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A prospective randomized trial of intravenous ketorolac vs. acetaminophen administered with opioid patient-controlled analgesia in gynecologic surgery

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HIGHLIGHTS

- Ketorolac and acetaminophen provide similar post-operative analgesia.
- Ketorolac decreased dilaudid usage and improved return to flatus time.
- Ketorolac patients had similar rates of transfusion compared to acetaminophen.
- Ketorolac patients had improved return of bowel function compared to acetaminophen.

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ABSTRACT

Objective: To determine which non-narcotic analgesic, acetaminophen (Ofirmev®) or ketorolac (Toradol®), provides better post-operative pain control when combined with an opioid patient-controlled analgesia (PCA) pump. Secondary objectives include comparisons of the rates of ileus, post-operative bleeding, transfusions, and length-of-hospitalization (LOH).

Methods: A prospective, randomized trial of acetaminophen (A) 1-g intravenous (IV) every 6-h or ketorolac (K) 15-mg IV every 6-h from post-operative day 1–3 in addition to an opioid PCA for patients undergoing benign or malignant gynecologic laparotomy procedures was performed. Abstracted data included pain levels via visual analogue pain scales (VAS), amount of narcotic used, hepatic enzyme levels, hemoglobin, urine output, blood transfusions, time to return of flatus and LOH.

Results: One-hundred patients were accrued and underwent 55 benign gynecologic laparotomies and 45 cancer-related laparotomies. VAS pain levels (3.3 K, 3.5 A) and morphine PCA use (79.1 oral morphine equivalents [OME] K vs. 84.5 A) were not different, however dilaudid PCA usage was less by K patients (84.4 OME K and 136.8 OME A, $p < 0.001$). There was a significant hemoglobin change between the two groups (2.6 g K vs. 2 g A, $p = 0.015$), however blood transfusions were equal (28% K, 22% A, $p > 0.05$). Return of flatus was 2.7-days for K vs. 3.4-days for A ($p = 0.011$) and LOH was not different (4.4-days K vs. 5.1-days A, $p = 0.094$).

Conclusions: Both intravenous ketorolac and acetaminophen provide similar post-operative analgesia through VAS pain scales and total usage of morphine via PCA pumps. Use of ketorolac with dilaudid PCA was associated with less dependence on dilaudid and a quicker return of bowel function than acetaminophen, however length of stay and transfusion rates were not different.

1. Introduction

Post-operative pain control is integral to optimal surgical care and is a major quality indicator by hospitals and professional organizations interested in initiatives to improve patient satisfaction. Intravenous (IV) narcotics are effective and universally used for

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immediate peri-operative analgesia following laparotomy procedures; but are not without their drawbacks. Common narcotic side-effects include nausea, vomiting, ileus, constipation, and sedation, all of which may lead to other complications that delay discharge and increase cost of care.

In order to minimize the need for narcotics and their potential side-effects, non-narcotic anti-inflammatory medications such as acetaminophen and ketorolac are commonly given to augment pain control. Both acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) including ketorolac provide significant analgesic, anti-pyretic, and anti-inflammatory relief without narcotic-associated side-effects of nausea, vomiting or ileus [1,2]. Acetaminophen and ketorolac produce their effects by inhibition of prostaglandin synthesis [3,4]. Ketorolac (Toradol®) was approved by the U.S. Food and Drug Administration (FDA) in 1989 and IV acetaminophen (Ofirmev®) was approved in the U.S. in 2010. Because NSAIDs reduce platelet function through reversible inhibition of cyclo-oxygenase [3–6], use of ketorolac could be associated with more bleeding complications than acetaminophen in post-operative gynecologic patients, especially when combined with heparin prophylaxis. The analgesic efficacy of IV ketorolac compared to IV acetaminophen has not been tested in gynecologic surgery patients.

