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Research Article

Effect of Multi-Dose Intravenous Acetaminophen on Readiness for Discharge in Patients Undergoing Ambulatory Laparoscopic Cholecystectomy: A Randomized Controlled Trial

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ABSTRACT

Study objective: To determine whether every four-hour dosing of intravenous (IV) acetaminophen can expedite discharge readiness in patients undergoing ambulatory laparoscopic cholecystectomy. Secondary outcomes investigated included the stress hormone response (IL-6, -8, -10, C-reactive protein, epinephrine, norepinephrine, and cortisol), postoperative pain scores, minutes to first rescue medication, need for additional antiemetics, the overall dose of postoperative opioids administered, Postoperative Nausea and Vomiting (PONV) incidence, and patient satisfaction.

Design: 65 patients were included in the final analysis of this double-blinded, randomized, placebo-controlled, two-arm parallel trial. Blood samples were drawn immediately following IV catheter insertion, prior to incision, and one hour after arrival in recovery while readiness for discharge was evaluated using the SPEEDs criteria (saturation, pain, extremity movement, emesis, dialogue, stable vital signs).

Results: Discharge readiness within 2 hours was observed in 97.1% of patients in the study group and 83.9% in the placebo group (p=0.096). Median VAS pain scores at 15 min and the worst VAS scores were higher in the placebo group (nine vs. seven, p=0.013). Patients that received the placebo were 96% less likely to be ready for discharge in 2 hours when stratifying across race and controlling for ASA status, IL-6, cortisol, and norepinephrine levels (p=0.0424).

Conclusion: Although the use of every four hour intravenous acetaminophen dosing increased the number of patients ready for discharge at 2 hours, the study failed to show a statistical significance due to the low sample size. Larger studies can potentially show an economic impact.

Keywords: Ambulatory; Analgesia; Acetaminophen; Laparoscopic; Recovery; Discharge

INTRODUCTION

Acetaminophen has been used orally for decades. Since the approval by the Food and Drug Administration of its Intravenous (IV) formulation in 2011, acetaminophen has played a greater role in perioperative pain management. Although opioids are still the mainstay of treatment in the perioperative period, the last decade has seen a rise in the use of non-opioid medications as part of a multimodal approach to acute pain. This has been further exacerbated by establishing Enhanced Recovery After Surgery

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(ERAS) protocols across the US to decrease the perioperative stress response, achieve early return of organ function, and create safe and cost-effective methods, leading to prompt patient discharge [1].

The popularity of acetaminophen in the perioperative setting initially increased due to its purported narcotic-sparing benefits, decreased Postoperative Nausea and Vomiting (PONV), unaffected respiratory drive, and lack of interference with coagulation, with the latter precluding the use of non-steroidal anti-inflammatory drugs (NSAIDs) [2,3]. Many of these benefits should naturally contribute to expediting patient recovery, especially in the ambulatory setting. Furthermore, the minimum dosage interval of acetaminophen is every 4 hours, which is unlikely to exceed the maximum daily dose of 4 grams in an ambulatory setting [4]. Lastly, pre-emptive dosing of non-opioids has been shown to contribute to enhanced recovery and has become a part of ERAS protocols for various surgeries, including total joint replacements, spine surgery, and gynecologic cases [5-10]. Evidence has also been demonstrated using preoperative oral acetaminophen; however, through bypassing gastrointestinal absorption and achieving rapid plasma and cerebrospinal fluid concentration levels, the IV formulation may have additional benefits [6,9-11].

Therefore, the present study hypothesized that acetaminophen dosage every 4 hours in the ambulatory surgical setting leads to faster readiness for discharge, defined as a 30% difference in time compared to the placebo group. Secondary hypotheses were that patients in the IV acetaminophen group would have a longer duration prior to requesting the initial dose of rescue medication, lower overall opioid consumption, lower incidence of PONV, and greater overall satisfaction with their operative experience. Additionally, although it has been claimed that oral acetaminophen has no anti-inflammatory properties, the present study also analyzed whether this absent effect extended to other stress markers. We thus hypothesized that pre-emptive dosing of IV acetaminophen leads to a decreased surgical stress response. The biochemical markers examined included CRP, epinephrine, norepinephrine, cortisol, and IL-6, -8, and -10.

