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Original Article

Effect of intraoperative or postoperative intravenous acetaminophen on postoperative pain scores and opioid requirements in abdominal and spinal surgery patients

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Abstract: Acetaminophen is a commonly used non-opioid analgesic with a well-established safety and tolerability profile. This retrospective study investigated the effects of intraoperative vs postoperative administration of intravenous (IV) acetaminophen on opioid consumption and pain scores in surgical patients. We included 147 patients who underwent abdominal or orthopedic spinal surgery who met all inclusion criteria; 41 patients received IV acetaminophen intraoperatively, 52 patients received it postoperatively and 54 control patients who did not receive IV acetaminophen. Patient outcomes were measured through 24-hour Visual Analog Scale (VAS) for pain scores, 24-hour opioid consumption, post-anesthesia care unit (PACU) pain scores, PACU and hospital length of stay and the time to first ambulation. The patients in the intraoperative IV acetaminophen group had a) significantly decreased 24-hour average pain scores (4.3±1.7) compared to the postoperative IV acetaminophen group (6.3±1.5) and to the control group (5.3±1.5) ($p<0.05$), b) decreased 24-hour opioid consumption (102±168) compared to the control group (189±153) ($p<0.001$), and c) had lower PACU initial pain scores (4±3.5) compared to the control group (6±4) ($p<0.05$). Also, the patients in the intraoperative IV acetaminophen group had reduced length of hospital stay (4.2±3.2) when compared with those in the control group (5.6±3.3) ($p<0.05$). Intraoperative IV acetaminophen significantly reduced the intraoperative opioid requirements compared to the controls (54±97 vs 119±149) ($p<0.05$). Intraoperative IV acetaminophen administration as an adjunct analgesic decreased postoperative opioid requirements and enhanced analgesia.

Keywords: Perioperative intravenous acetaminophen, pain, opioids, outcomes

Introduction

Despite advances in the current armamentarium of analgesic drugs and techniques for the management of postoperative pain, up to 80% of patients experience unacceptable levels of pain in the postoperative period [1, 2]. Unrelieved postoperative pain may result in clinical and psychological changes which increase morbidity and mortality, hamper the rehabilitation process, and decrease patient satisfaction with their surgical experience [3, 4]. Adequate postoperative pain control is critical to improve the recovery process following major surgery. Extensive use of opioids as a means of controlling postoperative pain is associated with a variety of perioperative side effects, including cardiorespiratory depression, drowsiness, sedation, hallucinations, postoperative nausea and vomiting (PONV), pruritus, urinary retention, ileus, and constipation, which can contribute to delayed hospital discharge and resumption of normal activities of daily living [5]. Safe and effective pain management requires a proactive approach using a variety of treatment modalities to obtain an optimal outcome. The adaptation of multimodal (or "balanced") analgesic techniques as the standard approach for the prevention of postoperative pain is one of the keys to improve the recovery process [6].

Acetaminophen is a safe and tolerable non-opioid analgesic available in oral, rectal, or intravenous (IV) formulation. As compared with peak acetaminophen plasma concentrations following oral (45-60 minutes) and rectal administration (4 hours), IV administration of acetaminophen results in rapid peak plasma concentrations (15 minutes) and a quick analgesic effect (5 minutes) with a duration of action up to 4 hours [6]. Several clinical studies have confirmed the efficacy and safety of IV acetaminophen in the management of mild-to-moderate pain as monotherapy as well as in the management of moderate-to-severe pain as an adjuvant to opioids [7]. IV acetaminophen is a key component of many pain management approaches. The objective of this retrospective study was to investigate the impact of administration time of a bolus dose of 1 g IV acetaminophen (intraoperative versus postoperative) on postoperative pain control following major surgery. Therefore, to validate this hypothesis, we recorded within the first 24-hour postoperative period: the Visual Analog Scale (VAS) pain scores in the PACU and on the floor, the total dose of opioids consumption (in oral morphine equivalents), opioid-related side effects and length of stay in the PACU and overall hospitalization.

