Acetaminophen reduces acute and persistent incisional pain after hysterectomy

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OBJECTIVE: *Acetaminophen is effective for acute surgical pain, but whether it reduces persistent incision pain remains unknown. We tested the primary hypothesis that patients given perioperative acetaminophen have less incisional pain three months after surgery. Our secondary hypotheses were that patients randomized to acetaminophen have less postoperative pain and analgesic consumption, and better functional recovery at three months.*
METHODS: *140 patients having abdominal hysterectomy were randomly assigned to: 1)intravenous acetaminophen (4 g/day for 72 postoperative hours); or, 2) saline placebo. The primary outcome was incisional pain visual analog scale (VAS) at three months after surgery. The secondary outcomes were (1, 2) postoperative VAS scores while laying and sitting and (3) total patient-controlled intravenous tramadol consumption during the initial 24 hours, (4) DN4 questionnaires and (5) SF-12 at three months after surgery.*
RESULTS: *The persistent incisional pain scores at three months were significantly lower in acetaminophen (median [Q1, Q3]: 0 [0, 0]) as compared with saline group (0 [0, 1]) (P = 0.002). Specifically, 89%, 9%, and 2% of acetaminophen patients with VAS pain score at three months of 0, 1, and 2 or more, as compared with 66%, 23%, and 10% in the saline group (odds ratio: 2.19 (95% CI: 1.33, 3.59), P = 0.002). Secondly, postoperative pain scores both laying and sitting were significantly lower in the acetaminophen group. Acetaminophen group had significantly better DN4 score and mental health related but not physical health related quality of life.*
CONCLUSIONS: *Our results suggest that acetaminophen reduces the risk and intensity of persistent incisional pain. However, there are other mechanisms by which acetaminophen might reduce persistent pain.*

KEY WORDS: Anesthesia, acetaminophen, Persistent surgical pain, Postoperative acute pain

Introduction

Persistent incisional pain develops at least three months after surgical intervention [1]. It is often accompanied by psychological features resembling depression including poor sleep quality, difficulty concentrating, and fatigue [2]. Hysterectomies are among the most common surgical procedures performed in women , and the incidence of persistent pain after cesarean section is reported to range from 20 to 40% [4]. For example, Brandsborg et al reported that 32% of hysterectomy patients have pelvic pain one year after surgery, with 23% describing adverse effects on daily life [5] .

Non-opioid analgesics such as acetaminophen are often used alone or as adjuncts to opioid-based analgesia for treatment of moderate-to-severe pain. Perioperative administration of acetaminophen has been advocated as part of "multimodal" or "balanced" analgesia [6-7]. How acetaminophen reduces pain remains unclear, but numerous pathways appear to contribute.

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Central sensitization accounts for persistent incisional pain [8], and all analgesic pathways known to be influenced by acetaminophen contribute to development and maintenance of chronic pain [9]. Furthermore, acetaminophen ameliorates postoperative pain [10,11] which is strongly associated with development of persistent surgical pain [12].

There are thus compelling reasons to expect that acetaminophen might decrease persistent surgical pain in hysterectomy patients. We therefore tested the primary hypothesis that patients treated with acetaminophen have less incisional pain three months after surgery than those given placebo. Our secondary hypotheses were that patients given acetaminophen have less acute postoperative pain and analgesic consumption. Neuropathic pain was assessed, by the Douleur Neuropathique en 4 (DN4) test and health related quality of life assessed by the Short-form 12 Health Survey (SF-12) questionnaires.

Materials and Methods

This single-center, randomized, double-blind study was conducted at Mustafa Kemal University Hospital. Ethics Committee approval (April 2012, Approval number 154) and written consent was obtained from all patients. The trial was registered, Clinical Trials number NCT02086747.

We enrolled 144 American Society of Anesthesiologists Physical Status I-II women, 18-80 years old scheduled for hysterectomy under general anesthesia over the course of a year, starting April 2012. The study was restricted to women undergoing abdominal hysterectomies with Phannenstiel incision (an incision made transversely, and through the external sheath of the recti muscles, about 1 inch above the pubes) who were able to operate a patient-controlled analgesia (PCA) device.

We excluded emergency or urgent procedures; women with pre-existing chronic pain at any site requiring opioid analgesia; who had a history of significant Axis I psychiatric disease (major depressive disorder, bipolar disorder, schizophrenia, etc.); significant hepatic (ALT or AST >2 times normal) or renal (serum creatinine >2 mg/dl) impairment; allergy to acetaminophen.

Protocol

Participating women were premedicated with 1-2 mg intravenous (IV) midazolam per preference of the attending anesthesiologist. Anesthesia was induced with propofol (2 mg kg-1 IV); intubation was facilitated by rocuronium (0.6 mg kg-1 IV); and anesthesia was maintained by sevoflurane in combination with nitrous oxide 50% in oxygen. Fentanyl, 2 μg kg-1 intravenously, was given 3-5 min before the surgical incision. After endotracheal intubation, patients' lungs were mechanically ventilated to maintain end-expiratory PCO_2 between 34 and 36 mmHg. A Pfannenstiel approach was used in each woman, and the same surgeon conducted all operations. All patients received 0.5 mg kg-1 tramadol intravenously at the time of skin closure. Randomization was web-based and out of the control of any investigator. The web system was accessed by an independent investigator who prepared the assigned drug which was covered with opaque plastic to keep the surgical team and anesthesiologists blinded to treatment. Participating women were assigned to 100 ml saline or 1 g acetaminophen in 100 ml in 15 minutes, either given every 6 hours starting with skin closure for a total of 72 hours; the bags were labeled as "Study Drug" to maintain blinding. Women assigned to acetaminophen thus received 12 g over the three-day study period, an amount generally regarded as safe [13].

