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Acute Post-Operative Pain Management: Preventing Overuse of Opioids

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Abstract

Background: Surgical pain management with opioids is common. The use of multimodal analgesia has been proposed in order to provide opioid-sparing regimens and improve pain control post-operatively. Inadequate control of surgical pain can lead to development of chronic pain. Furthermore, studies have linked acute surgical opioid use to increased risk of long-term use. Long-term opioid use has undesirable, life-altering consequences, including physical dependence and addiction which may lead to overdose or death. Use of a variety of medications in the operative setting can lead to synergistic or additive effects on pain control, thus decreasing post-operative opioid consumption.

Methods: A literature review was conducted to answer the question of whether multimodal analgesic regimens decrease acute post-operative opioid consumption among opioid naive patients when compared to standard therapy.

Discussion: Review of literature on single opioid-sparing as well as multimodal opioid-sparing medication techniques in short-stay surgery suggest methods for decreasing post-operative opioid consumption. Limitations include smaller study groups and varying multimodal analgesic protocols and surgical procedures evaluated aside from barriers on implementing such protocols.

Conclusion: More consistent research is needed to evaluate specific multimodal analgesic protocols and use within specific types of surgeries. Review of the literature suggests that multimodal analgesic regimens have the capability to reduce acute post-operative opioid use in ambulatory surgical settings among opioid naive patients It will be key to identify individuals that are at higher risk for long-term opioid use in the preoperative stage in order to ensure implementation of multimodal analgesia at time of surgery. Research regarding the impact of multimodal analgesia on frequency of long term opioid use would be of benefit.

Introduction

Opioid use for acute and chronic pain management is a topic of ongoing debate and research, especially since the increased visibility of the opioid crisis in the United States. The International Association for the Study of Pain defines pain as "unpleasant sensory and emotional experience associated with actual or potential tissue damage."[1] Pain stems from multiple etiologies, making it complex to treat. Along with acute and chronic, pain is often classified as somatic, visceral or neuropathic. Somatic pain is defined as "a well-localized constant, achy area in skin and subcutaneous tissue and less well-localized in bone, connective tissue, blood vessels, and muscles."[1] Visceral pain is defined as a "poorly localized, crampy, diffuse, and deep sensation originating from an internal organ or a cavity lining".[1] Neuropathic pain is "a poorly localized, electric shock-like, lancinating, shooting sensation originating from injury to a peripheral nerve, the spinal cord, or the brain."[1] Different treatment modalities and medications are recommended and superior in regards to efficacy depending on the etiology of the pain. Since pain is complex and includes multiple pathways, the use of multiple agents for pain control appears to be a promising advancement in operative care.

Opioids are often prescribed for acute pain treatment, especially in surgical management, without the intention that patients will continue to use these medications for a prolonged period of time. It is of significant importance to better understand reasons for which short-term opioid use progresses to unintended prolonged use, especially in the opioid naive patient.[2] Preventing prolonged use of opioids will hopefully prevent associated adverse outcomes including life-alerting side effects along with intentional and unintentional overdose and death. Opioid overdose rates have tripled over the past couple of decades and many occur in non-chronic (< 90 days) users.[3] Opioids remain the standard of care for patients in acute moderate to severe post-

operative pain.[2] According to the 2015 National Survey on Drug use and Health, "2.7 million people aged 12 or older had a prescription drug use disorder in the past year."[4] Furthermore, opioid prescriptions from medical providers account for 34% of the misuse.[4] Almost all patients who have surgery have acute pain, "yet evidence suggests that less than half report adequate postoperative pain relief."[5] Surgical patients are almost four times as likely to get discharged with an opioid prescription when compared to non-surgical patients.[3] The use of multimodal analgesia in acute surgical care has been proposed as a way to better control post-operative pain and reduce opioid consumption.

The question to be addressed reads, "among opioid naive patients having outpatient or short-stay surgery, does providing multimodal analgesic (opioid-sparing) regimens versus providing standard opioid therapy decrease acute postoperative opioid use?" Poorly treated acute post-operative pain not only has a significant influence on quality of life, but also increases the risk for development of chronic pain which may lead to prolonged opioid use.[5] Multimodal analgesia often includes use of medications administered prior to, during, and after the surgical procedure. It can be defined as a pharmacologic method of pain management which combines at least two groups of medications that work via different mechanisms for pain relief.[6] This may be done through enhanced recovery after surgery (ERAS) protocols that begin in the outpatient setting and continue through post-operative care.[7] The purpose of multimodal analgesia is to offer opioid-sparing pain control. It could be hypothesized that use of such opioid-sparing pain management could limit consumption and need for opioids following surgery by more adequately controlling post-surgical pain. In order to answer this question, the objectives that need to be addressed include understanding the concept of unintended prolonged use of opioids, patient risk factors and pathways associated with prolonged opioid use and opioid use disorders,

and the use of and acceptability of multimodal analgesia (opioid-sparing) medications and protocols in surgical pain management, with focus on outpatient surgery.

Background: Literature Review

Prolonged Post-Operative Opioid Use and Associated Risk Factors

Opioids are the standard of care for patients in acute moderate to severe post-operative pain, however, research suggests that there is a continuation of opioid prescriptions in the days to months that follow surgery.[2,10,11] Overall, multiple studies have estimated that 3-13% of opioid naive patients who are prescribed opioids for acute pain continued to receive prescriptions long-term, defined by at least 90 days in most studies and measured up to 12 months in some studies.[2,10,11] Furthermore, it has been recently suggested that the potential for surgical patients to become dependent on opioids after brief perioperative exposure is as high as 15%.[4] The Center for Disease Control and Prevention (CDC) suggests that both dose and duration of opioid intake is important when considering potential for addiction.[4] The CDC noted that opioid treatment with a duration of even 10 days has the potential to turn into dependency.[4] Interestingly enough, some studies have found prolonged opioid use to be somewhat unrelated to the type of surgery.[2] Two studies found that persistent opioid use among previously naive patients post-operatively did not significantly differ between minor versus major surgeries and that many surgical procedures were associated with an increased risk of post-operative chronic use.[8,9] However, a different retrospective cohort study found that prolonged opioid use, defined as an opioid prescription within 1 to 90 days after surgery and an opioid prescription 91 to 180 days after surgery, was highest in patients who underwent open or minimally invasive thoracic surgeries.[10]