We theorized that ketorolac may provide better analgesia than acetaminophen; but could have more bleeding complications in post-operative patients. The primary objective of this prospective randomized study was to evaluate the analgesic efficacy of IV ketorolac versus IV acetaminophen measured by a comparison of the amounts of narcotic used during the hospitalization following gynecologic surgery. Secondly, we sought to compare visual analogue pain scales (VAS) scores, the duration of ileus, length of hospitalization (LOH), estimated blood loss (EBL), and bleeding complications for patients who received either ketorolac or acetaminophen as their post-operative pain adjunct with patient-controlled analgesia (PCA) narcotics.

2. Materials and methods

This study was a prospective, randomized comparison trial of patients receiving IV acetaminophen versus IV ketorolac post-operatively on a tertiary care gynecologic oncology service. Patients who underwent gynecologic laparotomy surgical procedures for benign or cancerous conditions were counseled pre-operatively and institutional review board (IRB)-approved informed consent was obtained. An estimated 100 patients would be randomized to the two treatment arms in order to have sufficient power (90%) for this study to detect a 20% difference in the amount of narcotic used, with alpha of 5%. Patients were randomized equally to the two treatment groups (acetaminophen vs. ketorolac) via a software randomization program (Research Randomizer®).

Patients were selected for entry into this study during their pre-operative visit if they were at least 18-years of age and consented for a laparotomy surgical procedure. Study exclusion criteria included renal insufficiency (creatinine >1.4 mg/dL), cirrhosis, hepatitis or hepatic insufficiency [aspartate transaminase (AST) or alanine transaminase (ALT) > 2 times normal], gastrointestinal (GI) bleeding, active peptic ulcer disease, pregnancy, allergies to acetaminophen or ketorolac, asthma, or current use of anticoagulation medications (warfarin or therapeutic enoxaparin). Also, any signs of post-operative bleeding (hypotension, tachycardia, oliguria, or abrupt drop in hemoglobin) were cause for withdrawal from the treatment aspect of this study.

All patients were given a PCA system in the recovery room with morphine sulfate (MS, 0.5–1 mg/push, 6 min delay, 30 mg/4 h lockout). Dilaudid was substituted for patients with morphine allergies (0.4 mg/push, 6-min delay, 6 mg/h lockout). Patients were randomized to IV acetaminophen versus IV ketorolac starting the morning of post-operative day-1 if there were no signs of post-operative bleeding (systolic blood pressure ≥90 mm Hg, heart rate <120 bpm, >80 mL urine output over a 4-h period, and/or a stable hemoglobin. As a study design, intravenous route was chosen for administration of acetaminophen and ketorolac to ensure equal absorption, anticipating that as some patients would be unable to tolerate per os (PO) medications early in the post-operative period. Patients continued their opioid PCA and given either acetaminophen 1 g IV every 6 h or ketorolac 15 mg IV every 6 h from post-operative day 1–3 (max 3 days), study medication was only discontinued early if the patient was cleared for discharge. Patients were allowed hydrocodone 5 mg/acetaminophen 1–2 tabs every 6 h following discontinuation of the PCA pump. Deep vein thrombosis (DVT) prophylaxis was accomplished with lower extremity sequential compression devices in all patients and subcutaneous enoxaparin (Lovenox®) or heparin in patients with malignancy or prior history of DVT. This study was conducted before the enhanced recovery after surgery (ERAS) protocols were instituted.

The patient's pain levels were measured through VAS [7] and by the amount of opioid used. Patients completed the VAS every 6 h when medication was administered. Other monitored values included daily hemoglobin measures, urine output, vital signs, blood transfusions given and date of flatus as well as date of discharge.

Data was presented as a percentage and/or mean with standard deviation (SD) for continuous and rates in the case of discrete variables. A Student's *t*-test or Chi-squared test was used for continuous and discrete variables, respectively. A z-test was performed to determine the statistical significance where data was analyzed for percent differences between the groups. In all instances, *p*-value <0.05 was used to determine the statistical significance.