After return of spontaneous ventilation and tracheal extubation, patients were transferred to the post anesthesia care unit (PACU). There, patients were connected to a patient-controlled analgesia (PCA) device programmed to provide 20-mg intravenous bolus injections of tramadol at a lockout interval of 15 minutes with a maximum 4-hour limit of 150 mg. The PCA device was discontinued when women made no demands for tramadol in the preceding 4-hour interval or at a maximum of 24 hours after surgery.

When pain scores exceeded 5 cm on a 10-cm visual analog scale, 75 mg diclofenac was given as a rescue analgesic. If systolic arterial pressure (SAP) was <90 mmHg or mean arterial pressure was <50 mmHg, 5 mg intravenous ephedrine was given. If the heart rate was <50 beats min-1, 0.5 mg atropine sulfate intravenous was given. When patients sustained nausea or vomiting lasting longer than 5 minutes, ondansetron (4 mg intravenously) was given. Participants were asked not to take acetaminophen or medications containing acetaminophen during the first three postoperative months.

Measurements

All postoperative measurements were conducted by a research assistant who was blinded to group allocation. All patients were educated about how to use a VAS tool consisting of a 10-cm-long ruler and a marker that patients moved to a point indicating their pain intensity; 0 cm was designated no pain, and 10 cm as the worst imaginable pain. Postoperative pain was separately assessed with patients resting in bed and while sitting.

Sedation was assessed using the Ramsey sedation scale [14]. Heart rate, blood pressure, oxygen saturation (SpO_2), respiratory rate, pain, sedation, opioid use, cumulative analgesic consumption, and antiemetic use were assessed upon arrival in the PACU, and then 1, 4, 8, 12, 16, 20, and 24 hours thereafter. After the 4th postoperative hour, postoperative pain management was additionally

assessed as 1 = unsatisfied, 2 = slightly satisfied, 3 = mostly satisfied, 4 = completely satisfied [15].

Postoperative side effects including nausea-vomiting, bradycardia (heart rate less than 50 beats per minute), hypotension, itching, headache, and respiratory depression (respiratory rate less than 10 per minute) were recorded at the intervals specified above. We also recorded time to first flatus, initial ambulation, and first oral intake of solid food. The total amounts of opioid, rescue analgesics, and antiemetics during the initial 24 postoperative hours were recorded.

An investigator blinded to group assignment evaluated all patients one and three months after discharge; evaluations were conducted in person, usually during clinic visits. Persistent incisional pain was evaluated with a VAS score for persistent incisional pain at rest. At each evaluation, patients were asked to report acetaminophen use. Short-form 12 health [16] and hospital anxiety and depression [17] surveys were evaluated before discharge from the hospital, one month after surgery, and three months after surgery. The 12 items in SF-12 represent one physical component summary score and one mental component summary score and assess a person's perceived health-related quality of life [16]. Scores range from 0 to 100, a higher score indicates better mental health, physical health and general health perception [18].

The Hospital Anxiety and Depression Scale (HADS) was constructed to allow a rapid and separate measure of depression and generalised anxiety in hospital, outpatient and community settings, and it is also widely used in research settings [17]. There are seven anxiety items alternating with seven depression items: six items are coded from 0 to 3, and eight items are coded from 3 to 0 (i.e., reversed) [19]. This is a self-rating scale used to assess the risk and to measure the level of depression and anxiety. It contains 14 questions, seven related to depression and seven to anxiety [20]. Aydemir *et al.* established the validity and reliability of the Turkish version, and determined cut-off points for the depression (HAD-D) and anxiety (HAD-A) [21].

One and three months after surgery, patients completed Sleep Interference [22] and Douleur Neuropathique en 4 (DN4) [23] questionnaires. A Turkish version of the DN4 questionnaire has been validated [24]. In contrast, the Sleep Interference questionnaire is not available in Turkish; we therefore translated into Turkish, and then independently back-translated them into English to confirm validity of the translations. Sleep Interference scores range from 0 (no interference) to 10 (complete interference) [22]. DN4 score ≥4 indicate that the pain is likely to be neuropathic in origin.

Statistical Analysis

Primary analysis. Our primary outcome, incisional VAS pain score at three months after surgery, was compared between the acetaminophen and the saline groups, using a proportional odds logistic regression model. This model takes into account the ordinal nature of the response variable (i.e. "no pain" better than "VAS of 1" better than "VAS of 2 or more"). The resulting odds ratio estimates the relative odds of rating a less serious level of pain (lower pain score) for acetaminophen patients vs. saline patients. VAS scores more than 2 were collapsed into 2 for modeling facility.