MATERIALS AND METHODS

The present study is a double-blind, randomized, placebo-controlled, two-arm parallel trial conducted at the University Hospital in Newark, New Jersey and New York Presbyterian Brooklyn Methodist Hospital in Brooklyn, New York between June 2017 and March 2020. The study protocol was approved by the Rutgers New Jersey Medical School and Methodist Hospital institutional review boards. All patients included in the study provided written consent. The trial is registered at ClinicalTrials.gov (NCT02832687).

The primary outcome was patient readiness at 2 hours while secondary outcomes included postoperative pain scores, minutes to first rescue medication, the total dosage of postoperative opioids administered, PONV incidence, and the need for additional antiemetics, the plasma concentration of stress /inflammatory makers, and patient satisfaction with the procedure.

The study comprised male and female adult (>18 years of age) subjects undergoing same-day laparoscopic cholecystectomy with an American Society of Anesthesiologists (ASA) physical classification of 1 to 3. Subjects were screened, recruited, and randomized during the preadmission visit or the day of surgery. Patients were excluded if they were cognitively impaired and unable or unwilling to consent. Additional exclusion criteria included chronic steroid or opioid use, an allergy to acetaminophen, pregnancy, hepatic or renal disease, and a history of substance abuse.

Eligible subjects were randomized to one of the two treatment groups in a 1:1 ratio to receive either IV acetaminophen or a matching placebo. Randomization was determined by the research pharmacist at both locations. Male and female study participants were recruited with no limitation to racial or ethnic origin, and race was self-identified. Participation in the study did not alter the anesthetic management of the patient. Patient's ≥50 kg received either 1000 mg IV acetaminophen or the placebo, with the first dose administered preoperatively in the holding area. Patients were redosed every 4 hours up to a maximum of four doses or 4000 mg in 24 hours. Patients <50 kg received a dose of 12.5 mg/kg of acetaminophen to a maximum of 75 mg / kg/day, according to the manufacturer.

In the operating room, routine anesthesia monitors were applied according to the ASA guidelines. To maintain study protocol adherence, all attending anesthesiologists were provided with the intraoperative drug regimen (Appendix A), and the use of other drugs was prohibited. After pre-oxygenation, general anesthesia was induced and the airway was secured with an endotracheal tube. Although the study permitted up to 100 mcg of fentanyl, to prevent opioid dosing variation, a remifentanil infusion (0.05-2 μg/kg/min ideal body weight) was administered. All patients were administered 4 mg ondensetron prior to the end of surgery. Patients were awakened and extubated in the operating room after fulfilling the standard extubation criteria. Once extubated, patients were transferred to the Post Anesthesia Care Unit (PACU), where they were assessed via the SPEEDs (saturation, pain, extremity movement, emesis, dialogue, stable vital signs) criteria 5 minutes after arrival, followed by every 15 minutes for the duration of their PACU stay. Criteria for discharge were defined as a VAS score of less than 4, systolic blood pressure between 90 and 180 mmHg, heart rate between 50 and 110 bpm, and an oxygen saturation >90 on room air. Pain was assessed using the Visual Analog Scale (VAS), which was explained to patients prior to surgery. Analgesia was provided according to our protocol, with 0.2 mg IV hydromorphone for mild pain (VAS 1-3), 0.4 mg IV hydromorphone for moderate pain (VAS 4-6), and 0.6 mg IV hydromorphone (VAS 7-10). All PACU data was recorded directly in real-time, whereas adherence to the study protocol was confirmed using the intraoperative record

of the patient during the recovery period. Patients were deemed ready for discharge once meeting the SPEEDs criteria and were transferred to phase II recovery. Following transfer and prior to discharge, a satisfaction survey was administered (Appendix B).

Blood samples (15 mL) were collected in vacutainer tubes without anticoagulant at three different time points: before administration of any drug (after IV-line placement), prior to incision, and 60 min following arrival in PACU. Samples were analyzed for cortisol, CRP, the cytokines IL-6, IL-8, and IL-10, epinephrine, and norepinephrine. Specimens were labeled with the study name, subject ID number, sample number, and date of sample collection. Samples were subsequently left at room temperature for at least 15 min until clot formation, followed by storage at 4-8°C until collection of all three samples at the different time points. Samples were processed daily in a refrigerated centrifuge, and serum was aliquoted and stored at -80°C until analysis. An identical protocol was applied at Methodist Hospital. Upon conclusion of the study, all samples were transported from Methodist Hospital to University Hospital on dry ice in compliance with International Air Transport Association (IATA) regulations by an individual with IATA shipping training. For a detailed description of the laboratory analysis please refer to Appendix C.