Methods

This was a retrospective, observational study, approved by the Institutional Review Board of Cedars-Sinai Medical Center. A total of 147 patients charts who underwent abdominal or orthopedic spine surgery between 2013 and 2014 were enrolled in this study. The enrollment was as follow: 100 patients who received IV acetaminophen perioperatively were identified, 93 were enrolled (41 received it intraoperatively and 52 postoperatively) and seven were excluded (they received IV acetaminophen in addition to epidural analgesia postoperatively). A total of 54 patients who did not receive IV acetaminophen were identified as the controls. The 147 study patients were divided into three groups: 1) Intraoperative IV acetaminophen (patients received 1 g of IV acetaminophen intraoperatively), 2) Postoperative IV acetaminophen (patients received 1 g of IV acetaminophen within the first 24-hour in the postoperative period), and 3) Control group (patients who did not receive any IV acetaminophen). Patients were included if they received IV acetaminophen (Ofirmev acetaminophen injection, Cadence Pharmaceuticals Mallinckrodt) as a single dose (1 g) intraoperatively, or within the first 24-hour in the postoperative period. Exclusion criteria included patients who were younger than 18 years, required a postoperative ICU stay, underwent any regional anesthesia technique including an epidural or nerve block, received the first IV acetaminophen dose after 24 hours postoperatively, or used opioid agonist-antagonists during the perioperative period.

The following variables were collected: age, gender, weight, height, anesthesia time, perioperative opioid requirements and complications. Perioperative complications included those that occurred during the first 24 hours. For this study, opioid requirements were recorded intraoperatively, or within the first 24-hour in the postoperative period. To quantify the amounts of opioid, all the opioids were converted to oral morphine equivalents using Global RPH with 0% cross-tolerance (http://www.globalrph.com/opioidconverter2.htm).

The primary outcomes were described as an average VAS for pain scores and opioid consumption in oral morphine equivalents during the first 24-hour in postoperative period. Secondary outcomes were identified as initial, maximum, and average PACU VAS for pain scores, PACU opioid consumption, PACU and hospital length of stay and the time to first ambulation.

Statistical analysis

The statistical analysis was performed using SAS 9.3 for Windows (SAS Institute, Cary, NC, USA). Continuous variables were reported as mean ± standard deviation (SD) and the categorical variables will be reported as number of cases (n) and percentage (%). We conducted the Wilcoxon Rank Sum test for two-group comparison: Intraoperative IV acetaminophen versus the Control group and Postoperative IV acetaminophen versus the Control group. The Kruskal-Wallis rank sum test was applied to test the difference among the three groups - Intraoperative IV acetaminophen group, Postoperative IV acetaminophen group and the Control group by surgery types - abdominal surgery and spine surgery. If there is a significant

Table 1. Demographic and clinical characteristics of study subjects

	Intraoperative IV acetaminophen n=41	Postoperative IV acetaminophen n=52	Control n=54	*p*-value for Intra vs Control	*p*-value for Post vs Control
Age (Years)	62±13	52±16	57±13	0.124	0.118
Sex (M/F)	22/19	14/38	26/27	0.407	0.027
BMI (Kg/m^2)	27±7	27±8	27±6	0.642	0.560
Anesthesia time (min)	215±70	267±141	246±106	0.169	0.766
Intraoperative opioids consumption (mg)	54±97*	68±82*	119±149	<0.0001	0.025
The length of PACU stay (min)	181±74	182±54	210±87	0.095	0.145
Time until ambulation (day)	1.2±0.7	1.7±1.5	1.6±1.4	0.242	0.466
The length of hospital stay (day)	4.2±3.2*	6.9±6.5	5.6±3.3	0.006	0.323

PACU: post-anesthesia care unit. *p<0.05 versus the control group.

Table 2. Pain scores and analgesic consumption within the first 24-hour postoperative period

	Intraoperative IV acetaminophen n=41	Postoperative IV acetaminophen n=52	Control n=54	*p*-value for Intra vs Control	*p*-value for Post vs Control
PACU initial pain score	4±3.5*	6.7±3.3	6±4	0.014	0.459
PACU maximum pain score	6.8±33	8.6±1.3	7.8±2	0.198	0.088
PACU average pain score	4.7±2.4	6.8±1.9	5.7±1.8	0.067	0.013
PACU opioids consumption (mg)	21±30*	39±30	42±31	0.006	0.631
24-hour post-surgery opioids consumption (mg)	102±168#	253±212	189±153	<0.0001	0.144
24-hour average pain score	4.3±1.7*	6.3±1.5#	5.3±1.5	0.004	0.0004

PACU: post-anesthesia care unit. *p<0.05 versus the control group; #p<0.001 versus the control group.

difference among those three groups, then post hoc pair wise comparisons using Nemenyi-test was conduct. A two-sided *p* value of ≤0.05 was considered to be statistically significant.