Secondary analyses. Our secondary outcomes included three short-term measurements within the initial 24 hours after arrival PACU, (1) VAS pain scores while laying and (2) sitting, and (3) total analgesic consumption, and two long-term measurements at 3 months after surgery (1) DN4 questionnaire and (2) SF-12 survey. VAS pain scores were assessed at arrival in PACU, 1, 4, 8, 12, 16, 20, and 24 hours after. The two groups were compared on VAS pain scores while laying and sitting separately, each using a linear mixed model with repeated measures and autoregressive correlation matrix. The total analgesic consumption and SF-12 survery using the Wilcoxon rank-sum test. The DN4 score was assessed using a proportional odds logistic regression model. DN4 scores more than 3 were collapsed into 3 for modeling facility. The overall significance level was 0.01 for each secondary outcome (Bonferroni correction). Further correction for multiple comparisons within each outcome was made. The significance criterion was $P < 0.00125$ (i.e., 0.01/ 8 assessments) for the each individual pain score assessment, $P < 0.01$ for the average effect on pain score over time, total analgesic consumption, and DN4, and $P < 0.005$ for each component of the SF-12.

Standard descriptive statistics were used to descriptively compare the randomized groups on baseline variables, short-term assessments including hemodynamics, usage of rescue analgesics and anti-emetics, complications, satisfaction of pain management, time to first flatus, ambulation time, and oral nutrition times, and long-term assessments at 1 and 3 months after surgery including incisional pain score, limted to daily activity, sleep interference test, DN4 questionnair, and SF-12 survery.

Sample size consideration. A sample-size estimate indicated that 64 patients provided 95% power for detecting a clinically important absolute 20% reduction (i.e., from 40% to 20%) in persistent pain level at three months at an alpha level of 5% (25). We used the percentage, two samples method for sample-size calculation. Results are presented as percentages, means ± SDs, medians (interquartile range), or numbers as appropriate.Normal distribution of continuous variables were tested with Kolmogorov-Smirnof test. Chi-square test was used for comparisons between categorical variables. Mann-Whitney U test and Students's T were used for comparison of groups for continuos variables. Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered significant.

Results

We enrolled 140 consenting patients who fulfilled the entry criteria. Two patients from the saline group were excluded because of PCA pump technical failures. We were unable to contact two patients in the acetaminophen group after discharge. Therefore a total of four patients were excluded from the analysis (Fig. 1). The two groups were comparable with respect to age, body weight, height, ASA physical status, and duration of surgery (Table I).

Incisional pain severity was significantly lower in acetaminophen group (median [Q1, Q3]: 0 [0, 0]) as compared to the saline group (0, [0, 1]) at 3 months after surgery (Wilcoxon rank sum test: P = 0.002). We observed 89%, 9%, and 2% of acetaminophen patients with VAS pain score of 0, 1, and 2 or more, as compared to 66%, 23%, and 10% of saline patients. Acetaminophen patients were 2.19 times more likely (95% CI: 1.33, 3.59) to rate a lower pain score as compared to saline patients (P = 0.002) (Table II).

Acute postoperative VAS pain scores while laying and sitting were both significantly lower in the acetaminophen group than the saline group patients across the initial 24 postoperative hours (both P-value < 0.001). The estimated mean difference in VAS pain score was -0.81 (99.5% CI: -1.10, -0.52) (acetaminophen – saline) for laying and -1.13 (-1.57, -0.69) for sitting (Table III). VAS pain scores were descriptively lower in the acetaminophen group than the saline group at every measurement time (Table III, Figs. 2, 3). Furthermore, no difference on the total analgesic consumption during the intial 24 postoperative hours between the acetaminophen and the saline groups (median [Q1, Q3]: 300 [200, 400] vs. 290 [240, 460], P = 0.67) (Table III and Fig. 4).

Persistent surgical pain, assessed by DN4, was significantly lower in the acetaminophen group than the saline group at three months after surgery (Table III). We observed 80%, 10%, 4%, and 5% of acetaminophen

TABLE I - *Demographics and baseline characteristics (N = 140)*

Variable	Acetaminophen (N = 70)	Saline (N = 70)
Age (year)	49.5 [45.0, 62.0]	50.5 [45.0, 57.0]
Body mass index (kg/m^2)	28.5 [25.7, 31.3]	30.7 [25.8, 33.2]
ASA physical status		
I	12 (17%)	10 (14%)
II	58 (83%)	60 (86%)
Duration of operation (min)	130 [105, 170]	143.5 [120, 193]

Summary statistics are presented as number (%) of patients or median [Q1, Q3], respectively.

