A Randomized Controlled Trial Comparing Preemptive Versus On Demand Administration of Analgesics after Mohs Surgery and Cutaneous Reconstruction

A thesis submitted to the University of Arizona College of Medicine—Phoenix in partial fulfillment of the requirements for the degree of Doctor of Medicine

Lauren Crow, Class of 2016

Mentor: David Brodland, MD
Acknowledgments

This project would not have been possible without the support of my mentor, Dr. David Brodland, and the entire staff at Zitelli & Brodland, P.C., who helped with patient recruitment and execution of the clinical trial. Thank you to everyone involved.
Abstract

BACKGROUND: Mohs Micrographic Surgery (MMS) affords a high cure rate for cutaneous carcinoma.

OBJECTIVE: This study was designed to characterize the pain patients experience after MMS and reconstruction of the head and neck, and to determine if preemptive dosing of analgesics was superior to patient-initiated dosing on an "as needed" basis.

METHODS: A controlled trial of 200 subjects undergoing MMS and reconstruction of skin cancers on the head and neck were randomized to either receive acetaminophen at the time of discharge or to take it on an "as needed" basis. The two groups were evaluated for differences in peak pain, satisfaction with pain management, and the need for narcotic analgesic "rescue" postoperatively.

RESULTS: Peak pain levels after surgery were surprisingly low and rated, on average, 2/10 using an analog pain scale. Peak pain occurred at four hours postoperatively for both subgroups and patients were satisfied with pain control 72.5% of the time. There was no significant difference in any of the parameters between the two dosing regimens.

CONCLUSIONS: Mohs surgery peak pain typically occurs four hours postoperatively. Patient satisfaction with pain management was high with acetaminophen regardless of the dosing regimen. Preemptive analgesia with acetaminophen does not appear to be superior to "as-needed" regimens.
Table of Contents

- Figures and Tables Page I
- Background/Significance Page 1
- Methods Page 3
- Results Page 5
- Discussion Page 10
- References Page 13
Figures and Tables

- Page 6, Figure 1. Mean Pain Scores.
- Page 8, Table 1. Summary of Patient Metrics.
Background

Mohs micrographic surgery is a tissue-sparing surgery that affords the highest cure rate among all treatments for basal cell carcinoma and squamous cell carcinoma.1 The incidence and prevalence of all types of skin cancers are increasing in the United States.2,3 To better serve this growing number of patients, it is important to understand approximately how many patients experience pain after surgery and what factors affect postoperative pain. Due to increasing efforts from the Department of Health and Human Services as well as the Institute of Medicine, the movement to assess and improve patient outcomes has become an integral part of every aspect of medical practice, and has become a requisite of the standard of care.4 This movement has started to involve outpatient medical and surgical subspecialties such as Mohs Surgery and Dermatologic Oncology. Several subspecialties have started to systematically investigate measures of postoperative pain in response to analgesics, including the use of over-the-counter medications such as acetaminophen.5

Patients undergoing outpatient surgery frequently require some form of analgesia that can be taken at home in the first few hours to days after the operation. Past studies of outpatient post-operative temporal pain management have often focused on the use of prophylactic analgesics to reduce postoperative emesis.6 A study in the general surgery literature revealed that the combination of acetaminophen plus ibuprofen was an effective alternative to Codeine derivatives for pain control following outpatient procedures.7 Mitchell et al examined 146 patients undergoing either herniorrhaphy or laparoscopic cholecystectomy and found a combination of acetaminophen plus ibuprofen to have fewer side effects and higher patient satisfaction when compared with acetaminophen plus codeine for postoperative pain. There is currently no population-based data examining timing of post-operative analgesic regimens following dermatologic surgery and Mohs micrographic surgical (MMS) procedures. Although the dermatologic literature is replete with studies addressing the safety, cost effectiveness, and high cure rates of Mohs surgery, an optimal post-operative pain control dosing regimen that is safe and effective remains to be elucidated. A recent randomized controlled trial investigated the use of different medications or combination medications for postoperative pain control after Mohs micrographic surgery, and found that the combination of
acetaminophen and ibuprofen elicited the best control of postoperative pain. In addition, they found that pain from MMS and reconstruction appears to be greatest 4 hours after surgery across all medication groups. This study outcome merits the need for further exploration of postoperative dosing regimens to supplement the current studies evaluating medication options.