Results

The three groups were comparable with respect to demographic characteristics (age, sex, and BMI), anesthesia time, length of PACU stay, and the time until ambulation (**Table 1**). The intraoperative IV acetaminophen group: A) significantly decreased the opioid consumption 24-hour post-surgery (102±168) compared to the postoperative IV acetaminophen group (253±212) and to the control group (189±153) (p<0.001) (**Table 2**). B) showed a significant reduction in the PACU initial pain score (4±3.5) compared to the postoperative IV acetaminophen group (6.8±3.3) and to the control group (6±4) (p<0.05) (**Table 2**). C) showed a significant reduction in the PACU opioids consumption (21±30) compared to the postoperative IV acetaminophen group (39±30) and to the control group (42±31) (p<0.05) (**Table 2**). D) significantly decreased the 24-hour average pain score (4.3±1.7) compared to the postoperative IV acetaminophen group (6.3±1.5) and to the control group (5.3±1.5) (p<0.001) (**Table 2**). E) showed a significant reduction in the length of hospital stay (4.2±3.2) compared to the postoperative IV acetaminophen group (6.9±6.5) and to the control group (5.6±3.3) (p<0.05) (**Table 1**). Compared to the control group, intraoperative IV acetaminophen groups showed a significant decrease in the intraoperative opioids requirements compared to control group (54±97 vs 119±149, p<0.05) (**Table 1**). No significant differences were observed for the maximum and average PACU pain scores, and the time until ambulation between the intraoperative IV acetaminophen group and the control group (**Table 1**). Intraoperative IV acetaminophen administration in the spinal surgery significantly decreased PACU initial pain scores and the length of hospital stay compared with postoperative administration (**Table 3**). However, there were no significant differences for PACU initial pain scores and the length of hospital stay in the abdominal surgery (**Table 4**). No

Table 3. Pain scores and analgesic consumption in the spinal surgery

	Spine intraoprative group	Spine postoperative group	Spine control group	*P*-values of Kruskal-Wallis test
Age (years)	64.23±12.76	56.24±13.06	59.00±13.31	0.12
BMI (Kg/m^2)	26.45±5.17	27.96±8.52	28.37±4.84	0.31
Anesthesia time (min)	204.69±66.77$^{**,\#}$	366.94±171.55	277.48±91.15	<0.001
Time until ambulation (day)	1.19±0.80	2.18±1.98	1.43±1.62	0.02
The length of hospital stay (day)	4.19±3.16*	8.82±9.84	4.81±2.47	0.02
PACU initial pain score	3.88±3.66*	8.25±2.05	5.70±4.17	0.02
PACU maximum pain score	6.92±3.17	8.75±1.39	8.26±1.75	0.19
PACU average pain score	4.72±2.42*	7.24±1.56	5.85±1.79	0.02
PACU opioids consumption (mg)	32.25±34.69	30.63±14.08	41.59±26.49	0.18
24-h post-surgery opioids consumption (mg)	125.56±206.18$^{*,\#}$	310.09±227.20	205.86±175.89	0.001
24-h average pain score	4.46±1.74**	6.54±1.53	5.44±1.21	<0.001

BMI: body mass index, PACU: post-anesthesia care unit. *p<0.05 versus the postoperative group; **p<0.001 versus the postoperative group; $^{\#}$p<0.05 versus the control group.

Table 4. Pain scores and analgesic consumption in the abdominal surgery

	Abdominal intraoperative group	Abdominal postoperative group	Abdominal control group	*P*-values of Kruskal-Wallis test
Age (years)	57.73±13.58	50.40±17.60	54.67±13.30	0.32
BMI (Kg/m^2)	26.84±8.79	26.86±7.89	25.96±7.03	0.94
Anesthesia time (min)	233.27±72.85	217.77±92.85	215.04±111.35	0.43
Time until ambulation (day)	1.20±0.41	1.47±1.05	1.67±1.36	0.63
The length of hospital stay (day)	4.13±3.40	6.00±3.79	6.30±3.90	0.055
PACU initial pain score	4.33±3.27	6.19±3.06	6.12±3.09	0.14
PACU maximum pain score	6.80±2.34	8.52±1.33	7.31±2.09	0.03
PACU average pain score	4.72±2.36*	6.68±2.09	5.58±1.98	0.02
PACU opioids consumption (mg)	21.20±18.62	42.48±33.99	42.63±34.74	0.04
24-h post-surgery opioids consumption (mg)	61.53±42.33$^{**,\#}$	222.99±201.08	171.22±128.1	<0.001
24-h average pain score	4.03±1.51**	6.23±1.50	5.17±1.74	<0.001

BMI: body mass index; PACU: post-anesthesia care unit. *p<0.05 versus the postoperative group; **p<0.001 versus the postoperative group; $^{\#}$p<0.001 versus the control group.

unusual or unexpected complications were observed with IV acetaminophen therapy during the study period.