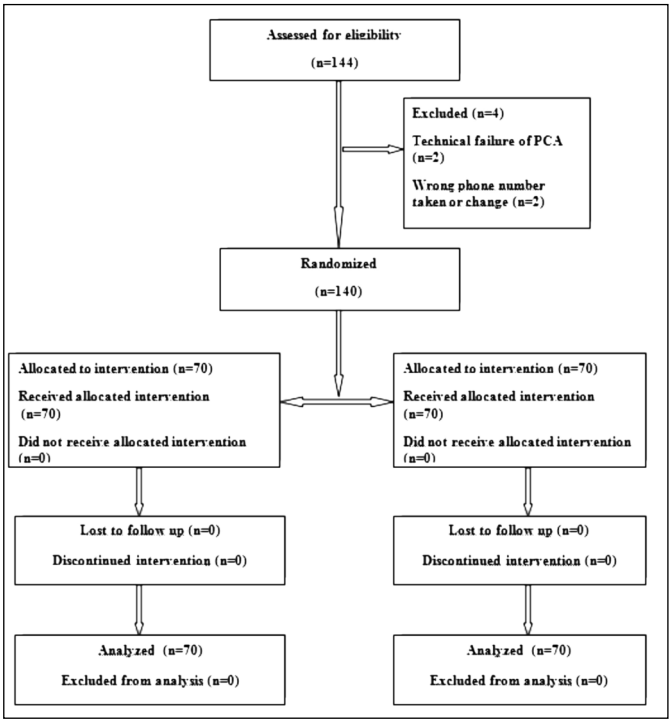

Fig. 1. Flow chart.

TABLE II - *Primary results - Comparisons between acetaminophen and saline groups on incisional pain score at 3 month after surgery.*

Incisional Pain Score at 3-month (VAS: 0 – 10)	Acetaminophen (N = 70)	Saline (N = 70)	Odds Ratio † (Acetaminophen vs. Saline) (95% CI)	*P-value*
			2.19 (1.33, 3.59)	0.002
0	62 (89%)	46 (66%)		
1	6 (9%)	16 (23%)		
2	1 (1%)	7 (10%		
3	0 (0%)	1 (1%)		
4	1 (1%)	0 (0%)		

VAS = Verbal Analog Scale - Summary statistics are presented as number (%) of patients. - † The pain score was compared between the two groups, using a proportional odds logistic regression model. Pain score of 3 and 4 were combined in the analysis as ≥ 3. The estimated odds ratio implies that acetaminophen patients were 2.19 times more likely (95% CI: 1.33, 3.59) to rate a lower pain score as compared to saline patients.

TABLE III - *Secondary results - Comparisons † between acetaminophen and saline groups on postoperative pain score, total analgesic consumption, DN4, and SF-12.*

Secondary outcome	Acetaminophen (N = 70)	Saline (N = 70)	Mean difference (Acetaminophen-Saline) (95% CI)†	P-value†
Pain score (VAS assessed with patients resting in bed) during the initial 24 hours after surgery [a]				
Arrival at PACU	4 ± 2	6 ± 2	-2.03 (-2.77, -1.28)	<.001‡
1 hour	3 ± 2	5 ± 2	-1.24 (-1.99, -0.50)	<.001‡
4 hour	3 ± 2	3 ± 1	-0.30 (-1.04, 0.44)	0.19
8 hour	2 ± 1	3 ± 1	-0.46 (-1.20, 0.29)	0.05
12 hour	2 ± 1	3 ± 1	-0.59 (-1.33, 0.16)	0.01
16 hour	2 ± 1	2 ± 1	-0.61 (-1.36, 0.13)	0.008
20 hour	1 ± 1	2 ± 1	-0.74 (-1.49, 0)	0.0013
24 hour	1 ± 1	1 ± 1	-0.50 (-1.24, 0.24)	0.03
Average treatment effect over time		-0.81 (-1.10, -0.52)	<.001‡	
Pain score (VAS assessed with patients sitting) during the initial 24 hours after surgery [a]				
Arrival at PACU	8 ± 3	10 ± 1	-1.67 (-2.62, -0.72)	<.001‡
1 hour	7 ± 2	9 ± 1	-1.46 (-2.41, -0.50)	<.001‡
4 hour	6 ± 2	7 ± 2	-0.99 (-1.94, -0.03)	<.001‡
8 hour	5 ± 2	6 ± 2	-0.90 (-1.85, 0.05)	0.002
12 hour	4 ± 2	5 ± 2	-0.81 (-1.77, 0.14)	0.006
16 hour	3 ± 2	4 ± 2	-0.94 (-1.90, 0.01)	0.0014
20 hour	3 ± 1	4 ± 2	-1.13 (-2.08, -0.18)	<.001‡
24 hour	2 ± 1	3 ± 2	-1.11 (-2.07, -0.16)	<.001‡
Average treatment effect over time		-1.13 (-1.57, -0.69)	<.001‡	
			Median difference	
Total analgesic consumption during the initial 24 hours after surgery (mg) [b]	300 [200, 400]	290 [240, 460]	20 [-40, 60]	0.67
			Odds ratio	
DN4 at 3 months after surgery [c]			2.00 (1.29, 3.11)	0.002‡
0	56 (80%)	38 (54%)		
1	7 (10%)	15 (21%)		
2	3 (4%)	5 (7%)		
3	3 (4%)	12 (17%)		
4	1 (1%)	0 (%)		
			Median difference	
SF-12 at 3 months after surgery [b]				
Physical component score	44 [43, 46]	44 [41, 52]	-0.5 (-3.7, 1.9)	0.57
Mental component score	28 [25, 31]	24 [21, 28]	3.6 (1.0, 6.2)	<.001‡

VAS = Verbal Analog Scale; PACU = Postoperative Anesthesia Care Unit

Summary statistics are presented as number (%) of patients, mean ± SD, or median [Q1, Q3], respectively.