3. Results

One-hundred patients enrolled and were randomly assigned to either IV ketorolac (n = 50) or IV acetaminophen (n = 50) [Table 1]. Twenty-nine patients in each treatment arm received enoxaparin or heparin prophylaxis. More transfusions were given in patients who received enoxaparin or heparin for prophylaxis than patients using sequential stockings (72% vs 28%, $p = 0.001$). Forty-four percent of patients on ketorolac plus heparin or enoxaparin underwent transfusions compared to 28% in the acetaminophen group on heparin or enoxaparin prophylaxis ($p < 0.05$). No statistically significant difference was found in regards to transfusion rate in the ketorolac (12%) and acetaminophen (16%) patients who used sequential stockings for DVT prophylaxis ($p > 0.05$). The majority of patients (n = 87) received morphine sulfate PCA while 13 patients had dilaudid PCA. Almost all patients completed either their ketorolac or acetaminophen maximum doses with mean 117.9 ± 8.57 mg K vs. 8 ± 0 g A. Relative cost of mean doses of acetaminophen and ketorolac was US$322.48 A vs $7.12 K per patient, respectively.

The mean VAS pain values were similar for acetaminophen (3.5) and ketorolac (3.3) patients ($p = 0.055$). The mean amounts of morphine used was not significantly different between the two groups (84.5 oral morphine equivalents [OME] vs 79.1 OME K, $p = 0.625$). The dilaudid requirements for patients randomized to acetaminophen exceeded that of the ketorolac users (136 OME) ± 46.8 OME and 84.8 OME ± 30.8 OME, $p < 0.0001$), respectively.

The estimated blood loss and transfusion rates were no different for the two groups, however the mean hemoglobin decrease was greater for the ketorolac patients (2.6 vs. 2.0 gm/dL, $p = 0.016$) [Table 1]. Patients receiving ketorolac had a significantly improved

Table 1
Acetaminophen vs. Ketorolac patients with primary and secondary endpoints.

	Acetaminophen	Ketorolac	*p*-Value
Patients (n)	50	50	N/A
Estimated blood loss (mL)	356 ± 326	295 ± 228	0.28
VAS pain scale	3.5 ± 1.6	3.3 ± 1.7	0.055
Hemoglobin change (g)	2.0 ± 0.87	2.6 ± 1.5	**0.016**
Morphine (OME), n = 87	84.5 ± 67.3 (n = 45)	79.1 ± 53.5 (n = 42)	0.625
Dilaudid (OME), n = 13	136.8 ± 46.8 (n = 5)	84.4 ± 30.8 (n = 8)	**<0.0001**
Transfusion rate (%)	22	28	0.645
Flatus (days)	3.4 ± 1.6	2.7 ± 1.1	**0.011**
Discharge (days)	5.1 ± 2.2	4.4 ± 1.9	0.094
Cancer staging performed (%)	50 (n = 25)	40 (n = 20)	N/A

Abbreviations: VAS = visual analogue scale, N/A = not applicable, OME = oral morphine equivalents.

Table 2
Comparative data representation for cancer vs. benign pathology cases.

	Benign Cases	Cancer Cases	*p*-Value
Patients (n)	55	45	N/A
Estimated blood loss (mL)	234.5 ± 195.11	427.5 ± 302.99	**<0.001**
VAS pain scale	3.59 ± 1.78	3.11 ± 1.56	0.154
Hemoglobin change (g)	2.09 ± 1.05	2.59 ± 1.29	**0.039**
Morphine (OME), (n = 87)	76.57 ± 61.55 (n = 47)	86.16 ± 68.16 (n = 40)	0.494
Dilaudid (OME), (n = 13)	107.76 ± 24.88 (n = 8)	105.8 ± 16.72 (n = 5)	0.869
Transfusion rate (%)	15	39	**<0.001**
Flatus (days)	2.66 ± 0.88	3.52 ± 1.62	**0.002**
Discharge (days)	4.02 ± 1.23	5.64 ± 2.49	**<0.001**

Abbreviations: VAS = visual analogue scale, N/A = not applicable, OME = oral morphine equivalents, POD = post-operative day. Hemoglobin change = difference between POD 0 and POD 1.

