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Multimodal Pain Management to Reduce Opioid Use after Cholecystectomy

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Abstract

The purpose of this research and systematic literature review is to determine effective pain management options for patients undergoing a cholecystectomy procedure while decreasing the use of postoperative narcotics. In this review, the databases searched included PudMed, Clinical Key and Dynamed Plus. A variety of key terms were used when searching. Studies chosen from this search were peer reviewed and included randomized control trials, systematic reviews and met analyses. Excluded studies did not particularly research the drug classes of interest or they dealt solely with different surgical pain interventions during the procedure. The research presented shows the use of gabapentinoids, non-steroidal anti-inflammatory drugs and acetaminophen to reduce opioid use in the postsurgical period. Of the medications reviewed, preoperative use of oral acetaminophen and non-steroidal anti-inflammatory drugs offer the greatest reduction in opioid use, while offering sufficient pain control. For gabapentinoids, additional research is needed to determine optimal dosing and to balance analgesic benefits with potential adverse effects.

Keywords: Analgesics, laparoscopic cholecystectomy, humans. postoperative pain, opioid analgesics, nonopioid analgesics, gabapentin, pregabalin, NSAIDs, acetaminophen.

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Introduction

For patients undergoing major surgery, opioids have been the mainstay for pain control. They work quickly and effectively to reduce or eliminate pain and discomfort. Appropriate pain management has been shown to have many benefits, including increased patient satisfaction, shorter hospital stays, quicker recovery and decreased hospital cost. However, the use of opioids also sparks concern for potential abuse and unused pills being a contributing source to the opioid epidemic. Research has provided an abundance of data to evaluate the role of different analgesic regimens for postoperative pain control. However, there is increasing interest in procedure specific analysis. This approach can provide more individualized evidence-based pain management. The purpose of this study is to reveal the most effective pain management options for patients undergoing a cholecystectomy procedure.

Statement of the problem

In the last two decades, the opioid epidemic has been an ongoing national crisis. In the 1990's healthcare started to focus on pain as a measure of patient satisfaction. This led to an increase in opioid prescribing, opioid addiction, transfer of addiction and deaths due to overdoses on these medications. In 2017, the U.S Department of Health and Human Services declared the issue a public health emergency. To address the issue a 5 – Point Strategy was developed to lessen the burden of opioid use. One area of focus includes better pain management. Therefore, medical providers need to be informed on procedure specific pain control to aid in better pain management without the unnecessary risks.

Research Question

In patients undergoing a cholecystectomy, what is the effectiveness of acetaminophen, non-steroidal anti-inflammatory drugs and gabapentinoids at reducing opioid use in the postsurgical period?

Methodology

A literature review was performed using electronic search databases; PubMed, Clinical Key, and Dynamed Plus. Both keyword and mesh terms were used to define a set of the literature discussing laparoscopic cholecystectomy and postoperative pain management. The literature was further searched for opioid and nonopioid treatment studies relating to cholecystectomy. The search revealed a total of 914 studies. There were several studies excluded as they did not particularly research the drug classes of interest. Multiple other studies were excluded as they dealt solely with different surgical pain interventions during the procedure.

Keywords: Analgesics, laparoscopic cholecystectomy, humans, postoperative pain, opioid analgesics, nonopioid analgesics, gabapentin, pregabalin, NSAIDs, acetaminophen.

Multimodal Pain Management

Current literature shows that several medication classes offer efficacious treatment options for postsurgical pain. However, with different mechanisms of action and administering methods, one class may provide optimal pain control for patients undergoing a cholecystectomy.

Efficacy of Acetaminophen

Acetaminophen is a widely used analgesic that is a nonopioid option in multimodal analgesia. It can easily pass through the blood-brain barrier and is able to reach high concentration levels in the cerebrospinal fluid. The mechanism by which acetaminophen prevents and reduces pain is yet to be fully understood. The analgesic effects work by preventing prostaglandin production in the central nervous system and working peripherally to inhibit pain impulses. Acetaminophen has been the first-step analgesic agent, mostly due to its lower adverse effects and safety.

Ekinci et al. (2020) looked at 90 patients randomized in to 3 equal groups: 30 patients received ibuprofen, 30 received acetaminophen and 30 were in the control group. Those in the ibuprofen group were administered 800 mg of IV ibuprofen. Those receiving acetaminophen were administered 1000 mg and the control group was given 100 ml of normal saline. All medications were provided 30 minutes prior to their procedure. All operations were completed by the same surgical team using the same technique. After surgery the medications continued to be administered every 8 hours. The patients were also given a PCA device containing fentanyl. This is typically not standard practice for laparoscopic cholecystectomy surgery. However, was utilized to compare opioid usage. All patients were asked to rate their postsurgical pain using visual analog scale (VAS; 0 = no pain and 10 = worst imaginable pain). Meperidine 0.25 mg/kg IV was administered for rescue analgesia if the VAS score was 4 and above. Baseline demographic data showed no statistical difference between groups ($P > 0.05$).