† The overall significance criterion was 0.05 for the 5 secondary outcomes, including (1) pain score (resting), (2) pain score (sitting), (3) total analgesic consumption, (4) DN4, and (5) SF-12, thus and the overall significance level was 0.01 for each outcome (Bonferroni correction). Further correction for multiple comparisons within each outcome was made. The significance criterion was $P < 0.00125$ (i.e., 0.01/ 8 assessments) for the each individual pain score assessment, $P < 0.01$ for the average effect on pain score over time, total analgesic consumption, and DN4, and $P < 0.005$ for each component of the SF-12.

‡ Statistical significant.

The two randomized groups were compared using

a. Linear mixed model with repeated measures

b. Wilcoxon rank-sum test

c. The pain score was compared between the two groups, using a proportional odds logistic regression model. Pain score of 3 and 4 were combined in the analysis as ≥ 3. The estimated odds ratio implies that acetaminophen patients were 2.19 times more likely (95% CI: 1.33, 3.59) to rate a lower pain score as compared to control patients.

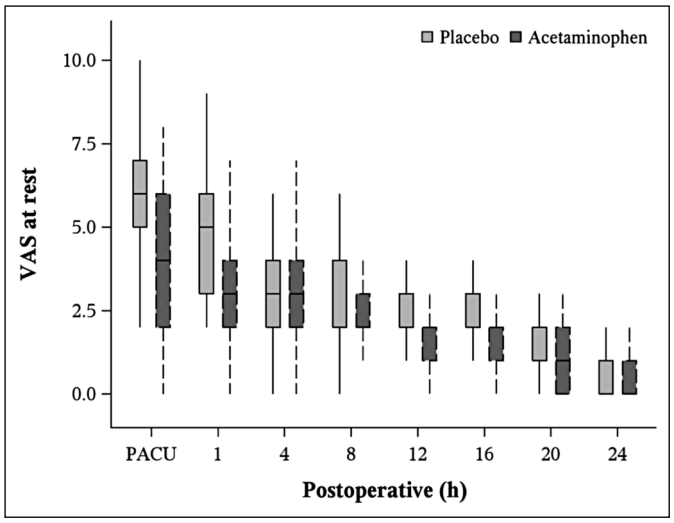

Fig. 2. Boxplot of pain visual analog scale (VAS) while laying over the initial 24 hours after surgery. The first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the inter-quartile range of the first and third quartiles, respectively.

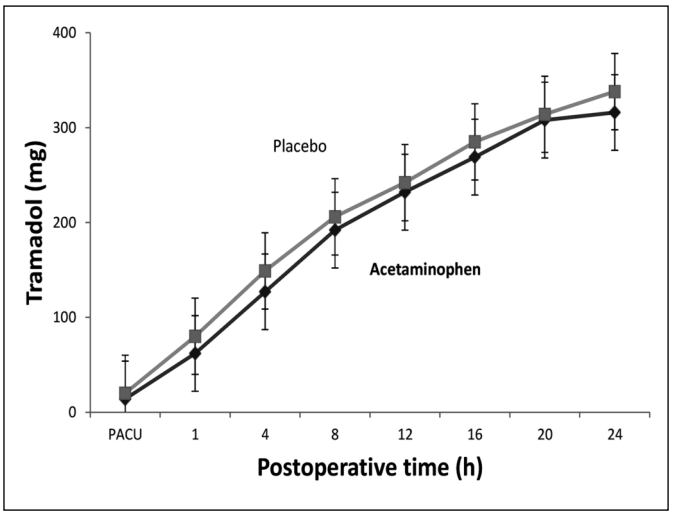

Fig. 4. Boxplot of cumulative patient-controlled tramadol consumption during the initial 24 hours after surgery. The first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the inter-quartile range of the first and third quartiles, respectively.

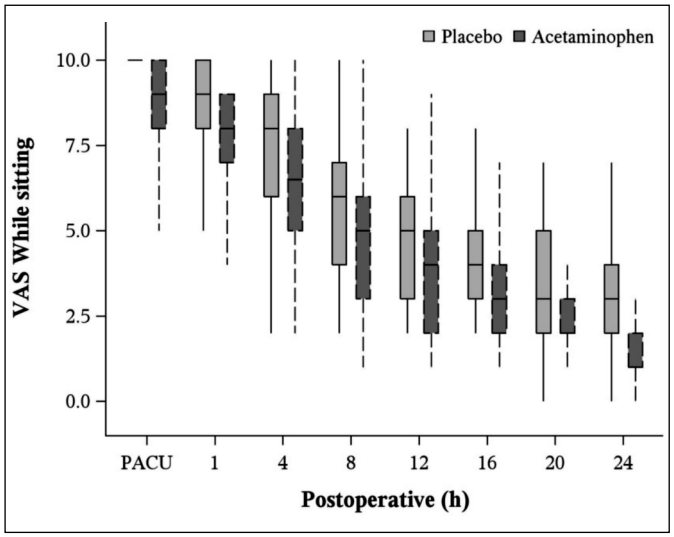

Fig. 3. Boxplot of pain visual analog scale (VAS) while sitting over the initial 24 hours after surgery. The first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the inter-quartile range of the first and third quartiles, respectively.

patients with DN4 score of 0, 1, 2, and 3 or more, as compared to 54%, 21%, 7% and 17% of saline patients. Acetaminophen patients were twice more likely (odds ratio (99% CI): 2.00 (1.29, 3.11)) to have a lower (better) score on the DN4 score as compared to the saline group (P = 0.002).