($p = 0.011$) time to flatus (2.7 days) compared to the acetaminophen patients (3.4 days), however a shorter length of stay was not recognized [Table 1]. Forty-five patients underwent cancer staging or debulking procedures and 55 patients had benign gynecologic surgeries [Table 1]. Each arm of the study was balanced for benign (25 acetaminophen, 30 ketorolac) and oncologic cases (25 acetaminophen, 20 ketorolac) [Table 2].

Benign surgery patients used more PCA dilaudid in the acetaminophen arm (145.6 OME) compared to the ketorolac arm (70 OME, $p < 0.0001$). Time to flatus was longer for those in the acetaminophen arm (2.9 days) compared to the ketorolac arm in these benign cases (2.4 days; $p = 0.04$). There were no significant differences in VAS pain scales, amount of morphine narcotic used, estimated blood loss, change in hemoglobin, transfusions, and LOH for benign surgical cases randomized to either ketorolac or acetaminophen [Table 2].

Patients who underwent cancer staging laparotomies also had similar VAS pain scales and narcotic usage comparing the ketorolac and acetaminophen treatment arms [Table 3]. Even though the EBL was similar between the groups, there was a significant decrease in hemoglobin in that receiving ketorolac, post-operatively (3.0 g K vs. 2.2 g A, $p = 0.045$). Blood transfusions were not different for acetaminophen versus ketorolac patients (11 patients vs. 14 patients, respectively, $p > 0.05$). The time to initiation of flatus and hospital LOH for cancer patients were also not different between acetaminophen and ketorolac (see Table 4).

We observed differences in pain control comparing benign and cancer staging cases [Table 2]. The mean amounts of morphine sulfate (76.57 OME for benign cases vs. 86.16 OME for cancer cases) and the VAS pain scores (3.59 benign cases vs. 3.11 for cancer cases) were no different. The EBL was higher for cancer cases 427.5 mL vs. 234.5 mL for benign cases ($p < 0.001$) and transfusions were more frequent with 39% of patients being transfused vs. 15% of benign cases ($p < 0.001$). Return to flatus was 3.5 days for cancer versus 2.7 days for benign cases ($p = 0.002$) and LOH was 5.6 days for cancer and 4.0 days for benign cases ($p < 0.001$).

4. Discussion

Adequate post-operative pain control is a key metric in quality outcomes for surgical care. In addition, avoidance of the unpleasant side-effects of narcotics leads to shorter length of stay, fewer complications, lower cost, and better patient satisfaction. Prior studies done separately on acetaminophen and ketorolac have focused on pain control and reduction of narcotic use when given in the intra-operative and immediate post-operative settings. Burns et al. [8] examined patients receiving either intermittent ("prn") or

Table 3
Acetaminophen vs. Ketorolac patients with benign pathology, N = 55.

Benign Pathology	Acetaminophen	Ketorolac	*p*-Value
Patients (n)	25	30	N/A
Estimated blood loss (mL)	221 ± 163	248 ± 228	0.622
VAS pain scale	3.6 ± 1.8	3.6 ± 1.7	1.0
Hemoglobin change (g)	1.8 ± 0.8	2.4 ± 1.3	0.051
Morphine (OME), n = 47	69.6 ± 44.1 (n = 22)	82.5 ± 53.5 (n = 25)	0.34
Dilaudid (OME), n = 8	145.6 ± 20.4 (n = 3)	70 ± 29.6 (n = 5)	**<0.0001**
Transfusion rate (%)	16	13.3	0.987
Flatus (days)	2.9 ± 1.0	2.4 ± 0.8	**0.04**
Discharge (days)	4 ± 1.2	4 ± 1.3	1.0

Abbreviations: VAS = visual analogue scale, N/A = not applicable, OME = oral morphine equivalents, POD = post-operative day. Hemoglobin change = difference between POD 0 and POD 1.