In examining the literature of other medical specialties, it appears that the trend is to examine the use of different pain medications, but not to examine the timing of the allocation of analgesics. Counterparts in the fields of general surgery, obstetrics, otolaryngology, and pediatrics have examined and compared different post-operative analgesics with interesting results. Deciphering the optimal timing for post-operative dosing might prove to be a safe and effective adjunct to the dermatologic surgeon’s armamentarium in alleviating pain after Mohs micrographic surgery. Studies in the field of MMS and cutaneous surgery have already established the safety and efficacy of these procedures. A multicenter cohort study by Merritt et Al. from 2012 evaluated 1550 patients undergoing MMS, and concluded that the procedures were safe (2.6% minor postoperative complication rate) and were generally well-tolerated by patients. While assuring patients they will not likely experience severe pain and encouraging the use of OTC pain medications has become an evidence-based practice as the result of such studies, the timing of an optimal dosing regimen has yet to be established, and is one of the goals of this study. This study will compare the efficacy of preemptive acetaminophen administration with on-demand dosing for postoperative pain control in order to clarify differential value for each dosing regimen in cutaneous surgery patients using an analog pain scale.
Methods

Institutional review board approval was obtained (Western IRB Study #1128053), and the study protocol conformed to accepted ethical guidelines established by the 1975 Declaration of Helsinki. This prospective, randomized trial was conducted in the setting of a private practice.

Consecutive patients undergoing MMS and reconstruction for tumors of the head and neck were eligible for inclusion. Subjects were excluded if they were taking warfarin/Coumadin or Plavix (clopidogrel), had a history of hepatitis or liver disease, had a history of renal disease, had a history of stomach ulcers/bleeding, or if they had known allergies to acetaminophen, ibuprofen, codeine, or any other NSAID. Current research on the effects of anticoagulation for postoperative outcomes is inconclusive. A systematic review that evaluated thirty-one recent anticoagulation papers found that while anticoagulation should definitively be stopped for large procedures, the literature is substantially limited in its ability to define an optimal strategy for anticoagulation in less-invasive procedures. Until further and more rigorous studies can be conducted to better inform this decision, we decided to exclude patients using anticoagulants from our study.

After informed written consent was obtained, patients were randomly assigned by a computerized random number generator (1:1 ratio) to one of two treatment groups. Two hundred patients with single site skin cancers of the head or neck undergoing MMS and subsequent reconstruction were enrolled in the study then randomly assigned to one of two treatment groups: Treatment Group A (n=100, pre-emptive dosing regimen) and Treatment Group B (n=100, as-needed dosing regimen). The first treatment group, Group A, was to receive 1,000 mg Acetaminophen immediately postoperatively (prophylactic dosing). The second group, Treatment Group B, was instructed to take acetaminophen on an as-needed basis. All patients were given a prescription for a narcotic pain medication, and were instructed to fill the prescription and use it only if needed. The U.S. FDA’s recommended maximum dosage of 3,000 mg of Acetaminophen per day was not exceeded in this study. No preoperative or intraoperative analgesics were used. Patients then received a 100-mm visual analog pain scale (VAS) and questionnaire. A physician or research assistant then explained the forms to the
patient. Patients were instructed to rate their pain on a VAS at 0, 2, 4, 8, and 12 hours after surgery. They also were given space to record whether they took a dose of medication at the allotted intervals, and a space to record any side effects from the medication, such as nausea, vomiting, constipation, dizziness, or bleeding from the surgery site. A VAS has often been used as a reliable and meaningful assessment of postoperative pain in many specialties.\textsuperscript{11,12} Participants also were asked to record dichotomous responses to satisfaction (Yes/No) and use of narcotic prescription for uncontrolled “break-through” pain (Yes/No).

