Preoperative Acetaminophen Use in Hysterectomy to Reduce Postoperative Opioid Consumption

Anna Lee
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Abstract

Background: Hysterectomy is a common surgery amongst females and is occasionally considered a same-day outpatient surgery. There is a lack of adequate postoperative pain control thus leading to extended use of postoperative opioid use. As a result, in addition to other postoperative side effects, patients suffer from adverse side effects of opioid use, including sedation, respiratory depression, constipation, nausea, and pruritus. This indirectly prolongs patients’ hospital stay and recovery. There have been recent studies suggesting non-opioids, such as acetaminophen, could decrease opioid use postoperatively. The aim of this review is to evaluate whether preoperative acetaminophen use will decrease postoperative opioid use within the first 24-hours after a hysterectomy.

Methods: An exhaustive literature search of available medical literature was performed using MEDLINE-Ovid, Web of Science, and CINAHL-Ebscohost. Keywords used included: preoperative care and acetaminophen. Relevant articles were assessed for quality using the GRADE system.

Results: Nine articles were found and reviewed for relevancy. Two studies qualified for both the inclusion and exclusion criteria for this review. Both studies were randomized controlled trials. One study used 76 subjects with the Pfannestiel incision and the other used 90 subjects with the laparoscopic method. Both studies revealed decreased use of opioid consumption within the first 24-hours of surgery. Additionally, both studies revealed patients had decreased incidents of PONV and pruritus.

Conclusion: Preoperative acetaminophen showed significantly lower use of opioid postoperatively in both open and laparoscopic hysterectomies. Although the mechanism of action of acetaminophen is unclear, there is evidence of efficacy and safety when acetaminophen is used for pain, especially in comparison to the risks of opioid use. Use of preoperative acetaminophen should be strongly considered with both open and laparoscopic hysterectomies to decrease not only opioid consumption but also the adverse side effects of its use. Studies in the future should use randomized controlled trials with larger sample sizes, different surgical modalities, explore different acetaminophen doses, and varying postoperative opioids to further examine the efficacy and acceptability of preoperative acetaminophen use.

Keywords: Preoperative care and acetaminophen

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First Advisor
Annjanette Sommers

Second Advisor
Brent Norris

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Anna Lee

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Faculty Advisor: Brent Norris, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Anna Lee is a native of Chicago, Illinois but grew up in Honolulu, Hawaii. She received her Bachelor of Arts degree from University of Hawaii at Manoa in 2013 with a major in Korean Language Flagship Center while simultaneously completing her pre-requisites for physician assistant school. She received a scholarship to study abroad in South Korea and completed a student internship at Korea University Medical Center in the Family Medicine department, where she translated medical journal articles from Korean to English, in addition to participating in patient presentations and rounds with attendings and residents. She spent the year prior starting the Pacific University Physician Assistant program as a phlebotomist at a laboratory and a medical assistant and office manager at an internal medicine clinic.
Abstract

Background: Hysterectomy is a common surgery amongst females and is occasionally considered a same-day outpatient surgery. There is a lack of adequate postoperative pain control thus leading to extended use of postoperative opioid use. As a result, in addition to other postoperative side effects, patients suffer from adverse side effects of opioid use, including sedation, respiratory depression, constipation, nausea, and pruritus. This indirectly prolongs patients’ hospital stay and recovery. There have been recent studies suggesting non-opioids, such as acetaminophen, could decrease opioid use postoperatively. The aim of this review is to evaluate whether preoperative acetaminophen use will decrease postoperative opioid use within the first 24-hours after a hysterectomy.

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Conclusion: Preoperative acetaminophen showed significantly lower use of opioid postoperatively in both open and laparoscopic hysterectomies. Although the mechanism of action of acetaminophen is unclear, there is evidence of efficacy and safety when acetaminophen is used for pain, especially in comparison to the risks of opioid use. Use of preoperative acetaminophen should be strongly considered with both open and laparoscopic hysterectomies to decrease not only opioid consumption but also the adverse side effects of its use. Studies in the future should use randomized controlled trials with larger sample sizes, different surgical modalities, explore different acetaminophen doses, and varying postoperative opioids to further examine the efficacy and acceptability of preoperative acetaminophen use.

