CI 0.77, 1.41; P = 0.57). The findings in the GLM sensitivity analyses were also concordant, with significant risk reduction for Cesarean section, and no significant association for hysterectomy.

IV APAP and oral APAP showed no significant difference in pharmacy costs for hysterectomy patients. The IPW-RA model did not converge for Cesarean section patients, possibly due to some predictors being uncommon but correlated with both treatment and costs. Moreover, total pharmacy costs were not significantly different for IV APAP and oral APAP in either surgery in the GLM sensitivity analysis. We also examined

Table 2. Demographics and Baseline Characteristics for Hysterectomy Surgery Patients

Variable	IV APAP (N = 4,181)	%	Oral APAP (N = 5,586)	%
Age (mean, SD)	47.4 (12.0)		47.1 (11.5)	
Imputed BMI (mean, SD)	30.9 (7.7)		30.8 (7.4)	
Race				
Caucasian	2,833	67.8%	4,013	71.8%
African American	1,009	24.1%	1,069	19.1%
Asian/other	265	6.3%	369	6.6%
Hispanic	18	0.4%	79	1.4%
Missing/unknown	56	1.3%	56	1.0%
Admission source				
Emergency	31	0.7%	11	0.2%
Healthcare facility	10	0.2%	10	0.2%
Non-healthcare facility	3,448	82.5%	4,939	88.4%
Other	141	3.4%	95	1.7%
Unknown	246	5.9%	531	9.5%
Admission type				
Emergency	165	4.0%	136	2.4%
Urgent	56	1.3%	149	2.7%
Elective	3,833	91.7%	5,213	93.3%
Other	85	2.0%	2	0.1%
Unknown	42	1.0%	86	1.5%
Hospital characteristics				
Urban	2,690	64.3%	5,056	90.5%
Teaching hospital (22 patients missing)	2,962	71.2%	3,317	59.4%
Bed size				
< 200	848	20.3%	1,389	24.9%
200 to 299	763	18.3%	1,120	20.1%
300 to 499	1,533	36.7%	1,539	27.6%
500+	1,037	24.8%	1,538	27.5%
Census region				
Midwest	957	22.9%	1,298	23.2%
Northeast	1,046	25.0%	2,047	36.7%
South	1,507	36.0%	1,668	29.9%
West	671	16.1%	573	10.3%

A total of 9,767 hysterectomy surgery patients were analyzed. IV: intravenous; APAP: acetaminophen; SD: standard deviation; BMI: body mass index.

other known cost drivers, including 90-day readmissions, ICU admissions and mortality. ICU admissions showed no significant differences between IV APAP and oral APAP use in both surgery types and the other outcomes were too rare to model reliably in these populations (data not reported).

Discussion

Using a large, multi-center, retrospective database, we dem-onstrated that IV APAP use is associated with significantly shorter LOS (by approximately 12%) in Cesarean section and hysterectomy patients when compared to oral APAP. This analysis is one of the first to assess the clinical outcomes and costs of oral APAP versus IV APAP from EHRs, from a robust database of over 600 hospitals and over 62 million patients. Our study focused on Cesarean sections and hysterectomies, where reductions in LOS may be most impactful for hospital costs and resources, given that these patients generally have consistent LOS, with less variation when compared to other surgeries

Table 3. Multivariable Results for Cesarean Sections and Hysterectomies

Outcome	IPW-RA modeling results			GLM results		
	Sample size	Effect estimate/difference with 95% CI from the IPW-RA method	P value	N	GLM model summary	P value
Cesarean sections						
Length of stay	28,910	-0.45 days (-0.72, -0.17)	< 0.001	28,998	-0.51 days (-0.82, -0.19)	0.003
Total morphine consumption (MME) per day; Day 0 to Day 3	28,904	-1.6 mg (-2.5, -0.8)	< 0.001	28,992	-0.1 mg (-1.7, 1.5)	0.909
Total pharmacy costs (Winsorized at 2.5%) (USD)	N/D	N/D	N/D	27,552	-13 (-643, 617)	0.969
Opioid related adverse events (ORADEs)	28,910	RR = 0.45 (0.26, 0.78)	< 0.001	28,998	RR = 0.38 (0.16, 0.90)	0.027
Hysterectomies						
Length of stay	9,697	-0.27 days (-0.46, -0.08)	0.005	9,711	-0.28 days (-0.53, -0.04)	0.003
Total morphine consumption (MME) per day; Day 0 to Day 3	9,686	-1.7 mg (-3.1, -0.3)	0.014	9,700	-1.0 mg (-3.9, 1.9)	0.511
Total pharmacy costs (Winsorized at 2.5%) (USD)	9,204	-107 (-382, 167)	0.444	9,218	-189 (-828, 449)	0.562
Opioid related adverse events (ORADEs)	9,697	RR = 1.09 (0.77, 1.41)	0.565	9,711	RR = 1.39 (0.95, 2.05)	0.090