The primary outcome of the study was the proportion of patients achieving discharge readiness status 2 hours post-surgery. Using a two-sided alpha error rate of 5% (or significance level alpha of <0.05) and a power of 80%, we computed that a total of 78 patients, 39 in each arm, would be required to detect a difference of at least 30% between both groups. Originally, 45 patients were envisioned to be recruited in each arm across the two hospitals (total of 90 patients). At an alpha of 0.05, the study would have had an 86% power in detecting at least a 30% difference between the two treatment arms. However, alterations were made for several reasons. First, Methodist Hospital changed its surgical technique early in the study period to robotically-assisted laparoscopic cholecystectomies. Consequently, only 21 patients were recruited, with significant data missing. Without electronic medical records and no reliable way of obtaining the required information, data from Methodist Hospital was omitted. Patients were recruited solely from University Hospital to preserve the reliability and validity of the study. Second, following the recruitment of 65 patients from University Hospital, the study came to a halt in March 2020 due to the worldwide COVID-19 pandemic and cancellation of all elective surgeries. As a result, the current analysis is underpowered with a final sample size of 65 and a 45% power to detect the observed (15%) difference in treatment arms. Based on the current trend, a total sample of 146, 73 in each arm, would have been required to detect the observed difference of 15%, with a power of 0.8 and an alpha of 0.05.

Statistical analysis

Patient characteristics, laboratory values, and surgical outcomes were summarized using univariate statistics, including frequency and percentage for categorical variables and median (IQR) and range for continuous variables. Differences across randomization arms were assessed using Chi-square or Fisher's exact tests of association for categorical variables and the Wilcoxon sum rank test for continuous variables. Repeated measures MANOVA was used to assess the main effects of time and treatment arm as well as the interaction effect of time by treatment for all biomarkers.

Repeated measures logistic regression analysis was performed to assess the difference in odds of readiness for discharge within 2 hours across the treatment arms and the incidence of nausea and vomiting. Model covariates included patient characteristics, laboratory values, pain scores, and medication administration. The repeated design was utilized to assess how changes in biomarkers across the three time periods affected readiness for discharge and to account for the likely auto-correlation within individuals.

As there was a sample imbalance with regard to race, patients were matched across treatment arms based on race, and the regression model was stratified by these groups to facilitate direct comparison of the treatment within racial groups.

Two sets of spaghetti plots of pain scores were created to help visualize trends in pain in patients across treatment arms during the recovery period. In the first, patients were grouped based on the initial VAS score (at 15 min in the PACU). In the second, patients were clustered based on their maximum reported VAS score across their time in the PACU. Linear regression analysis was performed to assess differences in maximum VAS pain score across treatment arms when accounting for patient characteristics and medication administration. Blood biomarkers were not associated with pain, and, therefore, the repeated measures design was not required.

For model building, all covariates associated with the dependent variable ($p<0.25$) and the treatment arm were incorporated into initial models. Variables that were not significant ($p<0.10$) or did not contribute to the overall model fit were excluded from the final models. Given the small sample size, an alpha of 0.10 was used to evaluate significance. Statistical analyses were performed in SAS v9.4 (SAS Corporation, Cary, NC).

RESULTS

Eighty-eight patients were enrolled; with 47 randomized to receive IV acetaminophen and 41 received the placebo. Twenty-three patients were excluded after randomization, 21 due to lack of data and two due to surgical complications. Hence, 65 patients were analyzed, with 34 (52%) receiving IV acetaminophen and 31 (48%) the placebo. Patients in the study arm received between one and three acetaminophen doses, with a median of two doses for both arms. The majority of study participants was female (79%), Hispanic (65%), and classified as ASA II (68%). The placebo group had a greater proportion of Hispanics and lower proportions of Black and White patients than the study arm ($p=0.02$) (Figure 1) and (Table 1).