Keywords: Preoperative care and acetaminophen
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To Dr. Mark Pedemonte: Thank you for always motivating our class to pursue the light at the end of tunnel and supporting me both inside and outside of the classroom. I appreciate your efforts to ensure we all succeed after our studies.

To Mr. and Mrs. Christiansen: Thank you for being there for me since my arrival to Oregon – from berry picking and jamming to inviting me for the family holidays. I appreciate the motivational talks we shared in the kitchen and on the second floor living room to encourage me to be the best I can be and helping me embark onto the next chapter in my adventure.

To my family and friends: Thank you for never giving up my dream and cheering me on since the beginning of this adventure. Thank you for always being there for me despite the distance between us and helping me find a way home. I am forever grateful and blessed by such wonderful family and friends.
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List of Abbreviations

PCA.................................................................Patient Controlled Analgesia
ASA............................................................American Society of Anesthesiologist
PONV............................................................Post Operative Nausea and Vomiting
Preoperative Acetaminophen Use in Hysterectomy to Reduce Postoperative Opioid Consumption

BACKGROUND

Hysterectomy is a common surgery performed on women, for both imperative and elective reasons. Most hysterectomy patients complain of incision pain and are not supposed to lift weights for up to 6 weeks since both pain and facial adhesion can occur. Despite the technological advancements in medicine, postoperative pain is still undermanaged.¹ Recent national surveys¹,² suggest 11% of patients experience severe pain and pain alone delays recovery in 24% of patients undergoing ambulatory surgery. Pain is a predictable outcome of surgery; however, it is highly subjective and most patients are treated with opioids regardless of their adverse side effects and risk of dependency.³

Without effective pain control, it is not possible for patients to successfully discharge after a hysterectomy, as the patient must be able to return close to their baseline diet and exercise routine. Routinely used opioids to manage postoperative pain are fentanyl, morphine, hydromorphone, and oxycodone. Common adverse side effects of opioids include sedation, dizziness, nausea, vomiting, constipation, dependence, tolerance, pruritus, and respiratory depression.³ Less common adverse side effects are delayed gastric emptying, hyperalgesia, immunologic and hormonal dysfunction, muscle rigidity, and myoclonus.⁴ As a result, there have been proposals of using alternative non-opioid analgescics peri-operatively.⁵
According to the World Health Organization, mild pain is to be treated with non-opioid analgesics, such as acetaminophen, and moderate to severe pain is to be treated with non-opioid analgesics adjunctively to opioids. Acetaminophen is widely used as an anti-pyretic with nonsteroidal anti-inflammatory properties; however, the mechanism of action is unknown. There are strong suggestions that the patient’s pain threshold is elevated due to an inhibition of central prostaglandin synthesis (cyclooxygenase-2). There are also theories of acetaminophen having a central effect. As the cerebrospinal fluid is able to cross the blood brain barrier and is able to have a high concentration of acetaminophen, it has an anti-nociceptive effect that is controlled by the central nervous system. Additionally, evidence shows acetaminophen to be a relatively safe drug to manage pain as it has low incidences of adverse side effects and is excreted through urine within 24 hours. However, it is strongly contraindicated in patients with severe liver disease. This review targets specifically the use of acetaminophen preoperatively in abdominal hysterectomy to evaluate for a potential decrease in the use of opioids postoperatively.

METHODS

This review was based on the PRISMA checklist. An exhaustive literature search was performed using the following search engines: MEDLINE-Ovid, Web of Science, and CINAHL-Ebscohost. The keywords used in the search engines were the following: “acetaminophen AND preoperative care.” References of articles were also screened for possible studies. The search was further narrowed to include studies with the following inclusion criteria: adults, abdominal
hysterectomy surgery, randomized and controlled, and preventive acetaminophen versus placebo. Articles that used other analgesics preoperatively in addition to acetaminophen were excluded. The articles were examined using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.¹³

RESULTS

There were 138 articles from MEDLINE-Ovid, Web of Science, and CINAHL-Ebscohost and 5 articles through searching the references of relevant articles, resulting to a total of 143 articles. Eight articles were removed due to duplication. After reviewing abstracts, 122 articles were excluded since they did not address the clinical question and 9 additional articles were further excluded due to use of other analgesics preoperatively in addition to acetaminophen. The following studies were evaluated in this review: Moon et al¹⁴ and Arici et al¹⁵ (Table 1).