Results are provided as value (95% CI). RR: relative risk; N/D: not determined due to lack of convergence; GLM: generalized linear model; IPW-RA: inverse-probability-weighted regression adjustment. Sample sizes in the IPW-RA method are smaller than the GLM/logistic regression models by a small amount because patients with extreme propensities are dropped from the analysis as per convention; the IPW-RA method was unable to derive an estimate for Total pharmacy costs in Cesarean sections

requiring hospitalization. Additionally, research indicates that pain management may differ by gender [5], but the potential for confounding by sex is eliminated by focusing on Cesarean sections and hysterectomies.

A previous claims-based study of Cesarean section and hysterectomy surgeries showed significantly less daily opioid use and lower hospitalization costs in patients receiving IV APAP as part of MMA versus patients receiving IV opioid-only analgesia in Cesarean section and a non-significant trend towards less opioid use and lower cost in hysterectomy; however, the claims-based analysis did not show reductions in LOS in the IV APAP cohort following adjustment [24]. The current study demonstrates statistically significant reductions in LOS and opioid consumption for both Cesarean section and hysterectomy patients. The LOS reductions approached 12%, translating to a reduction of approximately 8 to 12 h, or potentially one nursing shift per day. In the Cesarean group, IV APAP patients also had lower risk of developing an ORADE. There were no statistically significant differences in total pharmacy costs between oral APAP and IV APAP, despite cost differences between these formulations.

These findings are consistent with prior studies of MMA protocols including IV APAP, demonstrating a reduced LOS in orthopedic and spine surgery patients [38, 39]. Retrospective studies in orthopedic and other surgery types have found similar associations [24, 40-42]. MMA is thought to improve surgical outcomes by reducing opioid dosing, resulting in decreased ORADEs and complications, and creating synergies that result in pain reductions. APAP exerts its effects in the central nervous system, and versus oral APAP, IV APAP has a faster T max and a higher C max, with pharmacokinetics that achieve greater concentration in cerebrospinal fluid, suggesting better analgesia from this formulation [43, 44]. Our results support these findings and suggest that IV APAP use may be cost-effective for Cesarean section and hysterectomy surgeries through the reduction of LOS, opioid consumption, and ORADEs.

Other studies have also found that MMA following Cesarean sections or hysterectomies can help to minimize/manage postoperative pain and drive positive clinical outcomes [26, 45]. MMA after Cesarean section has been shown to provide better clinical outcomes with less reliance on opioid pain medications [45, 46]. Supplemental uses of non-opioid medications have been associated with superior pain relief, improved analgesia, and opioid sparing (reduced morphine consumption) [47, 48].

Similar to Cesarean section surgeries, MMA in hysterectomy surgeries is associated with reduced hospital LOS following both open abdominal surgeries and minimally invasive/laparoscopic surgeries [23, 26]. Likewise, MMA in hysterectomy surgeries decreased total opioid utilization perioperatively on postoperative days 1 and 2 [25]. Furthermore, this reduced opioid consumption via MMA does not reduce the efficacy of pain relief [25].

While our results demonstrate an association between IV APAP and shorter LOS, further studies should examine other aspects of efficacy, including pain reduction. Additionally, multimodal therapy including IV APAP may help to reduce sedation associated with opioids to promote mother-baby bonding, caretaking, breast-feeding, and ambulation [15, 16]. Furthermore, reducing the LOS and ORADEs could also help

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