This same study found an overall incidence of 3.1% prolonged opioid use in opioid naive patients yet it is important to note that the rate of prolonged opioid use was 8.5% after open

thoracic surgery and 6.3% after minimally invasive thoracic surgery, the greatest associated surgical risk to prolonged use.[10] A limitation of this study was the inclusion of only patients who were 66 years and older.[10] This is especially significant given previous studies findings that showed an increased risk of prolonged opioid use in younger male patients.[3]

Aside from inadequate control of post-surgical pain, it is suggested that a transition from short-term to long-term opioid use after an acute event such as surgery may occur due to presence of other sources of pain that are present prior to surgery.[9] Pre-existing conditions including heart failure, pulmonary disease, diabetes mellitus, and post-traumatic stress disorder (PTSD) have been noted in multiple studies as contributory risk factors for the development of prolonged opioid use in surgical settings.[2,10] Further identified risk factors included history of substance abuse (alcohol and tobacco misuse), depression, anxiety, and pain catastrophizing, benzodiazepine, selective serotonin reuptake inhibitor (SSRI) or angiotensin converting enzyme (ACE) inhibitor use prior to surgery, back and neck pain, arthritis, and centralized pain.[4,8,9,10] Demographic risk factors included younger age and lower socioeconomic status with mixed data regarding differences of risk in females versus males.[3,4,10]

In a retrospective cohort study by Brat et al., a post-discharge opioid prescription was the strongest predictor of future misuse.[3] When patients received a refill, the rate of misuse almost doubled when compared to patients who did not receive a refill.[3] The authors found that the dose of the opioid prescribed was a weaker predictor of future misuse when compared to duration or number of prescriptions.[3] Often times, opioids are prescribed by providers at a standard dose based on the expectation and anticipation of post-operative pain despite the fact that this may contribute to an unneeded extra amount of medication.[11] In a study by Alam et al., of 391,139 opioid naive patients 66 years and older who underwent low-risk surgery, 27,636 (7.1%)

received an opioid prescription within 7 days of discharge and 30,145 patients (7.7%) received an opioid prescription 1 year from the time of surgery.[11] Although the study was unable to determine the exact reason or need for an opioid prescription up to 12 months post-procedure, there may be a relationship between postoperative opioid prescriptions and long-term use.[11] Overall, both studies estimated that patients who received a opioid prescription at time of discharge had a 44% increased risk of using opioids long-term when compared to those who did not receive a prescription at time of discharge.[3,11] According to the CDC, the risk for chronic opioid use in an opioid naive person increases with each day of use beginning with the third day with the biggest increase of risk associated with the fifth and thirty-first day of opioid use.[4]

In addition, strong evidence exists that suggests opioids are an ineffective way to manage chronic nonmalignant or movement associated pain.[2,10] A vicious cycle of chronic opioid use and inadequate pain control is often created. Although the majority of patients may not experience prolonged opioid use after surgery it is important to identify high risk patients and ensure appropriate management of pain they may be experiencing in the days and months that both precede and follow their surgical procedure. For example, a retrospective cohort study by Clark et al. explained that 40-80% of patients that are status post thoracotomy procedure develop post-thoracotomy pain syndrome which can trigger long-term use of pain medications.[10] In over half of these cases, the origin of the pain is neuropathic due to nerve injury during the procedure itself and would therefore be better controlled with neuropathic pain drugs such as gabapentinoids or tricyclic antidepressants rather than opioids.[10]

Pathway to Opioid Misuse Disorders

Understanding how opioid use disorders develop in individuals is imperative. It is known that patients with chronic pain, mental health diagnoses, and prior substance abuse or misuse

already are at higher risk for opioid dependency or addiction with prescription use, however, less is known about how a person may develop such a problem.[12] In an effort to better understand how patients go on to develop opioid use disorders researchers interviewed patients with opioid use disorders. The results of these interviews showed an emergence of five themes, one of which included the idea that "some individuals are vulnerable to opioid dependence after brief opioid exposure."[12] This quote was taken directly from one interviewed patient who underwent an outpatient procedure, "I never was one that experimented or did drugs, or even really drank a lot…but four years ago, I had gastro-bypass surgery, and that's when I got hooked on [hydrocodone/acetaminophen]. They gave me the liquid [version]. I liked it. And it kind of went from there."[11] This theme fits into the concern that even use of opioids in the acute post-operative phase alone could lead to unintended long-term use in some opioid-naive patients.

Overview of Potential Opioid-Sparing Medications

Many studies have looked at multimodal analgesia (opioid-sparing) pain management protocols in order to reduce opioid consumption in the acute surgical phase. The American Pain Society recommends "that clinicians offer multimodal analgesia, or the use of a variety of analgesic medications and techniques combined with non-pharmacological interventions, for the treatment of post-operative pain in children and adults."[5] Use of drugs with differing mechanisms of actions is warranted in order to act on multiple aspects of the pain pathway which allows for an additive or synergistic effect and better pain management.[13] Agents that are used in the multimodal pain regimen include but are not limited to opioids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, gabapentinoids (gabapentin and pregabalin), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), N-methyl-D-aspartate (NMDA) receptor antagonists, alpha-2 adrenoreceptor agonists, lidocaine,

esmolol, and caffeine.[13,14] Furthermore, epidural and intrathecal interventions, peripheral nerve block interventions, and local analgesia may be utilized.[13] Determining the most effective analgesic during surgery is a challenge as there are multiple combinations with relatively few of them being adequately evaluated in studies.[5]