Moon et al

This study¹⁴ was double-blinded, randomized, and placebo-controlled with a total of 76 subjects. Subjects had an ASA classification (preoperative health status classification system) of 1-2, between 20-65 years of age, and underwent elective abdominal hysterectomy with general anesthesia. Those with allergic reactions to any medication, previous or current alcohol or drug abuse, liver or renal dysfunction, or use of daily analgesics were excluded from the study. Subjects were divided into 2 groups: Group A was given 2 g of acetaminophen and Group C was given a placebo, preoperatively. Throughout the study, Group A
lost 1 subject due to a defective PCA device and Group C lost 3 subjects due to intolerance of PCA side effects despite antiemetic use and 1 subject sustained a postoperative ureteral injury, which needed another operation. However, the demographic was not significantly altered. The surgery performed for the subjects was the Pfannestiel incision, which is a type of open abdominal surgery.\textsuperscript{14}

Thirty minutes prior to surgery closure, 0.7 mg of hydromorphone was given over 5 minutes and after closure to all subjects and PCA was set at 0.2 mg of hydromorphone with a lock-out of 10 minutes, without continuous infusion. In the event post-operative analgesia was felt to be inadequate in both groups, 30 mg of ketorlac was administered and recorded.\textsuperscript{14}

The study was recorded over a 24-hour period and subjects were visited at 1, 2, 6, 12, and 24 hours. The authors determined that a decrease of 30\% of opioid use would be considered clinically relevant. The primary outcome was measured by hydromorphone consumption and secondary outcome was measured by VAS at rest and with movement.\textsuperscript{14}

Both groups were similar in number of subjects given ketorolac for postoperative analgesic relief (Group A: 11\% and Group C: 14\%). Primary outcome revealed 24-hour hydromorphone consumption was lower in Group A compared to Group C, 2.9 ± 1.8 mg (95\% CI at -0.7 and 6.5) vs 4.3 ± 2.3 mg (95\% CI at 0.3 and 8.9) (Figure 1). Additionally, the secondary outcome revealed VAS scores during rest and movement were similar in both groups. The study also revealed that Group A had lower incidences of PONV and pruritus (Table 2).\textsuperscript{14}
Authors of this study acknowledged there were limitations to the study. This study used 2 g of acetaminophen, in comparison to other studies using 1 g, and suggested further investigations are required with specific focus on comparing the standard regiment of acetaminophen dosage. Additionally, they recognized that a larger sample size is required to determine if preoperative acetaminophen influences postoperative nausea and vomiting as Group C excluded 3 subjects due those reasons. Lastly, they noted that abdominal hysterectomy is more of a visceral pain rather than somatic pain. Visceral pain is connected with automatic reflexes, such as nausea and vomiting, therefore stating that more studies with other surgical modalities should be evaluated in order to accurately determine the effects of preoperative acetaminophen use.\textsuperscript{16}

Overall, the authors concluded that although preoperative acetaminophen did not reduce pain intensity, preoperative acetaminophen did decrease postoperative hydromorphone consumption, PONV, and pruritus. Therefore, preoperative acetaminophen may still be beneficial in patients to decrease adverse side effects of opioids.\textsuperscript{14}

\textbf{Arici et al}

This study\textsuperscript{15} was randomized and placebo-controlled with a total of 90 subjects. Subjects had an ASA classification of 1-2 and underwent elective abdominal hysterectomy with general anesthesia. Those with allergic reactions to acetaminophen or morphine, a past history use of acetaminophen, opioids, or NSAIDs, liver or renal dysfunction, cardiovascular disease, or incompetence to use PCA device were excluded from the study. Subjects were divided into the following 3 groups: Group 1 received 1 g of acetaminophen 30 minutes prior to
induction, Group 2 received 1 g of acetaminophen prior to skin closure, and
Group 3 was given a placebo. During the study, Group 1 lost 2 subjects and Group
2 and 3 lost 3 subjects each, however the demographic of the remaining subjects
was not significantly altered. A laparoscopic hysterectomy was performed on all
the subjects in this study.\(^\text{15}\)

Prior to leaving the operating room, a loading dose 2 mg of morphine were
given to all subjects and PCA was set at 2 mg of morphine with a lock-out of 10
minutes, 0.4 mg/kg limit, without continuous infusion.\(^\text{15}\)