Discussion

Several clinical studies have confirmed the efficacy and safety of IV acetaminophen in patients undergoing a wide variety of surgical procedures [8-10]. A meta-analysis with 3896 patients from 36 studies found that the patients receiving IV acetaminophen significantly improved postoperative pain management compared with the placebo (50% vs 16%) [8]. A study demonstrated that the patients who received IV acetaminophen (1 g) every 6 hours decreased pain intensity and morphine consumption compared with placebo at 6 and 24 hours after total hip or knee replacement [9]. Similarly, the current study revealed that the orthopedic spine and abdominal surgery patients who received intraoperative IV acetaminophen (1 g) showed decreased 24-hour pain scores compared to the matched controls.

The optimal timing for administration of acetaminophen in relation to surgery has also been investigated. A randomized controlled trial found that the patients who received IV acetaminophen during surgery or oral acetaminophen after surgery experienced similar pain relief and adverse effects in laparoscopic cholecystectomy [10]. A systematic review and meta-analysis found that when patients received IV acetaminophen prophylactically, a concomitant reduction in pain was observed, but not a reduction in postoperative opioid con-

sumption [11]. In the present study, intraoperative IV acetaminophen reduced postoperative pain scores as well as total analgesic opioid consumption in the first 24 hours. However, postoperative IV acetaminophen administration failed to significantly reduce opioid requirements compared with the controls.

The opioid-sparing effect of IV acetaminophen remains controversial. Sinatra and colleagues compared IV acetaminophen to placebo and found IV acetaminophen had an opioid-sparing effect and enhanced patient satisfaction by reducing opioid requirements [9]. Wininger and colleagues found that the patients receiving IV acetaminophen experienced lower pain intensity (1 g every 6 hours or 650 mg every 4 hours). However, there were no differences in opioid requirements during the initial 24-hour postoperative period [12]. Hiller et al also revealed no effect on total opioid needs with IV acetaminophen after major spine surgery in children and adolescents [13]. In this study, only intraoperative IV acetaminophen administration decreased the total analgesic opioid consumption. The opioid-sparing effect of IV acetaminophen depend on the dose of acetaminophen, the type of surgery, anesthesia regimen, type of opioid and the time of IV acetaminophen administration.

The concept of fast track surgery has been widely adopted, resulting in shorter lengths of stay and improved patient outcomes [14, 15]. Many reasons leading to prolonged hospital stay following major surgery include poor pain control, and protracted nausea and vomiting secondary to the use of opioids [16]. Thus, decreasing dependence on opioid-containing medications for the treatment of postoperative pain will lead to decreased nausea and vomiting, less constipation and ileus, and diminished incidence of urinary retention in the surgical population. Acetaminophen has a well proven track record of efficacy in terms of analgesia and an excellent safety profile with minimal side effects [17]. In this study, we have demonstrated that the intraoperative use of IV acetaminophen resulted in an earlier patient discharge.

Oral and rectal acetaminophen formulations are associated with a relatively slow onset of action (45-60 minutes and 4 hours) and more variable analgesic activity, making them less useful in perioperative, postoperative, and acute care settings. A major advantage of IV acetaminophen is rapid peak plasma concentrations at 15 minutes following infusion and a quick analgesic effect (5 minutes) with a duration of action up to 4 hours [6]. Noticeable advantages of IV acetaminophen compared with NSAIDs include a reduced likelihood of gastrointestinal bleeding, cardiovascular issues, as well as its use in pregnancy. Furthermore, IV acetaminophen is especially beneficial in perioperative setting when oral (e.g., vomiting) or rectal routes are not available routes of access or when a faster onset of analgesic effect is required.

The limitations of this retrospective study include the nonrandom distribution of patients into three groups, the different adjunctive analgesia regimens received by the patients in the perioperative period. There are variations in frequency of VAS pain score recording in the electronic chart. To decrease this bias, we recorded only the highest pain score for any given hour and averaged those over the 24-hour period. The evaluation time was limited to the initial 24-hour postoperative period. To achieve maximum short-term and long-term benefits of using IV acetaminophen, the analgesic therapies should extend into the postoperative period for 3-7 days.

The ideal postoperative analgesic regimen would be safe while providing effective pain relief with minimal side effects. The non-opioid analgesic drugs are likely to assume an increasingly important role as preventative analgesics, facilitating the recovery process and improving overall patient satisfaction. Therefore, IV acetaminophen is an attractive component of a multimodal analgesic treatment. Intraoperative administration of IV acetaminophen as an adjunct analgesic enhances analgesia and decreases postoperative analgesic opioid consumption. Well controlled clinical studies are needed to determine the optimal timing for administration of IV acetaminophen to attain the maximum benefits of the medication.

Disclosure of conflict of interest

None.

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