Multimodal analgesia targets different aspects of the nociceptive pain process. Phases included in the pain process are transduction and conduction, transmission, perception, and modulation and are shown in the Figure.[13] Transduction occurs after there is cell damage and activated nociceptors release an electric signal.[13] Transmission occurs when the electric signal migrates from the area of damaged cells to the central nervous system.[13] Perception is the ability of the somatosensory cortex of the brain to become aware of the pain that one is experiencing and is known as the conscious aspect of pain.[13] Finally, the modulation phase is the adaptive process and the step at which pain is "modulated" in some way, enhanced or diminished.[13] Increasingly surgeries are being done as an outpatient basis thus, conventional opioid-based pain regimens are not as conducive or practical for peri-operative management.[14] Intravenous or patient controlled-analgesia (PCA) is not an outpatient option and patients are under less supervision from providers or nurses when it comes to weaning off oral medications. Although many complex surgeries are able to be completed on an outpatient basis, patients still experience moderate-severe pain, thus the need for adequate multimodal pain management is relevant. There are several subtypes of opioids but the ones most commonly used in practice "stimulate mu receptors found primarily in the peripheral and central nervous systems, inhibit nociception in the spinal cord, and activate descending pain pathways controlled by circuits from the forebrain and midbrain."[13] The most commonly used opioids include morphine, hydromorphone, fentanyl and oxycodone which may be administered intravenously, via PCA, or orally for acute pain.[13]

Adverse effects include but are not limited to confusion and sedation, hypotension, constipation, nausea, vomiting, and respiratory depression. Furthermore, even with acute use as discussed earlier, opioids have to potential to lead to physical dependence, addiction, intentional or unintentional overdose, and death.[4,11,13] The potential for undesirable effects from use of opioids is the drive to introduce multimodal analgesia in the pre-, intra-, and postoperative phases.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are often used for pain due to inflammation as they inhibit the enzyme cyclooxygenase, which synthesizes prostaglandins that promote inflammation, thus contributing to pain.[13] NSAIDs are a common aspect of multimodal analgesia for pain control in ambulatory care.[15] NSAIDs have been known to reduce opioid consumption by 25-30% but can also provide improved pain control when combined with opioids.[4] Adverse effects of NSAIDs include: platelet inhibition and bleeding, gastric irritation, renal dysfunction, cardiotoxicity and hepatoxicity thus limiting their overall use in some patient populations.[13] A concern in the ambulatory surgery setting is the potential risk for bleeding at the surgical site or gastrointestinal bleeding due to platelet and prostaglandin synthesis inhibition, as prostaglandins help to provide gastric protection.[13,15] For that primary reason, studies looking at selective cyclooxygenase-2 (COX-2) inhibitors in particular have become of interest.

A randomized controlled study by White et al. evaluated postoperative celecoxib use in outpatients undergoing laparoscopic surgery.[15] Of note, the study excluded those who used opioids within a 12-hour timeframe prior to surgery, thus excluding patients that were opioid dependent. The study group received 400 mg oral celecoxib for four days following surgery and were compared to a placebo control group.[15] The authors found less fentanyl administration in the celecoxib group immediately after surgery and less required rescue opioid use in the

celecoxib group at 24, 48 and 72 hours after surgery.[15] Furthermore, no wound or cardiovascular complications were reported in either group at the week and month follow-up visits.[15] A prospective cohort study by Stepan et al., came to a different conclusion regarding use of celecoxib in the post-operative phase. These authors found no difference in opioid intake among the control patients versus the celecoxib patients when a dose of 200 mg oral celecoxib was taken twice daily the day prior to surgery and 5 days following surgery.[16] Opioid consumption by both groups in the 7 days following surgery was statistically insignificant; the authors suggest a possible reason for this being a mild amount of pain generally experienced after elective outpatient hand surgery.[16]

Yet another randomized controlled study by Shuying et al., suggested preoperative intravenous parecoxib to be effective in reducing additional analgesic consumption in the post-operative state.[17] They randomized patients to receive parecoxib before surgery, after surgery, or not at all which was the placebo group.[17] The only statistically significant finding was a reduced need for opioids immediately following surgery in the before surgery group when compared to the placebo group.[17] It is important to note that these studies evaluated short term use of NSAIDs as previous studies have found significant cardiovascular concerns with long term use.[15] Although these studies have mixed findings, two of the randomized controlled studies suggest that NSAIDs have the potential to provide opioid-sparing pain management in ambulatory surgery.

Acetaminophen

Acetaminophen's mechanism of action against pain is not as well understood; however, it may "inhibit the cyclooxygenase enzyme, interfere with NMDA receptor activation, and promote descending inhibitory serotonergic pathways that interfere with spinal nociceptive processing."[13]

Acetaminophen is best for pain control when scheduled and when combined with NSAIDs, given the inability for acetaminophen to affect inflammation.[4] Acetaminophen use is limited in patients that have severe hepatic impairment or disease but is often preferred in patients who may be advised to avoid NSAIDs due to cardiac, renal disease or bleeding risk. Two randomized controlled trials found preoperative intravenous acetaminophen to increase time to first request for rescue analgesia as well as decrease the overall need for opioid (oxycodone or morphine) use, especially in the first 24 hours following outpatient laparoscopic surgical procedures.[14] Other studies have suggested a decrease in opioid consumption of 33% at 24 hours in orthopedic surgeries.[14] Importantly, intraoperative intravenous and preoperative oral compositions of acetaminophen have similar benefits and therefore oral formulation is appropriate for those able to take medications by mouth.[4]

Acetaminophen is a widely used and accepted analgesic; however, patients often benefit when it is combined with opioids.[18] Tramadol is an atypical, weak opioid agonist that has been studied in combination with acetaminophen due to its action on the combination of mu, serotonin, and norepinephrine receptors.[4] The fact that it has a weak opioid effect makes it more desirable to reduce potential opioid-related side effects, however, data has not shown it to be less addictive than other opioids.[4] A retrospective cohort study by Solmaz et al. suggested that use of a combination of acetaminophen and tramadol versus either medication alone was greater for adequate pain control.[18] The patients who received the combination had less rescue analgesic requirements initially after surgery (hour 0) when compared to the tramadol alone group and the patients who received the combination had less rescue analgesic at hour 1 when compared to the acetaminophen alone group.[18] The author explains that the findings of this study are consistent with previous studies evaluating tramadol and acetaminophen combinations.[18]