The acetaminophen group had significantly better mental health related but not physical health related quality of life at 3 months after surgery as compared to the saline group (Table III).Acetaminophen patients, on average, had a higher (better) SF-12 mental component score than saline patients; the estimated median difference was 3.6 (99.5% CI: 1.0, 6.2) (acetaminophen – saline), P < 0.001. However, the SF-12 physical component score was not different between the two groups (median difference: -0.5 (99.5% CI: -3.7, 1.9) acetaminophen – saline, P = 0.57).

During the initial 24 hours after surgery, the average heart rate, systolic, diastolic, mean arterial blood pressure, oxygen saturation, respiratory rate, and Ramsey sedation scale were descriptively similar between the two groups (Table IV). The total number of times patients pressed PCA was descriptively higher in the saline group then the acetaminophen group (median [Q1, Q3]: 183 [44, 518] vs. 61 [31, 147]). However, then total number of times patients received from PCA was descriptively similar (16 [11,20] vs. 15 [12,23]). Among the acetaminophen patients, 66% required additional analgesic, 73% had complications, and 72% received antiemetics over the initial 24 hours. The corresponding fractions among the saline patients were 86%, 80%, and 76%, respectively (Table IV).

Patient satisfaction with pain treatment was descriptively better in the acetaminophen group (26% slightly satisfied, 67% mostly satisfied, and 7% completely satisfied) as compared to the saline group (31% unsatisfied, 50% slightly satisfied, and 19% mostly satisfied) (Table V). Time to first flatus, ambulation time, and oral nutrition times were descriptively similar between two groups (Table V). Hospital Anxiety and Depression scale score was descriptively lower (better) in the acetaminophen

TABLE IV - *Summary of measurements during the first 24 hours after surgery*

Measurement	Acetaminophen (N = 70)	Saline (N = 70)
Average heart rate, beats/minute	80 ± 7	81 ± 6
Average blood pressure, mmHg		
Systolic	124 ± 12	124 ± 11
Diastolic	74 ± 6	76 ± 6
Mean	91 ± 8	92 ± 7
Average oxygen saturation, %	98 ± 4	98 ± 2
Average respiratory rate, breaths/minute	14 ± 2	14 ± 1
Average Ramsey sedation scale	2.0 ± 0.1	1.9 ± 0.1
Number times pressed PCA	61 [31, 147]	183 [44, 518]
Number times received from PCA	16 [11, 20]	15 [12, 23]
Usage of rescue analgesics		
Arrival at PACU	33 (47%)	53 (76%)
Initial hour	26 (37%)	39 (56%)
1 - 4 hour	20 (29%)	20 (29%)
4 - 8 hour	10 (14%)	14 (20%)
8 - 12 hour	5 (7%)	7 (10%)
12 - 16 hour	2 (3%)	2 (3%)
16 - 20 hour	0 (0%)	3 (4%)
20 - 24 hour	0 (0%)	2 (3%)
Any time above	*46 (66%)*	*60 (86%)*
Complications (yes)		
Arrival at PACU	22 (31%)	24 (34%)
Initial hour	18 (26%)	23 (33%)
1 - 4 hour	15 (21%)	14 (20%)
4 - 8 hour	25 (36%)	25 (36%)
8 - 12 hour	15 (21%)	14 (20%)
12 - 16 hour	12 (17%)	11 (16%)
16 - 20 hour	8 (11%)	10 (14%)
20 - 24 hour	3 (4%)	4 (6%)
Any time above	*51 (73%)*	*56 (80%)*
Usage of anti-emetics		
Arrival at PACU	19 (27%)	18 (26%)
Initial hour	15 (21%)	18 (26%)
1 - 4 hour	14 (20%)	12 (17%)
4 - 8 hour	25 (36%)	24 (34%)
8 - 12 hour	15 (21%)	13 (19%)
12 - 16 hour	12 (17%)	10 (14%)
16 - 20 hour	8 (11%)	7 (10%)
20 - 24 hour	3 (4%)	4 (6%)
Any time above	*50 (72%)*	*53 (76%)*

PCA = patient-control analgesia
Summary statistics are presented as number (%) of patients, mean ± SD, or median [Q1, Q3], respectively.