The study was recorded over a 24-hour period and subjects were visited at
1, 2, 4, 8, 12, and 24 hours. The authors estimated a 0.85 probability in standard
devation would report both lower opioid consumption and VAS scores. The
results were measured by morphine consumption and VAS scores measured pain
during rest and with movement.\(^\text{15}\)

Overall results revealed morphine consumption was significantly reduced
in Group 1 and Group 2 in comparison to Group 3: 25.93 ± 5.69 mg (95% CI at
14.55 and 37.31), 35.73 ± 5.24 mg (95% CI at 25.25 and 46.21), and 62.93 ± 8.67
mg (95% CI at 45.59 and 80.27), respectively. Additionally, VAS scores during
rest and with movement in Group 3 were significantly higher in comparison to
both Group 1 and Group 2. Also, there was a decrease in incidences of PONV,
pruritus, and shorter hospital stay for Group 1 and Group 2 compared to Group 3
as well (Table 3).\(^\text{15}\)

Authors of this study admit there were limitations and factors to this
study, which include, inference to confounders such as patient anxiety,
communication with service nurses, and preoperative enlightenment.
In conclusion, the study results revealed that Group 1 and 2 had lower morphine consumption and VAS scores at rest and in motion, and less incidences of PONV and pruritus. The study concludes that preoperative acetaminophen does not have negative effects on intraoperative or postoperative hemodynamic parameters, manages postoperative pain, and overall increases patient’s satisfaction by reducing morphine consumption and decreasing side effects and hospital stay.\textsuperscript{15}

**DISCUSSION**

As of 2004, there have been approximately 600 000 hysterectomies performed annually in the United States and it is estimated that by the age of 60, more than one third of all women will have had a hysterectomy.\textsuperscript{17} In 2008, approximately 18\% of hysterectomies were performed as a same-day outpatient surgery.\textsuperscript{18} As surgeries are aiming towards surgical procedures to short-stay basis, this further emphasizes the importance of pain control in order to decrease the consumption of opioids postoperatively. Based on this review, it is effective to administer preoperative acetaminophen to decreased postoperative opioid consumption. Moreover, there are other studies\textsuperscript{19} supporting the hypothesis that acetaminophen use has not only reduced opioid consumption in postoperative patients, but also decreases events of nausea, vomiting, constipation, and respiratory depression.

The results of the two studies are remarkable. In the Moon et al study,\textsuperscript{14} there was a 33\% reduction in hydromorphone consumption, and the Arici et al study\textsuperscript{15} demonstrated an approximate 59\% decrease in morphine consumption in
comparison of Group 1 to Group 3 (Tables 2 and 3). Additionally, the Arici et al study\textsuperscript{15} revealed that acetaminophen administration alone, even prior to skin closure, decreases opioid consumption, further supporting pre-emptive use of acetaminophen (Figure 2). With the additional benefit of a decreased incidence of PONV and pruritis, it is clear to administer acetaminophen preoperatively to patients undergoing hysterectomies.

Despite their results, the studies had some limitations. The Moon et al study\textsuperscript{14} used hydromorphone for their choice of opioid and the Arici et al study\textsuperscript{15} used morphine. The opioid equi-analgesic dose is as follows: morphine 10 mg to 1.5 mg hydromorphone. Commonly used opioids for postoperative pain include morphine and hydromorphone but also fentanyl and oxycodone. Though opioids can be converted to the morphine equivalent, future studies should include the different types of opioids used as the mechanism of action, duration, and side effects for each opioid differ. Both studies used PCA devices to measure the amount of opioids consumed and VAS scores during rest and with movement to determine postoperative pain and side effects. The overall result of 24-hour postoperative opioid consumption in both studies revealed that there was a significant decrease in consumption (Figure 1 and 2).

Additionally, the two studies differed in doses of acetaminophen but yielded results favoring use of preoperative acetaminophen. The Moon et al study\textsuperscript{14} used 2 g of acetaminophen based on previous studies\textsuperscript{20} that revealed decrease of postoperative pain, where as the Arici et al study\textsuperscript{15} used 1 g of acetaminophen. However, in order to effectively use preoperative
acetaminophen, future studies should compare different doses of acetaminophen to validate a standard dose.