Most patients were ready for discharge within 2 hours, with an

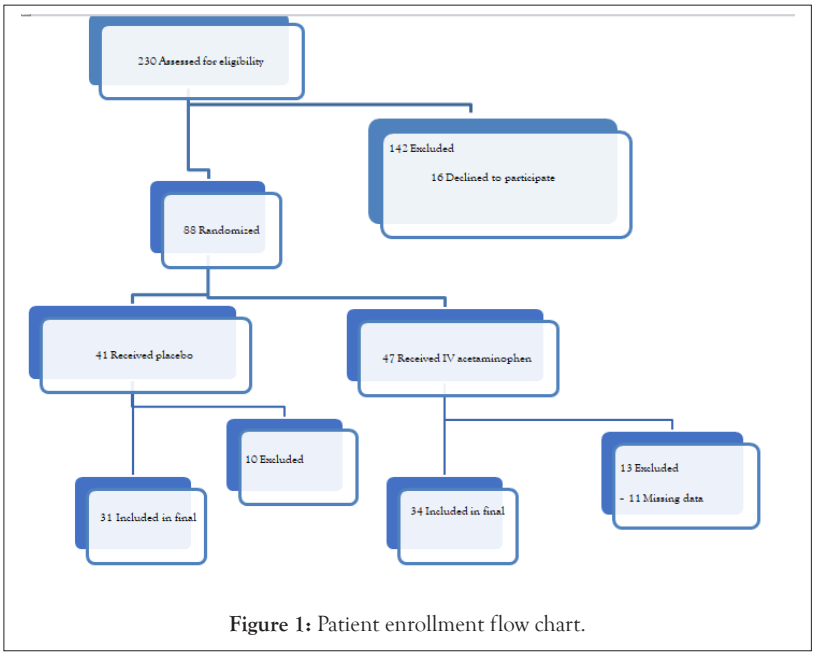

Figure 1: Patient enrollment flow chart.

Table 1: Characteristics of the study participants.

Characteristic	All	Acet	Placebo	P-value
Sample size	65	34(52.3)	31(47.7)	
Female	51(78.5)	25(73.5)	26(83.9)	0.375
Race				0.019
Black	16(24.6)	11 (32.4)	5(16.1)	
White*	7(10.77)	4 (11.8)	3(9.68)	
Hispanic	42(64.6)	19(55.9)	23(74.2)	
ASA status				
1	18(27.7)	6(17.6)	12(38.7)	0.161
2	44(67.7)	26(76.5)	18(58.1)	
3	3 (4.62)	2 (5.9)	1 (3.2)	
Obese	29(44.6)	16(47.1)	13(41.9)	0.804
Postoperative Nausea/ vomiting	19(29.2)	10(29.4)	9(29.0)	0.973
Received post op antiemetics	15(23.1)	7(20.6)	8(25.8)	0.618
Ready for discharge in 2 h	59(90.8)	33(97.1)	26(83.9)	0.096

Note: P-value refers to the significance level according to the Chi-Square test.

*Includes one Asian patient in the placebo group.

Acet: Acetaminophen

approximate 13% difference observed between the study (97%) and placebo (84%) groups (p=0.096). Analysis of secondary outcomes indicated a potential benefit in the study group for most outcomes; however, statistical significance was not observed. A contributing factor to readiness for discharge is the pain experienced by patients in the PACU. Median VAS pain scores at 15 min and the worst VAS scores reported during recovery in the PACU were higher in the placebo group than in the study group (nine vs. seven, p=0.013). Pain scores at greater durations did not differ between the groups. The time to VAS pain score of 4 is borderline significant (p=0.10), with participants in the study group achieving adequate pain control within 75 min compared to 90 min in the placebo group. The median time to first rescue medication was 23 min in the study group compared to 19 min in the placebo arm (p=0.14). Patients in the acetaminophen group received a median dose of 1 mg of hydromorphone, while participants in the placebo group received 1.2 mg (p=0.14). Given the small sample size and the fact that the study is unpowered, these trends require further exploration as they suggest the potential benefit of IV acetaminophen (Table 2).

Table 2: Surgical Outcomes: Comparison of medians across treatment arms.