Gabapentinoids

Gabapentinoids, both gabapentin and pregabalin, are antiepileptic drugs that can be used to treat neuropathic pain as they inhibit transmission of painful stimuli as well as reduce potential for central sensitization.[13] A meta-analysis of 17 randomized controlled trials found that patients who received preoperative gabapentin prior to elective surgery had a significant decrease in post-operative opioid intake when compared to those who did not receive gabapentin.[13] Of note, "this reduction was most pronounced in patients undergoing breast cancer surgery; cholecystectomy; and orthopedic, spinal, or thyroid surgeries."[13] A randomized controlled study found no significant difference between preoperative gabapentin (300 mg) versus pregabalin (150 mg) in post-operative pain scores or opioid consumption following laparoscopic cholecystectomy surgiers.[19] Yet a comparative clinical study of preoperative gabapentin (900 mg) versus pregabalin (150 mg) use in laparoscopic cholecystectomy patients found pregabalin to contribute to decreased opioid consumption more so when compared to gabapentin.[20] Both studies found a statistically significant prolonged time to first needed rescue analgesic dose in the pregabalin groups.[19, 20] Dose dependent studies are important as a significant side effect of gabapentinoids is the potential for over sedation, especially when high-doses are provided. Furthermore, research suggests a likely advantage of gabapentinoids in reducing opioid consumption when it is part of a multimodal analgesic regimen.[14]

Other Modalities Currently Under Investigation

Ketamine and lidocaine are also of interest as they may decrease post-operative opioid use as well as decrease opioid-related side effects, including a faster return of bowel function and decreased post-operative nausea and vomiting.[13,14,21,22] Ketamine is an NMDA receptor antagonist thought to decrease postsurgical pain by inhibiting central sensitization but also has

the ability to act on inflammatory pain.[4,13,22] One concern with the use of ketamine is the risk for psychomimetic side effects including hallucinations and although rare, this has prompted researchers to evaluate low-dose infusions of the medication.[21] Ketamine may have opioid-sparing capabilities when used in orthopedic surgery given the tendency for these patients to experience more significant pain in comparison to laparotomy type procedures.[23] One randomized controlled study found a 45% reduction in morphine up to 24 hours with use of ketamine versus placebo during total knee replacement surgery.[23] A review by Jouguelet-Lacoste et al. pursued to understand the effect of low-dose intravenous ketamine, in a continuous or bolus form, on opioid-sparing capabilities in the post-operative phase.[21] The authors looked at 5 meta-analyses and 39 randomized controlled trials with 2482 patients and concluded a 40% decrease in opioid consumption when low-dose intravenous ketamine was used in a multitude of surgeries.[21] The authors failed to come to a conclusion regarding the degree to which low-dose intravenous ketamine can improve pain scores.[21] The side effects that were observed were inconsequential and reversible with titration or discontinuation of the medication.[21] However, this review looked at studies that evaluated patients undergoing spine, cardiac, bowel, orthopedic, and ear, nose, and throat surgeries rather than outpatient surgeries.[21] Whereas a study evaluating ketamine as part of a multimodal pain regimen during outpatient hemorrhoid surgery failed to show a difference in opioid consumption as well as a difference in pain scores up to 3 months after surgery in opioid naive patients.[24]

Lidocaine is a local anesthetic that is incorporated into both neuraxial and peripheral nerve blocks.[22] Injected lidocaine has been associated with arrhythmias making use limited. Randomized controlled trials evaluating intravenous lidocaine have shown mixed results in its opioid-sparing capabilities. One randomized controlled study insinuated that patients receiving a

combination of intravenous fentanyl and lidocaine versus fentanyl alone among other multimodal agents had a lower requirement of fentanyl after laparoscopic cholecystectomy surgery.[25] Research has suggested abdominal surgery to be the surgical subtype in which intravenous lidocaine has the biggest impact.[22] However, another randomized controlled study found no significant difference in pain scores or opioid consumption in patients who received intravenous lidocaine versus a placebo in colorectal surgery.[26] Regional anesthesia utilizes local anesthetic medications like lidocaine to block peripheral or central nerves. Due to its ability to block nerves, regional anesthesia can help to decrease or remove the need for opioid regimens.[4,22] ERAS protocols focus on use of regional anesthesia in order to reduce perioperative opioid consumption and several observational studies evaluating pre- versus post-ERAS protocols have shown a decrease in post-operative opioid consumption in many surgeries.[4]

Multimodal Analgesic (Opioid-Sparing) Regimens

Although research has shown both promising and mixed results for independent use of opioid-sparing medications, there remains the question of whether or not the combination of these medications in protocols can contribute to adequate pain control and therefore decreased opioid consumption post-operatively. The proposed benefit of the combination of multiple non-opioid medications is that they may have a synergistic or additive effect on pain control and thus possibly have a greater effect on reducing opioid consumption when compared to the use of a single medication alone. Although ERAS protocols differ in which medications and doses they may administer, one end goal of all the protocols is to provide opioid-sparing techniques and regimens.

Two retrospective cohort studies and a randomized controlled study evaluated ERAS protocols in patients undergoing outpatient or short-stay surgeries including mastectomy,

robotic-assisted laparoscopic radical prostatectomy, and anorectal surgery.[27,28,29] Although the protocols all had slight differences, they included pre-, intra-, and post-operative interventions. Preoperative regimens consisted of acetaminophen and gabapentin or pregabalin and celecoxib. Intraoperative regimens consisted of regional anesthesia, dexamethasone, and ondansetron with minimal use of opioids or ketorolac or ketamine and dexamethasone. Post-operative regimens consisted of ibuprofen, acetaminophen, and as needed opioids or pregabalin, acetaminophen and as needed opioids.[27,28,29] Results are summarized in Table 1. All three studies showed the intervention or ERAS groups to experience a lower total amount of opioid consumption when compared to the standard or placebo groups; with a decrease of 30-59% per the retrospective cohort studies and a relative risk reduction of 76% (post anesthesia care unit) to 92.5% (8 hours post-operatively) per the randomized controlled study[27,28,29] Of note, the randomized controlled trial evaluating outpatient anorectal surgery, showed a trend toward less opioid use at 24 hours which was not significant, however, it was significant at 8 hours.[29] Furthermore, there was no significant difference in pain control or opioid use between groups undergoing the hemorrhoidectomy procedure.[29] The studies reviewed suggest ERAS protocols to contribute to opioid-sparing pain management.