Table 4
Acetaminophen vs. Ketorolac patients with cancer pathology, N = 45.

Cancer Pathology	Acetaminophen	Ketorolac	*p*-Value
Patients (n)	25	20	N/A
Estimated blood loss (mL)	490 ± 391	365 ± 215	0.207
VAS pain scale	3.3 ± 1.5	2.9 ± 1.7	0.407
Hemoglobin change (g)	2.2 ± 1.0	3.0 ± 1.6	**0.045**
Morphine (OME), n = 40	98.1 ± 81.7 (n = 23)	74.2 ± 54.6 (n = 17)	0.269
Dilaudid (OME), n = 5	102.8 ± 18.8 (n = 2)	108.8 ± 14.4 (n = 3)	0.25
Transfusion rate (%)	28	50	0.216
Flatus (days)	3.8 ± 1.9	3.2 ± 1.4	0.245
Discharge (days)	6.2 ± 2.4	5.1 ± 2.5	0.147

Abbreviations: VAS = visual analogue scale, N/A = not applicable, OME = oral morphine equivalents, POD = post-operative day.
Hemoglobin change = difference between POD 0 and POD 1.

scheduled ketorolac with and without a morphine PCA pump for post-operative pain control and found a significant reduction in morphine use in the scheduled ($p < 0.001$) and intermittent ($p < 0.01$) ketorolac groups compared to the morphine PCA alone. In two separate studies, O'Hara et al. [9] and Severino et al. [10] examined the use of ketorolac with a morphine PCA pump versus a morphine PCA pump alone and showed significant decreases in the amounts of morphine used (27 mg and a 20% reduction, respectively).

Intravenous acetaminophen administered peri-operatively has been evaluated in patients undergoing hysterectomy [11,12]. Morphine use was lower in patients who received acetaminophen before the procedure (37 mg less) or immediately following the procedure (28 mg less) compared to those who did not receive any acetaminophen ($p < 0.05$). Alhashemi et al. [13] completed one of the few studies that compared acetaminophen and NSAID for post-operative analgesia. This study examined patients' pain following cesarean section while receiving either acetaminophen (1 g PO every 6 h for 48 h) or ibuprofen (400 mg PO every 6 h for 48 h) and found that both had comparable analgesic effects as shown on visual analogue scales and similar amounts of narcotics used. These studies suggest analgesic efficacy for non-narcotic pain medication in the post-operative setting, but there is no data directly comparing IV acetaminophen and IV ketorolac in gynecologic surgery patients.

Our study found that there was similar morphine use for patients randomized to acetaminophen or ketorolac. However, dilaudid requirements were significantly higher in those patients who randomized to acetaminophen compared to ketorolac ($p < 0.0001$). Even though this was a smaller subset of patients who received dilaudid, it is interesting that acetaminophen did not appear to have the similar effect as ketorolac in these patients. However, this smaller subset of patients does make it hard to generalize the effect of acetaminophen or ketorolac combined with dilaudid. Using the VAS pain scale to define the patient's perception of pain, we found that acetaminophen and ketorolac resulted in equal pain control from the patient's perspective (3.5 for A vs. 3.3 for K). Taking into account the amount of narcotic usage and the VAS pain scales, both acetaminophen and ketorolac seem to adequately augment pain control when PCA analgesia was used.