	Median (q1, q3)			Min, Max	
Measure	Acet	Placebo	P- value	Acet	Placebo
Age	44(33, 59)	40(28, 56)	0.361	20, 74	21, 75
BMI	30(27, 32)	29 (24, 33)	0.694	21, 39	19, 39
Time in minutes:					
In surgery	88(73, 103)	82(69, 106)	0.679	44, 129	46, 189
In PACU	130(112, 187)	140(106, 219)	0.922	80, 295	85, 291
To 1st rescue rx	23(17, 30)	19(15, 28)	0.148	0.4, 0.5	0.4, 0.6
To discharge	67.5(60, 90)	85(60, 105)	0.11	15, 185	30, 165
To VAS=4	75(60, 90)	90(60, 105)	0.105	15, 180	30, 165
Dosage of:					
Ofirmev/placebo	2 (2, 2)	2 (2, 2)	0.541	1, 3	1, 5
Intra-op fentanyl	100(100, 150)	100(100, 150)	0.833	50, 250	50, 250
Hydromorphone	1(0.6, 1.6)	1.2(1, 1.6)	0.143	0.2, 2	0.4, 2.6
Satisfaction	4(3, 4)	4(3, 4)	0.897	1, 4	2, 4
VAS (pain score)					
Worst (n=64)	8(7, 10)	8(8, 10)	0.031	0, 10	4, 10
15 min (n=64)	7(5, 9)	9(7, 10)	0.013	0, 10	0, 10
30 min (n=63)	7(6, 8)	8(6, 10)	0.108	0, 10	2, 10
45 min (n=62)	6(4, 8)	7(5, 8)	0.147	0, 10	2, 10
60 min (n=57)	4(2, 6)	5(3, 7)	0.329	0, 10	2, 10
75 min (n=40)	4(3, 6)	5(4, 7)	0.199	2, 10	0, 10
90 min (n=29)	3(3, 6)	5(3, 6)	0.639	0, 10	0, 8
105 min (n=17)	3(2, 8)	5(3, 7)	0.584	2, 8	2, 8
120 min (n=9)	3(2, 7)	6.5(5, 7)	0.291	2, 7	3, 8

Note: Comparison of medians across the randomization arm was performed using the Wilcoxon Rank Sum test as the data were not normally distributed ($p<0.01$).

Acet=Acetaminophen

Mean biomarker levels varied across all time points in both groups. While patients experienced changes in values across the three time points, the mean levels and the extent of change across time did not significantly differ between both groups. To differentiate patterns in the time that patients were ready to be discharged, patients were grouped based on their pain scores at 15 min after discharge and categorized as having low (VAS=0-3), moderate (VAS=4-6), or severe pain (VAS=7-10). Initial and maximum pain scores were lower in the study groups compared to the placebo. Only one patient in the placebo group had a low (0-3) initial pain score than seven patients in the study group. In the placebo group, 90% of patients reported a maximum pain score of 10 compared with 80% of patients that received IV acetaminophen. Patients in the study group reported lower initial pain values and experienced less pain during recovery than patients who received the placebo. Patients who received IV acetaminophen reported a VAS score of 4 faster than patients who received the placebo, enabling the discharge process to commence faster (Figures 2 and 3) (Tables 3 and 4).

Patients who received the placebo were 96% less likely to be ready for discharge in 2 hours when stratifying across race and controlling for the ASA status, IL-6, cortisol, and norepinephrine levels ($p=0.0424$). Higher IL-6 levels were associated with a reduced odds of readiness for discharge (OR=0.949, $p=0.008$). The interaction of cortisol according to treatment suggests that compared to patients who received IV acetaminophen, patients who received placebo were approximately 2% less likely to be discharged. A similar, albeit smaller effect, was observed for norepinephrine. Patients with higher ASA scores were 88% less likely to be discharged within 2 hours. Similarly, patients with higher levels of pain and higher IL-6 concentrations (after 1 hour in the PACU) were more likely to report postoperative nausea or vomiting. There was no difference in the incidence of nausea or vomiting (or in receiving additional antiemetics) across both treatment arms. Maximum pain scores were almost a full point higher in the placebo group compared to the study group. Women also reported higher levels of pain, in addition to patients that experienced nausea and vomiting (Tables 5-7).

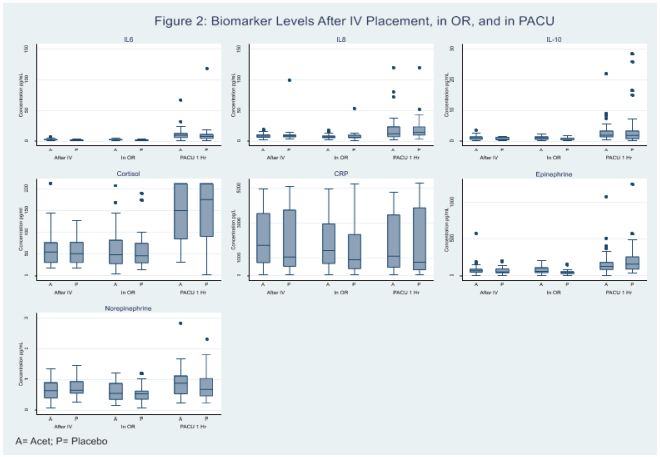

Figure 2: Boxplot distribution of biomarkers and comparison between treatment arms and time.