Methods

In order to conduct the above literature review, PubMed, Ovid, and Google Scholar databases were utilized. The pain terms that were searched included multimodal analgesia, post-operative pain, acute pain, prolonged opioid use, opioid use risk factors, acute opioid use leading to prolonged use, and opioid-sparing or ERAS protocols. The medication terms that were searched included opioids, NSAIDs/celecoxib, acetaminophen, pregabalin, gabapentin, ketamine, and lidocaine. The surgical terms that were searched included ambulatory surgery,

outpatient surgery, laparoscopic surgery, and short-stay surgery. Other terms included barriers to ERAS protocols and implementing ERAS protocols. In order to provide some comparison or cite related concepts or findings, studies involving surgeries outside of ambulatory or outpatient type procedures were also included. Studies included in the literature review included human studies and excluded animal studies in order to better apply findings to the general population and in medical or surgical practice. Studies reviewed included randomized controlled trials, meta-analyses and reviews, qualitative analyses, prospective cohorts, as well as retrospective cohorts.

Discussion

Although unintended prolonged opioid use may not occur in the majority of opioid naive patients undergoing surgical procedures, the life-altering and potentially devastating side effects from long-term opioid use is enough to evaluate reasons and risk factors that contribute. Opioid naive patients are those who do not chronically receive daily opioid analgesics. In studies, this term is loosely defined for exclusion criteria and is based on the amount of time prior to surgery that patients are opioid free, ranging from days to years.[3,30] The studies reviewed suggest approximately 3-13% of opioid naive surgical patients either receive opioid prescriptions long term (typically evaluated up to 180 days) or have the potential to become opioid-dependent with just limited access after surgical procedures.[2,410,11,30] It is important to acknowledge that one study showed prolonged opioid use among opioid naive patients undergoing minimally invasive or open thoracic procedures to be 6.3-8.5% which was higher than the overall rate of 3.1%.[10] Table 2 summarizes study results. A reason for this may be the complexity of adequately controlling pain in patients that are undergoing more invasive procedures like thoracotomy procedures. Yet a cohort study by Johnson et al., evaluated prolonged opioid use in opioid naive patients who underwent elective or traumatic hand surgery and found an increased rate of

prolonged use among the elective group, at 13.5%, versus the trauma group, at 10.5%, at 90 days post-operatively.[30] The authors found prolonged risk to be associated with demographic and psychosocial findings; younger age, lower socioeconomic status, mental health disorders, and substance abuse, which is consistent with previous findings in the studies already mentioned.[30] Furthermore, specific chronic disease states have been connected to increased risk for continuing opioid use following surgery. It may be inferred that such chronic diseases are contributing to preoperative pain which may or may not be adequately controlled. The chronic disease states that have been identified as risk factors through studies include common conditions like heart failure, pulmonary disease, diabetes mellitus and PTSD.[2,10] Commonly used medications such as benzodiazepines, SSRIs and ACE inhibitors have also been identified as risk factors for prolonged opioid use when consumed prior to surgery.[4,10]

Opioids are generally prescribed for acute pain even after ambulatory surgical procedures as providers expect patients to experience some degree of pain. Research has linked post-discharge prescriptions for opioid medications as a strong predictor for eventual misuse, even stronger than the opioid dose received.[3] A retrospective cohort study by Waljee et al., noted that over half (58.5%) of the patients undergoing outpatient hand surgery received and filled an opioid prescription following their surgery.[31] Surprisingly, it was more common for these patients to fill a prescription for a stronger opioid like hydrocodone than it was for them to fill a weaker opioid like tramadol or codeine.[31] Providers share responsibility when it comes to contributing to risk for prolonged opioid use among naive surgical patients. Surgeons are not always provided with specific guidelines or education for pain management following surgery.[30] Although the majority of providers may write an opioid prescription with the intention of providing safe and effective control of acute post-operative pain, this brief exposure can

contribute to risk for long-term use.[30] A qualitative analysis identified themes amongst opioid misuse in previous opioid naive patients.[12] "Pathway 1: Inadequate controlled chronic physical pain leads to misuse; Pathway 2: Some individuals are vulnerable to opioid dependence even after brief exposure; Pathway 3: Prior substance use problems and introduction of prescribed opioids; Pathway 4: Relief from emotional distress reinforces misuse or abuse; Pathway 5: Recreational initiation or non-medically supervised use of opioids."[12] Ongoing research to determine characteristics that contribute to opioid misuse vulnerability following short-term use is warranted.[12] Patients undergoing ambulatory surgery could fall into one of these pathway categories and it important for providers to be aware of factors outside of acute surgical pain that could contribute to ongoing and possible misuse of opioids. In order to prevent or limit the risk, providers ought to transition patients, especially those at highest risk, to non-opioid analgesic medication options as soon as appropriate.[30] Furthermore, studies have suggested that some patients undergoing outpatient procedures receive a surplus of opioids.[32,33] One study found patients undergoing various orthopedic outpatient procedures to have an average of 13 unused opioid pills.[32] Another study evaluated patients undergoing outpatient procedures including partial mastectomy with or without sentinel lymph node biopsy, laparoscopic cholecystectomy, and laparoscopic or open inguinal hernia repair.[33] This study found only 28% of prescribed pills to be consumed.[33] The concern with this is that patients then need to be properly educated on how to dispose of the remaining pills.[5] One study in particular reported proper disposal of remaining opioids among only 41% of patients.[34] Without proper disposal, opioids become available for potential misuse at later times; self-medicating or recreational use. Overall, studies have found prescribing patterns to vary among surgeons and surgeries.[32,34] This suggests the

need for increased education provided to surgical providers regarding post-operative pain management as well as tailored research to evaluate the need for more standardized protocols.