Interestingly, Arici et al study\textsuperscript{15} included Group 2 that received acetaminophen prior to skin closure. Although the results showed that morphine consumption was higher than those who received acetaminophen prior to skin incision, it was lower than those who did not receive pre-emptive acetaminophen at all (Table 3 and Figure 2). This opens doors for more studies to explore the comparison of acetaminophen use prior to skin incision and skin closure.

Although the two studies varied between the types of surgery approached for the hysterectomy, Moon et al study\textsuperscript{14} used Pfannestiel incision and Arici et al study\textsuperscript{15} used laparoscopic hysterectomies for all their patients. Therefore, there was consistency within both studies. Future research comparing the two hysterectomy surgical modalities should be pursued, as there are primarily two different approaches to hysterectomies: open abdominal hysterectomy and laparoscopic hysterectomy.\textsuperscript{21} Both surgical modalities are commonly used and the final surgical decision depends on the patient’s demographics and medical history.\textsuperscript{22}

Also, both groups did not receive a downgrade for their sample size, as they were both close to an “n” of 100; however, future studies should have larger sample sizes to yield a narrower confidence interval. Even though the standard deviations in both studies were small, a narrower confidence interval could further strongly support preoperative acetaminophen use in hysterectomies.

Both studies did not show any indirectness of evidence or lack of precision resulting to no downgrades in accordance to the GRADE system (Table 1).
Additionally, the samples that were lost during each study were less than 10%, which did not significantly alter the results. Therefore, both studies resulted to in a final GRADE score of “high.”

**CONCLUSION**

In conclusion, preoperative acetaminophen significantly decreases opioid use postoperatively. This may then lead to decrease of opioid dependency, adverse side effects, and hospital stay. Furthermore, use of acetaminophen even prior to skin closure during surgery can significantly decrease opioid use in comparison to no acetaminophen use at all. Although there are many theories, the mechanism of action of acetaminophen is still unclear. Nevertheless, there is evidence supporting the safety of acetaminophen use in individuals without liver disease. The risks of acetaminophen when weighted against the risks of opioid use are far less. Future studies using randomized control trials with larger sample sizes, different acetaminophen dose, and different postoperative opioids to further examine its effects on postoperative opioid consumption would be beneficial. Based on the reviews of the two studies, there is strong evidence supporting the efficacy of using preoperative acetaminophen. Therefore, preoperative acetaminophen should be implemented to individuals without liver disease in both open abdominal and laparoscopic hysterectomies to not only decrease postoperative opioid use but to increase patient satisfaction and recovery.
REFERENCES


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during the first 24 h with a 2-g starting dose. *Clinical Pharmacology & Therapeutics.* 2007;81:401-405.


### Table 1
**Quality Assessment of Reviewed Articles**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon et al(^\text{14})</td>
<td>Double-Blinded, RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Unlikely</td>
<td>High</td>
</tr>
<tr>
<td>Arici et al(^\text{15})</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Unlikely</td>
<td>High</td>
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</table>

### Table 2
**Moon et al: Postoperative Side Effects\(^\text{14}\)**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone Consumption (mg)</td>
<td>4.2 ± 2.3</td>
<td>2.9 ± 1.8</td>
</tr>
<tr>
<td>PONV</td>
<td>36%</td>
<td>60%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>6%</td>
</tr>
</tbody>
</table>

### Table 3
**Arici et al: Postoperative Side Effects and Hospital Stay\(^\text{15}\)**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine Consumption (mg)</td>
<td>25.93 ± 5.69</td>
<td>35.73 ± 5.24</td>
<td>62.93 ± 8.67</td>
</tr>
<tr>
<td>PONV</td>
<td>17.4%</td>
<td>21.1%</td>
<td>60.9%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0%</td>
<td>3.3%</td>
<td>22.2%</td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>5.03 ± .076</td>
<td>5.20 ± 0.92</td>
<td>6.43 ± 1.38</td>
</tr>
</tbody>
</table>
Figure 1
Moon et al: Total 24-Hour Hydromorphone Consumption (mg)\textsuperscript{14}

Group A: With Preoperative Acetaminophen
Group C: Without Preoperative Acetaminophen

Figure 2
Arici et al: Total 24-Hour Morphine Consumption (mg)\textsuperscript{15}

Group 1: With Acetaminophen Prior to Skin Incision
Group 2: With Acetaminophen Prior to Skin Closure
Group 3: Without Acetaminophen