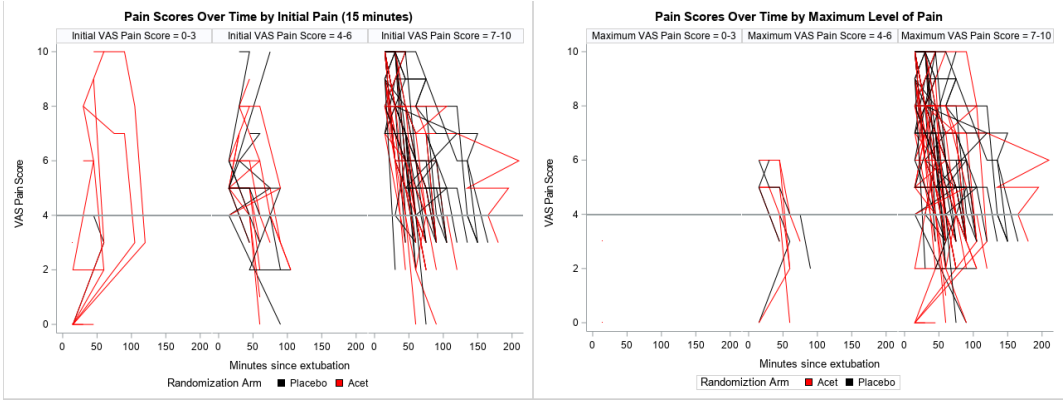

Figure 3: Distribution of initial and maximum pain scores.

Table 3: Distribution of biomarkers and comparison between treatment arms and time.

	Acet: Median concentration (IQR)			Placebo: Median concentration (IQR)			P-value: Arm * Time
Biomarker	After IV	In OR	In PACU	After IV	In OR	In PACU	
IL-6	2.6(1.6)	2.2(1.3)	12(12)	1.7(0.9)	1.8(1.0)	12(21)	0.27
IL-8	8.8(4.2)	7.1(3.5)	21(25)	12(18)	8.8(9.0)	20(22)	0.77
IL-10	1.1(0.8)	1.1(0.6)	3.2(3.9)	0.8(0.5)	0.8(0.5)	4.4(7.1)	0.74
CRP	2054(1608)	1913(1581)	1745(1603)	1913(1771)	1569(1650)	1697(1769)	0.99
Cortisol	62(44)	61(47)	139(65)	57(30)	60(46)	148(69)	0.64
Epinephrine	690(310)	623(302)	902(505)	718(299)	551(273)	810(489)	0.4
Norepinephrine	83(97)	68(49)	182(195)	67(52.2)	45(34)	210(228)	0.4

Note: *Median (IQR) concentration (pg/mL) reported for all biomarkers, with the exception of CRP, which is pg/L Differences in biomarkers across time and treatment arms were analyzed using repeated measures MANOVA. The main effect of time was significant for all biomarkers ($p<0.0001$). The main effect of the treatment arm and interaction between treatment and time was not significant for any biomarkers examined. Acet: Acetaminophen, OR: Operating Room, PACU: Post-Anesthesia Care Unit

Table 4: Initial and maximum pain scores.

	Initial VAS pain score			Maximum VAS pain score		
Treatment	0–3	4–6	7–10	0–3	4–6	7–10
Acet	7 (20.6)	9 (26.5)	18 (52.9)	2 (5.9)	5 (14.7)	27 (79.4)
Placebo	1 (3.2)	5 (16.1)	25 (80.6)	0 (0)	3 (9.7)	28 (90.3)
Trend test		0.005			0.07	

Note: The Cochran-Armitage Test (one-tailed) assesses whether there is a trend in pain towards higher VAS scores across the treatment arms. Acet: Acetaminophen, VAS: Visual Analog Scale

Table 5: Logistic regression analysis of the odds of readiness for discharge within 2 hours.

		95% confidence interval		
Variable	**Odds ratio**	**Lower**	**Upper**	**P-value**
Placebo (ref: Acet)	0.038	0.002	0.894	0.0424
ASA score of 2 or 3 (ref: ASA=1)	0.118	0.01	1.332	0.0839
IL-6 main effect	0.949	0.912	0.986	0.0082
IL-6* placebo (ref: Acet)	0.994	0.938	1.055	0.851
Cortisol main effect	1.02	1.007	1.032	0.0016
Cortisol* placebo (ref=Acet)	0.984	0.97	0.999	0.0346
Norepinephrine main effect	0.997	0.996	0.999	0.0001
Norepinephrine* placebo (ref: Acet)	1.003	1	1.005	0.0743

Note: The regression model was stratified across race. For the final model, covariates that improved the model fit or were significantly associated with the odds of discharge ($p<0.10$) were retained. Age, sex, obesity, epinephrine levels, cortisol levels, and time to first rescue medication were analyzed but did not meet the above criteria. The number of doses of rescue medication and maximum pain score were not included in the model because of issues with collinearity.