Upon completion of the 12-hour post-operative period, subjects were asked to mail back their completed questionnaires using the provided pre-stamped envelope. The primary outcome measured was patient-reported pain levels and satisfaction with the pain control regimens. We used a two-way Analysis of Variance to assess the influence of Group and Time on self-reported pain scores. We then used pairwise t-tests (with Bonferroni Correction) to observe interactions and permutations across groups. The Bonferroni Correction is a conservative statistical approach used to adjust for multiple tests across time points to avoid inflating the probability of type I errors.\textsuperscript{13} Differences in satisfaction with pain control and narcotic use were also evaluated between groups.
Results

Eighty-nine subjects in Treatment Group A (89%) and eighty-five subjects in Treatment Group B (85%) completed the study endpoints. The remaining participants were lost to follow-up. Efforts to contact these patients were made for old non-respondents. The two treatment groups were similar in terms of average age, post surgical wound size, mean surgical area, and baseline pain level. Initially, the two treatment arcs follow the expected trajectory for postoperative pain, with pain initially rising and peaking at 4 hours postoperatively. However, statistically significant differences were not found in efficacy for pain control for any of the measured time points (Figure 1).
Figure 1. Mean Pain Scores. Over 12 hours following MMS, this graph shows average pain levels according to analgesic treatment group. Group A received prophylactic analgesia and Group B used "as-needed" analgesia.
There was a statistically reliable effect of Time (p<0.001) but no effect of Group (p=0.15) and no interaction (p=0.40). Pairwise t-tests (with Bonferroni correction) showed that, across groups, average pain scores were higher at two hours ($M=1.37$, $SD=1.86$, $p<0.001$), four hours ($M=1.67$, $SD=2.09$, $p<0.001$), eight hours ($M=1.37$, $SD=1.86$, $p<0.001$), and 12 hours ($M=0.90$, $SD=1.67$, $p<0.001$) vs. baseline ($M=0.09$, $SD=0.45$) and higher at two hours ($p<0.001$), four hours ($p<0.001$), and eight hours ($p<0.001$) vs. immediate post procedure ($M=0.45$, $SD=1.28$) and lower at 12 hours ($p=0.0002$) vs. four hours (Table 1).
<table>
<thead>
<tr>
<th>Metric</th>
<th>Overall (n=174)</th>
<th>Group A (n=89)</th>
<th>Group B (n=85)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean score (SD)a</td>
<td>0.09 (0.45)</td>
<td>0.09 (0.45)</td>
<td>0.08 (0.45)</td>
<td>0.83</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.45 (1.28)</td>
<td>0.29 (0.69)</td>
<td>0.62 (1.67)</td>
<td>0.09</td>
</tr>
<tr>
<td>Post procedure</td>
<td>1.37 (1.98)</td>
<td>1.22 (1.78)</td>
<td>1.53 (2.16)</td>
<td>0.31</td>
</tr>
<tr>
<td>Two hours</td>
<td>1.67 (2.09)</td>
<td>1.63 (2.02)</td>
<td>1.72 (2.19)</td>
<td>0.78</td>
</tr>
<tr>
<td>Four hours</td>
<td>1.37 (1.86)</td>
<td>1.37 (1.86)</td>
<td>1.37 (1.87)</td>
<td>0.99</td>
</tr>
<tr>
<td>Eight hours</td>
<td>0.90 (1.67)</td>
<td>1.08 (1.95)</td>
<td>0.71 (1.29)</td>
<td>0.15</td>
</tr>
<tr>
<td>Twelve hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfied (%)b</td>
<td>72</td>
<td>72</td>
<td>73</td>
<td>0.99</td>
</tr>
<tr>
<td>Narcotics (%)b</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>0.62</td>
</tr>
</tbody>
</table>

aIndependent-samples t-test. bChi-square test.

**Table 1. Summary of Patient Metrics.** Comparison of Baseline Pain Scale Ratings, Patient Satisfaction, and Narcotic Use According to Group.
In terms of patient satisfaction, there was again no difference observed between the two groups. Both treatment group A and B demonstrated satisfaction rates of 72% and 73%, respectively (p=0.99). Overall, narcotics prescriptions were utilized by only 7% of participants. Between the two groups, Treatment Group B had a lower incidence of narcotic use (6%) than Treatment Group A (9%), which was not a statistically significant difference. In general, patient satisfaction was high for this procedure in both groups, and narcotic utilization was low.