Use of single, opioid-sparing medications, including NSAIDs, acetaminophen, gabapentinoids, ketamine, and lidocaine have been studied in various surgical procedures. Providing these medications independently has overall shown mixed opioid-sparing results. NSAIDs including selective forms like celecoxib may have the capability to reduce acute post-operative opioid use up to 25-30% but this pattern is inconsistent across all outpatient procedures, especially noted by the study done in outpatient hand surgery.[14,16] Although NSAIDs are generally considered a harmless analgesic option among healthy patients undergoing elective surgery, the use in patients with cardiac, renal, or bleeding disorders is less concrete. One randomized controlled trial that evaluated the use of ketorolac as part of a multimodal analgesic regimen in patients undergoing cardiac surgery not only found a decrease in opioid requirements post-operatively but also found an insignificant increase in creatine in the multimodal group versus the morphine group.[35] Furthermore, there were no differences in cardiac or cerebrovascular complications between the two groups. The authors also noted an increased risk for thromboembolism in the morphine group and inferred that this may be due to antithrombotic effects provided by the NSAID.[35] Further research regarding safety and efficacy of short-term use of NSAIDs in the post-operative patient is warranted.

Acetaminophen is a widely accepted pain management medication and research suggests a positive benefit for opioid-sparing capabilities when used in ambulatory surgical procedures, however, the research may not be as convincing for other procedures.[36,37] A randomized controlled study found pain scores but not opioid consumption to be lower with use of acetaminophen after induction in patients undergoing thoracotomy procedures.[36] Additionally,

another randomized controlled trial had similar findings in which intravenous acetaminophen reduced pain following sternotomy surgery but did not affect opioid consumption when compared to the placebo group.[37] Similar research has been noted with the use of gabapentin among patients undergoing thoracotomy procedures. A randomized controlled study found that patients undergoing thoracotomy procedure experienced neither a decrease in pain or opioid consumption in the 48 hours following surgery when a preoperative dose of gabapentin was given.[38] This research on use of opioid-sparing medications in non-ambulatory surgeries is less convincing. Furthermore, since thoracotomy procedures have been identified as having an increased risk for prolonged opioid use, it may be an area where more extensive research on effectiveness of multimodal regimens is needed.[10]

Studies on intravenous ketamine and lidocaine have shown some promising results as far as their ability to reduce opioid consumption in the post-operative phase, however, many times they are utilized alongside other pain medications in a multimodal approach. Regional anesthesia, another common aspect of the ERAS protocol, can reduce opioid consumption in a variety of surgical settings due to its abilities to block both peripheral and central nerves.[4] A potential limiting factor for use of regional anesthesia in ambulatory care is that patients may not always be able to go home with a regional catheter in place thus making the benefit time limited based on the type of local anesthetic used. Regional anesthesia can also decrease a patient's ability to mobilize or adequately ambulate so may not be appropriate for long periods of time or specific surgeries. Nevertheless, ongoing use of and research regarding peripheral and central nerve blocks is warranted given the opioid sparing effects already seen.[4]

Generally, combining medications in a protocolized manner to provide opioid-sparing operative treatment has shown consistent promising results among outpatient or short stay

procedures. Short-term opioid-sparing capabilities ranging from 30-59% have been reported in two retrospective cohort studies[27,28] and risk reduction of 76-92.5% has been reported in a randomized controlled study.[29] Although the lower end of the range is similar to some of the opioid-sparing capabilities of some single opioid-sparing medications, combining medications allows for potential additive or synergistic effects. Finding the most effective multimodal pain regimen should in theory provide effects that as a sum are greater than with use of one medication alone. Providing multiple medications may also allow for a lower administration dose, thus potentially lowering occurrence of side effects. Many of the articles reviewed utilized protocols (standardized medication doses) and randomized patients to a treatment or control group and blinded patients and providers as able, all of which are strengths. Furthermore, groups were often undergoing the same or similar surgical procedure, another strength of evaluating specific protocols. However, some studies that evaluated ERAS protocols in the surgical patient population included a smaller number of patients. It is important to recruit patients that meet the necessary criteria, are undergoing the same or similar procedure, and have the ability to potentially receive ERAS protocolized care which may be a limiting factor for recruiting larger numbers. Although many studies evaluating single or multimodal analgesic regimens only included patients if they were opioid naive prior to surgery, some studies did not state whether or not opioid-dependent patients were excluded. It is also important to consider surgical differences that may occur due to surgeon technique and patient history. Furthermore, although the ERAS protocol studies reviewed showed promising opioid-sparing results, each protocol consisted of different pre-, intra-, and postoperative medication administration and therefore, it is unknown which specific protocols are most effective. Findings are summarized in Table 1.

Research suggests that the use of multimodal analgesic regimens can provide opioid-sparing pain management in the acute post-operative phase and therefore further implementation and research of such protocols is warranted. The use of such protocols in an ambulatory surgical setting is of importance given the potential for quick discharge to home with the patient or caregiver becoming primarily responsible for pain management.[21] Providing multimodal analgesic regimens via ERAS protocols has not only been shown to decrease post-operative opioid use but also contributes to improved pain control evaluated by patient reported post-operative pain scores.[27,29] Thus, if pain is more adequately controlled post-operatively and can be managed with non-opioid medications, the hope is that patients may avoid need for an opioid prescription at discharge, thus limiting the risk for prolonged unintended use. Research evaluating the effect of ERAS protocols on opioid use beyond the acute post-surgical phase is also warranted. Loftus et al. evaluated opioid use among opioid-dependent patients following back surgery procedures that received ketamine.[39] The authors not only looked at short term (24-48 hour) opioid use following back surgery but also followed the patients at 6 weeks out from surgery.[39] They found a 71% reduction in opioid use among the group that received ketamine, suggesting the potential for ketamine to provide continued pain control.[39] It would be of significant benefit to conduct similar studies among opioid naive patients.