TABLE V - *Summary of other measurements during hospital stay*

Measurement	Acetaminophen (N = 70)	Saline (N = 70)
Satisfaction with pain treatment		
1 = unsatisfied	0 (0%)	22 (31%)
2 = slightly satisfied	18 (26%)	35 (50%)
3 = mostly satisfied	47 (67%)	13 (19%)
4 = completely satisfied	5 (7%)	0 (0%)
Time to first flatus (hour)	25 [21, 28]	24 [18, 27]
Ambulation time (hour)	10 [8, 14]	10 [8, 12]
Oral nutrition time (hour)	8 [7, 11]	8 [7, 12]
HADS	15 [10, 19]	17 [16, 20]

HADS = hospital anxiety and depression scale
Summary statistics are presented as number (%) of patients, mean ± SD, or median [Q1, Q3], respectively.

group than the saline group (median [Q1, Q3]: 15 [10, 19] vs. 17 [16, 20]) (Table V).

Long-term measurements at 1 and 3 months after surgery, including incisional pain score, daily activity, sleep interference, DN4 questionnaire, and SF-12 were summarized (Table VI). Consistent with the primary result that incisional pain severity was significantly lower in acetaminophen group at 3 months after surgery the pain severity at 1 month was also descriptively lower in acetaminophen group. DN4 score was descriptively lower in the acetaminophen group than the saline group at 1 month after surgery. The fraction of patients with limited daily activity was descriptively lower in the acetaminophen group at 1 moth after surgery (6% vs. 20%), but not 3 months (1% vs. 1%) than the saline group. Number of sleep interferences was descriptively similar between the two groups. Both mental and physical health related quality of life were descriptively similar both the two groups.

Discussion

Acetaminophen is a well established and effective [2]. It is therefore unsurprising that perioperative acetaminophen administration reduced acute pain, the fraction of patients requiring rescue analgesic, cumulative tramadol dose, and satisfaction with pain management. These results are broadly consistent with numerous previous studies [27,28].

Persistent surgical pain after hysterectomy originates from combination of inflammatory and neuropathic processes. Local tissue trauma promotes release of inflammatory mediators, causing peripheral sensitization, and the surgical transaction or trauma to the nerves during operations cause the neuropathic process leading to central sensitization (1). The overall incidence of persistent surgical pain in our post-hysterectomy patients was 22%. This value is consistent with previous report that pain after hysterectomy persists in between 5 and 32% of patients [29].

Acute surgical pain intensity is among the strongest predictors of persistent incisional pain [30]. While this association has been demonstrated numerous times [31-33] it remains unclear whether the relationship is causal. Our most important finding is that randomization to acetaminophen administration reduced not only acute pain,

TABLE VI - *Summary of other long-term assessments at 1 and 3 months after surgery*

	At 1 month after surgery		At 3 months after surgery	
	Acetaminophen (N = 70)	Saline (N = 70)	Acetaminophen (N = 70)	Saline (N = 70)
Incisional pain score (VAS: 0 no pain – 10)				
0	40 (57%)	31 (44%)	62 (89%)	46 (66%)
1	7 (10%)	10 (14%)	6 (9%)	16 (23%)
2	12 (17%)	11 (16%)	1 (1%)	7 (10%)
3	2 (3%)	10 (14%)	0 (0%)	1 (1%)
4	6 (9%)	5 (7%)	1 (1%)	0 (0%)
5	1 (1%)	1 (1%)	0 (0%)	0 (0%)
7	2 (3%)	2 (3%)	0 (0%)	0 (0%)
Limited to daily activity (yes)	5 (6%)	14 (20%)	1 (1%)	1 (1%)
Sleep interference test (0 – 10: no to complete interference)				
0	53 (76%)	52 (74%)	67 (96%)	63 (90%)
1	5 (7%)	8 (11%)	1 (1%)	4 (6%)
2	3 (4%)	2 (3%)	1 (1%)	0 (0%)
3	3 (4%)	5 (7%)	1 (1%)	1 (1%)
4	1 (1%)	0 (0%)	0 (0%)	1 (1%)
5	2 (3%)	0 (0%)	0 (0%)	0 (0%)
6	1 (1%)	2 (3%)	0 (0%)	1 (1%)
8	2 (3%)	1 (1%)	0 (0%)	0 (0%)
DN4 questionnaire*				
0	23 (33%)	8 (11%)	56 (80%)	38 (54%)
1	18 (26%)	13 (19%)	7 (10%)	15 (21%)
2	13 (19%)	26 (37%)	3 (4%)	5 (7%)
3	13 (19%)	20 (29%)	3 (4%)	12 (17%)
4	3 (4%)	2 (3%)	1 (1%)	0 (%)
5	0 (0%)	1 (1%)	0 (0%)	0 (0%)
SF-12 heath survey				
Physical component score	47 [45, 50]	45 [43, 49]	44 [43, 46]	44 [41, 52]
Mental component score	28 [25, 34]	28 [24, 31]	28 [25, 31]	24 [21, 28]

DN4 = Douleur Neuropathique en 4; VAS = Verbal Analog Scale
*DN4 ≥ 4 indicates that the pain is likely to be neuropathic in origin.
Summary statistics are presented as number (%) of patients, mean ± SD, or median [Q1, Q3], respectively.

as expected, but reduced persistent incisional pain by a third. This result from a randomized trial might be taken to suggest that the relationship between acute and persistent pain is indeed causal, and that better control of acute pain may reduce the risk of incisional pain becoming chronic.