Table 6: Logistic regression of postoperative nausea or vomiting.

Odds of nausea/vomiting	**Odds ratio**	**Standard error**	**P-value**
IL-6 concentration			
Time 1	1.173	0.163	0.329
Time 2	1.218	0.175	0.261
Time 3	1.033	0.019	0.094
Maximum level of pain	1.581	0.17	0.007
Treatment=placebo	0.659	0.66	0.527

Note: The regression model was stratified across race. For the final model, covariates that improved the model fit or were significantly associated with the odds of discharge ($p<0.10$) were retained. Age, sex, obesity, ASA status, norepinephrine and epinephrine levels, cortisol levels, number of doses of rescue medication, and time to first rescue medication were analyzed but did not meet the above criteria.

Table 7: General linear regression of maximum pain score.

Maximum pain score	**Estimate**	**Standard error**	**P-value**
Intercept	7.403	0.587	<.0001
Treatment=Placebo	0.938	0.458	0.045
Female	1.527	0.556	0.008
Postoperative nausea or vomiting	1.201	0.499	0.019

Note: For the final model, covariates that improved the model fit or were significantly associated with the maximum level of pain reported ($p<0.10$) were retained. Age, race, obesity, ASA status, norepinephrine and epinephrine levels, IL-6 and cortisol levels, and time to first rescue medication were analyzed but did not meet the above criteria. The number of doses of rescue medication was not included because of issues with collinearity.

DISCUSSION

As delays in the Post-Anesthesia Care Unit (PACU) account for an increase in both patient morbidity and hospital cost, with a single extra minute of PACU delay being estimated to cost $20 [12], our study set out to test whether IV acetaminophen contributed to accelerating readiness for discharge, particularly with Q4 hour dosing [13]. Furthermore, the present study aimed to investigate whether IV acetaminophen affected some of the secondary reasons for delayed discharge, such as pain, nausea/vomiting, and a pro-inflammatory state. As IV acetaminophen demonstrates a rapid onset of action, serum peak concentration at the end of the 15-minute infusion period, and duration of effect of 4-6 hours, there is a potential benefit in its use in ambulatory surgery [14-16]. The IV formulation is associated with doubled plasma and effect site concentrations compared to oral acetaminophen 17 and it is useful when patients are unable to tolerate enteral formulations, such as immediately post-surgery. Numerous studies have also shown IV acetaminophen to reduce postoperative nausea and vomiting as well as postoperative opioid consumption and improve early pain outcomes at rest and during movement. Such improvements are of particular interest, as they mirror the very reasons why patients do not meet early PACU discharge criteria [2,3-17,18-21]. Similarly, fast-tracking patients have been used as a streamlining strategy to minimize PACU delays, decrease healthcare costs, and improve patient morbidity. It facilitates stable patients to be discharged from same-day surgeries sooner as long as they meet criteria set forth by various validated assessments [22-24]. In our study, the SPEEDs criteria (saturation, pain, extremity movement, emesis, dialogue, and stable vital signs) were utilized to access patient readiness for discharge. Burke and co-workers developed these criteria and compared them to the modified Aldrete and Fast Track criteria. The authors found the SPEEDs criteria to be both more sensitive and specific in identifying patients who require phase I nursing interventions and those who can bypass phase I to phase II [24].

Indeed, we recognize that the study sample size was not achieved, which contributed to the study being underpowered. However, the data may still be clinically relevant, and a visible trend can be appreciated especially for the primary as well as some of the secondary outcomes. Whether this would equate to a significant clinical or financial difference depends on the surgical volume of the institution and further investigation may be warranted. It is worth nothing that although a number of previous studies demonstrated promising results using IV acetaminophen in the perioperative period, more recent findings report IV acetaminophen is not superior to its oral formulation, with no added benefit compared to a placebo alone. Similar non-superiority results can be found when specifically examining Q4 hour dosing regimens [2,3-19,25-31]. In a study of 67 patients undergoing laparoscopic cholecystectomy, subjects were randomized to receive either IV acetaminophen and oral placebo or IV placebo and oral acetaminophen every 4 hours. Results showed no difference between groups regarding summed pain intensity scores and total opioid consumption over the 24-hour postoperative period. Additionally, Winger and colleagues examined different dosing regimens in patients undergoing abdominal laparoscopic surgery [18-32]. Q4 hour dosing was not observed to be superior to Q6 hour dosing compared to a placebo; however, both regimens were more effective at controlling pain than the placebo alone.