Despite the fact that ERAS protocols have proven to reduce opioid consumption in the acute post-operative phase, barriers for initiation and maintenance of these protocols exist. Two qualitative studies asked surgeons, anesthesiologists, and nurses about both motivations and/or challenges or barriers faced when implementing ERAS protocols.[40,41] One study concluded that although the staff approved of ERAS, barriers existed and were most pronounced as need for better communication and collaboration, improved patient education, and further supportive

evidence.[40] Another study concluded that staff initiated ERAS to reduce complications, improve patient satisfaction, and shorten length of stay yet barriers to implementation existed.[41] Such barriers included lack of adequate timing and logistics and disagreement and hesitancy among coworkers along with some patient-related barrier.[41] These qualitative studies not only suggest the need for more evidence guided recommendations for ERAS protocols but also, the need for more collaboration among surgeons, anesthesiologists, and nurses as well as hospital administrators when it comes to developing and implementing such protocol.

Conclusion

The topic of multimodal, opioid-sparing analgesia is of significant importance given the opioid crisis in the United States and the potential for life-altering effects with long-term use. Effort must be placed on preventing unintended prolonged use, especially among opioid naive patients experiencing acute post-surgical pain. One avenue for access to such prescription opioids is through ambulatory surgical procedures. Postoperative opioid prescriptions are not uncommon, even in elective outpatient surgery as over half of patients may be discharged with an opioid prescription.[31] Since there are known risk factors that place patients at higher risk for developing misuse patterns, it would be of benefit to evaluate for such risk factors at the preoperative evaluation visit. It would be ideal for primary care providers or surgical team members that are completing preoperative evaluations to be aware of preoperative risk factors including psychological disorders and substance abuse history; but also, less obvious historical information like chronic diseases, medications, and socioeconomic or demographic factors that places the patient at risk. Uncontrolled pain may not always be obvious from a physical examination standpoint. Although emotional pain may be more difficult to pick up at office visits it is still an essential component and should be addressed in the interview and patients should be

properly referred to specialists if indicated. Providers must go the extra mile to understand the potential pathways that can lead to opioid misuse and pay special attention to patients who are undergoing ambulatory surgery as they may have brief exposure to opioids, which places them at risk for possible misuse.[12]

Overall, review of the literature suggests that multimodal analgesic regimens have the capability to reduce acute post-operative opioid use in ambulatory surgical settings among opioid naive patients. Since multimodal analgesic regimens have shown promising acute effects in decreasing opioid consumption after surgery, these protocols should be utilized in the appropriate patient populations and especially encouraged in those that may be identified preoperatively as high risk for opioid misuse following surgery. Multimodal analgesic regimens combine various medications in order to target different aspects of the pain pathway and by doing so, are able to better control post-surgical pain and decrease the need for rescue opioid use. Although research suggests some single non-opioid pain medications provide opioid-sparing capabilities close to or equal of that of multimodal pain methods, it will be of more significance to continue research on ERAS protocols given the potential for additive and synergistic effects.

Further research should be focused on studies that include a large number of patients undergoing similar surgical procedures with similar surgical techniques as well as standardized ERAS protocols. One limitation of the current literature is that a variety of different ERAS protocols are being studied within a variety of surgical settings making it difficult to conclude which combination of medications is most effective. Therefore, it may take many more years of randomized controlled trials to truly understand the most effective combination of pain medications when it comes to controlling acute surgical pain and decreasing post-operative opioid use. Furthermore, surgical procedures outside of ambulatory care may require more

extensive research given the potential for more associated pain. In their review, Kumar et al. explains that different surgeries produce varying degrees of somatic or visceral pain, "thus, the best adjuvant for each type of surgery also requires additional investigation."[21] In the future, randomized controlled trials comparing different multimodal regimens amongst one another and a control group will be essential. Furthermore, research should move toward evaluating the effect of multimodal analgesic techniques on long term opioid use among opioid naive patients following surgery. The majority of the current studies evaluate opioid use among opioid naive patients within the first few hours and possibly days of surgery but rarely evaluate if patients are experiencing adequate pain control and whether or not they are utilizing opioid medications in the weeks, months, or years that follow surgery. Given some of the promising research evaluating use in chronic pain patients, there would be benefit in pursing such studies among acute pain patients.

Overall, although multimodal analgesia is mainly a role of the anesthesiologist, operating surgeon, and post-anesthesia care unit staff, the primary care provider plays a significant role in providing preoperative assessment and testing to help indicate at risk surgical patients. A risk assessment for unintended prolonged opioid use should be a part of the preoperative risk assessment and communication between primary care providers, anesthesiologists, surgeons, and post-anesthesia care unit staff will be essential for providing the most appropriate pre, intra-, and post-operative pain management. With ambulatory surgeries especially, weaning off pain medications including opioids tends to become the responsibility of the patient and their caregivers.[21] Surgical providers must provide adequate education and direction for this process along with proper disposal processes.[5] Primary care providers continue to play an important role in the post-surgical phase by evaluating ongoing need for medication prescriptions, including

opioids. Patients may have difficulty bringing up pain control and opioid use to their provider given the stigma surrounding addiction of opioid medications or fear that discontinuing opioid medications could lead to exacerbation of symptoms.[12] Therefore, it becomes an essential component of history taking by the primary care or surgical provider at the time of follow-up visits.

Although it is unrealistic to assume that opioids can be completely eliminated from acute pain management, with multimodal analgesic approaches and safe opioid practices, it may be possible to decrease unintended prolonged use and thus decrease long term risks including unwanted side effects and overdose. Providers must consistently and adequately evaluate post-surgical pain to determine the best and most effective medication choice to not only optimize pain control but also potentially limit opioid misuse. Providers should assume responsibility when it comes to monitoring for and asking about pain medication use and misuse. Databases available to providers to track opioid prescriptions provided to patients can help tie the gaps when multiple providers are involved in a patient's care. Both a multimodal analgesic approach to post-operative pain management and a multispecialty approach to pre-, intra- and post-operative surgical care are essential for optimal patient care and recovery.