Interestingly, the peak pain for both treatment groups occurred at 4 hours postoperatively, which is congruent with previous data from studies of post Mohs pain levels that showed peak pain occurring at 4 hours after baseline.⁶
Discussion

Population-based data examining the efficacy of postoperative analgesic regimens for Mohs micrographic surgery has yet to be explored. Although previous studies, such as the randomized controlled trial done by Sniezek et Al., have examined postoperative pain by defect size and location, there has yet to be an evidence-based argument for or against the routine administration of analgesics in the postoperative period. With data suggesting a peak pain for MMS occurring 4 hours postoperatively, it was reasonable to assume prophylactic dosing of pain medication could reduce postoperative pain levels with a relatively quick onset and resolution. However, results from this study show that there is no significant difference between patients given prophylactic acetaminophen and those instructed to take PRN dosing of acetaminophen.

Current procedures for MMS often utilize an injection of local anesthetic (buffered 1% lidocaine with epinephrine) after identifying the skin cancer. For most skin cancer patients, postoperative acetaminophen is recommended as the first line of analgesic pain management. Mohs surgeons often advise patients undergoing Mohs surgery of the head and neck to take acetaminophen on an as-needed basis after surgery to manage postoperative pain. For defects in more sensitive areas such as the lips, eyelids, or nose, or for larger defects requiring more extensive repair and reconstruction, patients often experience higher levels of postoperative discomfort. For these patients, various narcotic analgesics are often prescribed. However, these practices have not yet been supported by evidence-based analysis of pain control by dosing regimen. Based on the literature, it can be hypothesized that pain control after MMS and reconstruction might be optimized through a better understanding of dosing. At the same time, routine administration of acetaminophen to all patients may not prove necessary, and therefore may be a drawback. This is especially so if simply informing patients to take acetaminophen on an “as needed basis” is as effective in controlling the postoperative pain, which would then make routine administration suboptimal. In contrast, if preemptive pain management is proven effective, it may actually obviate the need for prescriptive narcotic
analgesics, which in and of itself would reduce unnecessary prescribing of medication and its attendant costs and complications, as well as the potential for abuse.

There are several limitations of this study that could explain why no difference was observed between the two treatment groups. First, the power of n, the number of participants, began at only 200 and fell to 174 after some participants were lost to follow-up. Since any difference between the two treatment groups would be expectedly subtle, a substantially larger sample size would be needed to detect any potential statistically significant difference. In addition, the peak pain was reported at 4 hours postoperatively. The prophylactic analgesia administered to Treatment Group A at Time 0 may not have been optimal to cover peak pain experienced at Time=4 hours. The Tmax of acetaminophen is within 1 hour in adults, and the half-life of acetaminophen is 2-3 hours for adults. This means that after four hours, only about a quarter of the initial dose was active in the treatment population. The selected time of prophylactic dosing in this study may not have been optimal to address the most critical time period for pain postoperatively. Prophylactic dosing of acetaminophen at 2 hours postoperatively may prove more beneficial for pain control for MMS specifically.

Further studies could be done to better elucidate control of postoperative pain for MMS and dermatologic surgery procedures of the head and neck. Information regarding the appropriate timing of postoperative analgesics could further improve patient satisfaction, decrease pain, and limit narcotic use. The population typically undergoing MMS for skin cancer tends to be an older population, in which limiting narcotics and their side effect profile would greatly improve the patient experience and limit adverse events. As this procedure is an outpatient one, it is important to have confidence that patients have pain under control and will not experience increasing pain beyond their control, necessitating hospital and ER visits. Methods to further define optimal standards of postoperative analgesic care could involve stratifying subgroups according to different parameters such as mean surgical area or specificity of surgical site on the face. The study also confirmed that, in general, the intensity of pain after cutaneous surgery is relatively low (below 2/10 on average). This fact, in and of itself, is informative to the clinician when considering the use of narcotic analgesics. It also enables
clinicians to assure their patients that, on average, they will not experience severe postoperative pain.

In conclusion, postoperative prophylactic dosing with acetaminophen 1,000 mg does not decrease subjective pain scores for patients undergoing MMS and reconstruction of the head and neck. However, given the potential low cost and side effect profile of acetaminophen and other OTC analgesic medications, further studies to best define postoperative analgesic regimens could improve patient care in the future. In addition, a combination of acetaminophen and ibuprofen has been shown to have synergistic effects that have been shown to greatly improve pain control. Future studies to examine both optimal dosing and medication regimen are warranted.
References