Since our study administered remifentanil intraoperatively, the effect of Remifentanil-induced Hyperalgesia (RIH) cannot be excluded. This could potentially explain why the placebo arm had higher pain scores at arrival and took longer to achieve adequate pain control (VAS=4). A single dose of IV acetaminophen prior to incision has been previously shown to effectively prevent RIH; thus, further investigation may be warranted to exclude this as a confounding variable [33]. As all patients did respond favorably to hydromorphone, it is unlikely that RIH played a significant role.

Apart from the administration route, the timing of administration has been previously shown to be of importance. By providing analgesia before the noxious stimulus arises, there is a potential for a decrease in acute pain from a less pathologic modulation of the central nervous system. In a meta-analysis, prophylactic IV acetaminophen administration before incision or prior to arrival in the PACU reduces nausea and correlates with pain reduction [34]. Similarly, a single prophylactic dose of IV acetaminophen has been demonstrated to effectively reduce pain postoperatively [2,3]. Numerous additional studies have also reported on the benefits of administrating IV acetaminophen preoperatively, prompting the pre-emptive dosing followed in the present study, with the first dose administered in the holding area [35,36]. However, considering that drug levels of oral and IV acetaminophen are identical following 2 hours could explain why IV acetaminophen has failed to show superiority over oral administration when administered pre-emptively [29].

In the present study we also investigated the immune response (IL-6, -8, and -10, CRP, and cortisol) as well as the sympathetic response (epinephrine and norepinephrine) to surgery. As the body undergoes a period of stress, such as during the intraoperative period, stress hormones are expected to rise. Although there may be less surgical tissue trauma with a laparoscopic procedure than a laparotomy, there is peritoneal insufflation and carbon dioxide absorption, both of which contribute to the surgical stress response [37]. As an example, iatrogenic pneumoperitoneum can cause the vagus nerve to activate the Hypothalamic Pituitary Adrenal (HPA) axis and, in turn, increase cortisol levels [38]. Additionally, considering the circadian rhythm effect on cortisol levels, we only included patients who had their procedures commence prior to 9 am. We considered this aspect to be of importance as it may represent a contributing factor in expediting readiness for discharge, as reported by Robinson et al. Since cytokine increase is relative to tissue trauma this may explain why interleukin concentrations decreased between the first sample collected, immediately following after IV insertion, and prior to incision, but then increased between the first blood

sample collected and recovery [39]. As expected, this observation was most noticeable for IL-6 and -8, which start to rise after incision and peak quickly, returning to baseline usually within 24 hours [40]. IL-10 increases immediately following incision, peaking after 3-4 hours, which may explain why an increase was not observed in either of the study groups. A similar effect was expected for CRP. This inflammatory marker is mediated by IL-6, peaking 20-30 hours after surgical stimulation. However, our samples showed a decrease from baseline during the surgical procedure, with the study group showing a greater decline (309 µg/dL vs. 216 µg/dL) than the placebo. As the decrease occurred in both study groups without any statistical significance, the attenuation cannot be attributed to IV acetaminophen, and further investigation is warranted. Plasma cortisol levels increased in both cohorts, with a slightly lower increase in the study arm (77 µg/dL vs. 91 µg/dL). This could potentially be attributed to the fact that acetaminophen is known to decrease cortisol levels by inhibiting the enzyme CYP17A1. Finally, both epinephrine and norepinephrine increased after skin incision, consistent with previous reports [37-40]. No statistically significant difference was observed among the two groups.

CONCLUSION

Among patients undergoing laparoscopic cholecystectomy, the use of pre-emptive and Q4 hour dosing of IV acetaminophen did show a larger proportion of patients being ready for discharge at 2 hours compared to the placebo, however due to the low sample size, the results failed statistical significance and larger studies are required to illustrate a potentially significant economic impact.

DISCLOSURES

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CONFLICTS OF INTEREST

The authors declare no competing interests.

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