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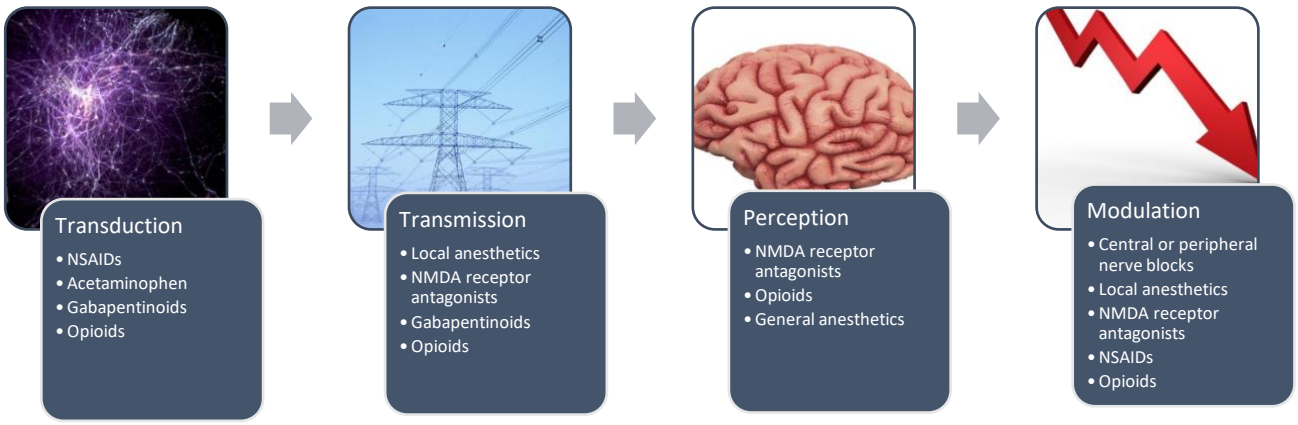
Appendices

Figure: Analgesic Targets Among the Pain Pathway[a]



Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs. NMDA, N-methyl-D-aspartic acid

[a]Data adapted from Polomano RC, Fillman M, Giordano NA, Vallerand AH, Wiltse Nicely KL, Jungquist CR.[13]

Images adapted from Pickit Images. www.pickit.com. Updated 12/12/13. Accessed 7/30/18.

Table 1: Comparison of Enhanced Recovery After Surgery (ERAS) Protocols Among Retrospective Cohort Studies and a Randomized Controlled Trial

Total Mastectomy[a]	**Laparoscopic Radical Prostatectomy**[b]	**Anorectal Surgery**[c]
Preoperative	*Preoperative*	*Preoperative*
• Gabapentin 600 mg po x1 • Acetaminophen 1000 mg po x1 • Scopolamine 1.5 mg td x1 if age <60	• Pregabalin 150 mg po x1 • Acetaminophen 975 mg po x1 • Celecoxib 400 mg po x1	• Gabapentin 600 mg po x1 • Acetaminophen 1000 mg po x1
Intraoperative	*Intraoperative*	*Intraoperative*
• Recommend total IV anesthesia • Minimize opioids • Regional anesthesia • Dexamethasone 8 mg IV • Ondansetron 4 mg IV • Limit IV fluids to <2L • Maintain normothermia (36-38 degrees Celsius)	• Not discussed	• Propofol, midazolam, fentanyl and local anesthesia • Dexamethasone 8 mg IV • Ketamine 0.15 mg/kg IV • Regional anesthesia
Postoperative	*Postoperative*	*Postoperative*
• Opioids prn • Ondansetron prn • Ativan prn • Encourage early oral intake • Encourage out of bed	• Standard ketorolac regimen (15-30 mg) • Pregabalin 150 mg po daily until hospital discharge • Acetaminophen 975 mg po daily until hospital discharge • Oxycodone 5 mg, 1-2 tablets every 4 hours prn	• Alternate acetaminophen 1000 mg po and ibuprofen 600 mg po every 3 hours on a scheduled basis • Hydromorphone 2 mg po for breakthrough pain every 3 hours as needed
Outcome	*Outcome*	*Outcome*
30% reduction in total perioperative opioid consumption in intervention group	59% reduction in the requirement for opioid analgesia in the intervention group	76% and 92.5% relative risk reduction for the PACU and 8-hour time points

Abbreviations: mg, milligram. po, by mouth. td, transdermal. IV, intravenous. L, liters. prn, as needed.
[a]Data adapted from Chiu C, Aleshi P, Esserman LJ[27]
[b]Data adapted from Trabulsi EJ, Patel J, Viscusi ER, Gomella LG, Lallas CD[28]
[c]Data adapted from Backer JTV, Jordan MR, Leahy DT, et al.[29]

Table 2: Rates of Acute and Prolonged Use of Opioids Among Opioid Naive Patients Undergoing Surgery

Major Elective Surgery[a,b]	**Low-Risk Surgery**[a,c]	**Elective or Trauma Related Hand Surgery**[d]
Acute Use of Opioids	*Acute Use of Opioids*	*Acute Use of Opioids*
• 49.2% of patients used opioids in the early post-discharge period	• 7.1% of patients prescribed opioids within 7 days of being discharged	• 77% of patients filled on perioperative opioid prescription
Prolonged Use of Opioids	*Prolonged Use of Opioids*	*Prolonged Use of Opioids*
○ 3-8% of patients used opioids 90 days after surgery ○ 3.1% of patients used opioids 3+ months after surgery (Note: 6.3-8.5% of patients had prolonged opioid use after thoracic surgery)	• Up to 13% of patients continued to used opioids 6-12 months after surgery • 7.7% of patients prescribed opioids 1 year after surgery	• 13% of patients filled opioid prescriptions 90 days after surgery

[a]Data adapted from Hooten WM, Brummett CM, Sullivan MD, et al.[2]
[b]Data adapted from Clarke H, Sonjei N, Ko DT, Yun L, Wijeysundera DN[10]
[c]Data adapted from Alam A, Gomes T, Zheng G, Mamdani MM, Juurlink DN, Bell CM[11]
[d]Data adapted from Johnson SP, Chung KC, Zhong L, et al.[30]

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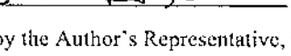
Author's Signature:  Date: 8/14/2019

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