The use of non-narcotic medications is helpful to decrease the amounts of narcotics required and the subsequent side-effects. Ferraz et al. [14] examined the use of ketorolac on patients undergoing a colectomy. Patients were given ketorolac (30 mg every 6 h) or a narcotic combination (ketorolac 30 mg every 6 h and morphine 2–10 mg as needed). Colonic myoelectrical activity was recorded and the ketorolac-only group reported a 2.3-day ileus versus 4.2 days that was seen in the narcotic combination group. Our study also suggested a reduction in ileus for patients receiving ketorolac compared to acetaminophen while using PCA narcotics. The decreased rate of ileus in our study did not result in a significantly decreased length of hospitalization however. Compared to the morphine control group in the Ferraz et al. study [14], our study observed less ileus using either acetaminophen or ketorolac.

Several studies have warned that the anti-platelet effects of ketorolac may result in post-operative bleeding when used in the pre-/intra–operative setting. However, data is rather limited with used in the post-operative setting alone. Studies by Greer [15] and Bauer et al. [16] examined ketorolac at doses of 10 mg and 30 mg twice daily, respectively, and found that bleeding times were increased. However, values were not outside the normal range and no significant bleeding episodes occurred in these patients. Rogers et al. [17] examined the bleeding effects of ketorolac in gynecology surgical patients who received ketorolac pre-operatively. This study showed an increase in blood loss of 140 mL in those patients who received ketorolac, but no assessment of post-operative bleeding or transfusion was collected [17].

The only contraindications for the use of ketorolac with respect to bleeding are a history of cerebrovascular hemorrhage, any hemorrhagic diathesis, and incomplete surgical hemostasis. In this study, the operative blood loss was not different between those patients receiving ketorolac or acetaminophen. Patients who received ketorolac did show a statistically significant ($p = 0.016$) change in hemoglobin level during the post-operative period (2.0 g A, 2.6 g K). The transfusion rate between these two groups was similar though (22% A vs. 28% K, $p = 0.645$). Patients who received DVT prophylaxis with subcutaneous heparin or enoxaparin did have a higher transfusion rate compared to patients using sequential compression stockings. Thus, ketorolac used in the post-operative setting in patients undergoing laparotomy procedures did not appear to cause significant post-operative bleeding. On the other hand, pain control was similar with IV acetaminophen, and patients at higher risk for bleeding such as those with extensive retroperitoneal dissections or documented intra-operative bleeding can use acetaminophen with near-equal pain control. Pelvic surgeons should therefore weigh the relative risks and benefits of using either acetaminophen or ketorolac combined with anticoagulants for post-operative pain management.

The cost discrepancy between intravenous acetaminophen and intravenous ketorolac at the time of this study was related to the availability of ketorolac in the generic form, whereas IV acetaminophen had no generic equivalent. Intravenous acetaminophen will become in 2020 and therefore the cost for this medication should decrease significantly, possibly eliminating cost as a decision point between these two therapies. Changing to oral ketorolac or acetaminophen would also reduce cost, and can be used for most gynecologic patients.

Weaknesses of this study include not having a third comparison group that received only a morphine or dilaudid PCA pump. This would solidify the effect of acetaminophen and ketorolac compared to a PCA pump alone. Also, a larger group of patients receiving a

dilaudid PCA would have been better in order to determine if there was a significant difference in total usage in those receiving acetaminophen over ketorolac. Strengths of the study are the prospective randomized design and the ability to study these medications in a large post-operative laparotomy patient group.

In summary, our study demonstrates that narcotic use in the post-operative period was similar for ketorolac and acetaminophen treated patients. While ileus was reduced for patients on scheduled ketorolac, LOH was similar to IV acetaminophen-treated patients. There were no differences in bleeding episodes or transfusions, however it would seem prudent to use IV acetaminophen preferentially in patients with higher risks for post-operative bleeding given that pain scores, amounts of narcotics used, and LOH were similar for acetaminophen and ketorolac.

Author contributions

JAR, JEK and RWH designed the study, and subsequently all the authors participated in the data collection, analyses, discussion on results and interpretation, and help drafting the manuscript and revisions.

Declaration of competing interest

All co-authors declare that there are no potential conflicts of interest associated with this clinical research manuscript.

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