However, there are other important mechanisms by which acetaminophen might reduce persistent pain independent from acute analgesia. The drug acts centrally and affects multiple pathways that play important roles in neuroplastic changes that characterize chronification of pain. Relevant pathways include descending inhibitory (serotonergic) and cyclooxygenase enzyme in the central nervous system, which plays important role in central sensitization of persistent surgical pain [34-35]. AM404 (N-arachidonoylphenolamine) is formed in the brain after deacetylation of acetaminophen in the liver. TRPV1 (Transient receptor potential vanilloid receptor 1) channels and CB1 (Cannabinoid receptor 1) receptors mediate the analgesic effects of AM404. TRPV1 receptor is increased in pathological pain conditions including neuropathic pain. Microglia have been directly implicated in the initiation of peripheral injury-induced pain and have been shown to express cannabinoid receptors. TRPV1 receptor activation also mediates microglial cell death, thus suggesting crucial role in chronic pain related diseases such as neuropathic pain. Given the many potential pathways, it seems likely that more then one mechanism contributes to the preventive effect of acetaminophen on persistent surgical pain related pathways [36]. Global function at one and three months, as evaluated by the SF-12 Health Survey, was improved in patients

randomized to acetaminophen — possibly reflecting reduced persistent pain. SF-12 is a multipurpose, short form health survey and provides easily interpretable scales for physical and mental health. In contrast, there was no significant benefit of acetaminophen with respect to other outcome measures (e.g., passage of flatus, oral intake, nausea and vomiting, and ambulation times). Presumably, the incidence of these opioid-related complications was comparable because opioid use was limited and similar in each group.
A natural consequence of evaluating hysterectomies is that we enrolled only women. Women generally experience more pain and require more analgesic than men [37]. Our follow-up period was restricted to three months. Future studies might evaluate whether the observed benefit of acetaminophen persists at six months or longer. Another limitation of the current study is about the timing of the randomization. Because of the short half-life of the study drug and the long duration of the procedures, we could randomize just before the skin closure.

Conclusion

Acetaminophen 4 g per day reduces persistent incisional pain and not surprisingly acute pain in women recovering from abdominal hysterectomies. About a fifth of the women reported incisional pain three months after surgery. Acetaminophen given for just 72 postoperative hours reduced the risk of persistent incisional pain by a third. Acetaminophen is thus not only acutely analgesic, but appears to reduce the risk of experiencing long-term pain. Whether the reduction in persistent pain is mediated by a reduction in acute pain or whether other mechanisms contribute remains to be determined. But by whatever mechanism acetaminophen reduces persistent incisional pain, it appears to be a reasonable drug to include in a multi-modal perioperative analgesic regimen.

Riassunto

L'acetaminofene (paracetamolo) è efficace nel trattamento del dolore chirurgico acuto, ma non è noto se riduce il dolore persistente delle incisioni. Abbiamo esaminato una prima ipotesi che la somministrazione perioperatoria dell'acetaminofene riduce il dolore dell'incisione tre mesi dopo l'interventi. Le nostre ipotesi secondarie erano che pazienti randomizzati al paracetamolo avessero minore dolore postoperatorio e minore consumo di analgesici, e migliore recupero funzionale a tre mesi.
Sono state utilizzate 140 pazienti sottoposte ad isterectomia per via addominale, suddivise a random e in doppio cieco tra un gruppo sottoposto alla somministrazione endovenosa per 72 ore nel postoperatorio di 4 g/die di paracetamolo, ed un secondo gruppo trattato con semplice placebo (soluzione fisiologica).
Come controllo primario è stata usata la scala analogica visiva (VAS) del dolore incisionale a tre mesi dopo l'intervento. Il controllo secondario sono stati la VAS del dolore 1) in posizione sdraiata, 2) in posizione seduta, 3) il consumo totale di tramandolo endovena richiesto dalla paziente nelle prime 24 ore dall'intervento , 4) il questionario Diagnostico del Dolore Neuropatico (DN4), e 5) il questionario sullo stato di salute SF-12 a tre mesi dopo l'intervento chirurgico .
Risultati: il punteggio del dolore persistente a tre mesi a livello dell'incisione è significativamente inferiore nel gruppo trattato con paracetamolo (in media [Q1, Q3]: 0 [0, 0]) a paragone col gruppo trattato con placebo (0 [0, 1]) (P = 0.002).
Più specificamente 89%, 9%, e 2% delle pazienti trattate con paracetamolo hanno presentato un punteggio 0, 1 e 2 o più nel VAS del dolore a tre mesi, a paragone col 66%, 23%, e 10% delle pazienti trattate con placebo (rapporto di probabilità : 2.19 (95% CI: 1.33, 3.59), P = 0.002). secondariamente i punteggi del dolore postoperatorio sia in posizione sdraiata che seduta sono stati sifgnificativamente inferiori nel gruppo trattato con paracetamolo. Questo gruppo ha presentato un DN4 significativamente migliore e correlata ad un migliore DF-12, ma non una qualità di vita correlata alla salute fisica.
Da questi risultati si conclude che il paracetamolo riduce richio ed intensità del dolore persistente a livello dell'incisione chirurgica. Però esistono altri meccanismi con cui il paracetamolo potrebbe ridurre il dolore persistente.

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