Pain scores for the patients receiving ibuprofen and acetaminophen were evaluated at all time periods and were lower than those in the control group ($P < 0.05$). The patients who

received ibuprofen had significantly lower VAS scores than those receiving acetaminophen at all time periods postoperatively ($P < 0.05$). The control group had significantly higher opioid consumption than the other groups ($P < 0.05$). Similar to VAS scores, opioid consumption in patients receiving ibuprofen at all time periods postoperatively was significantly lower than those receiving acetaminophen ($P < 0.05$). Finally, those taking ibuprofen had statistically lower rescue medication usage than the other groups at all time periods. This study showed that the intravenous form of ibuprofen reduced the pain scores and opioid consumption in the 24-hour postoperative period compared with acetaminophen or placebo. In addition, rescue analgesic utilization was significantly lower in those in the ibuprofen group. This study has some limitations. First, the 800-mg dose was used at every 8 hours during the first 24 hours postoperatively., It could be used more frequently up to 6-hour intervals also. Also, ibuprofen and acetaminophen can be used together for further multimodal analgesia treatment. However, that combination was not evaluated.

A study was conducted by Bandey & Singh (2016) of 60 adult patients between the ages of 18-55 scheduled for elective laparoscopic cholecystectomy under general anesthesia. The patients were divided at random into two groups: 30 patients receiving IV paracetamol 1 g and the remaining received IV tramadol 100 mg. Pain was assessed using a 10-point VAS and measured the following time increments: just before analgesic administration, 0.5, 1.5, 3, 6, 12, 18 and 24 hours. If during recovery they experienced a pain above 5 on the VAS scale, this was considered breakthrough pain. These patients then received intravenous diclofenac sodium 1.5 mg/kg, which is classified as a non-steroidal anti-inflammatory medication.

This study concluded that both drugs showed effective control on pain scores in the short term only. It was observed that mean scores indicative of acute pain (VAS score ≥5) were brought down to mild or bearable pain, which was considered a VAS score of less than 3, within 30 minutes of administration showing a significant change from baseline (Bandey, 2016).

However, paracetamol group showed a better efficacy as compared to tramadol group for most of the follow-up intervals being studied. By 18 and 24 hours both the groups had pain scores mild in nature (VAS scores ~ 2). Paracetamol proved to have superior pain control as compared to tramadol in terms of difference in mean VAS scores at 1.5, 3, 6, 12, and 24 hours follow up intervals. However, none of the patients required rescue analgesic. This study concluded that both tramadol and paracetamol were comparable and could be effectively used as postoperative pain management in laparoscopic cholecystectomy (Bandey, 2016). This study looked specifically at the postsurgical dosing of medication. This pain treatment option may be applicable to non-scheduled procedures or when preoperative administration of medication is not advised.

Mulita et al. (2021) conducted prospective, randomized study was to compare the analgesic efficacy of three analgesic regimens in the setting of laparoscopic cholecystectomy: acetaminophen monotherapy versus acetaminophen combinations with either pethidine or parecoxib. They selected 316 patients between the ages of 35 and 65 undergoing elective laparoscopic cholecystectomy. The patients were randomized to receive either IV acetaminophen 1000 mg every 8 hours and intramuscular pethidine (Demerol) 50 mg every 12 hours or IV acetaminophen 1000 mg every 8 hours and IV parecoxib (Celebrex) 40 mg every 12 hours. The third group received monotherapy of acetaminophen 1000 mg every 8 hours only. The patients

who asked for more postoperative analgesics were excluded from this trial. This included 30 patients from the monotherapy group. Following surgery, patients were transferred to the surgical ward. They were evaluated at the bedside at 45 minutes, 2 hours, 6 hours, 12 hours, and 24 hours after receiving the first analgesic dose from their allocated regimen. Pain scores were obtained using a VAS range from 0-10.

The pain scores for the patients only receiving paracetamol were significantly higher than those in the multimodal groups ($P < 0.01$). There was no significant difference between the patient's receiving pethidine/paracetamol or parecoxib/paracetamol ($P = 1.00$). According to the results of this study, the combinations of pethidine/paracetamol and parecoxib/paracetamol showed a comparable analgesic effectiveness, and they were better than paracetamol monotherapy for the management of postoperative pain. The parecoxib/paracetamol also experienced less sedation side effects, improvement in pulmonary function and decreased constipation by reducing opioid use.

The outcomes of this study suggest that there was no statistically significant difference in postoperative analgesic treatment among acetaminophen/parecoxib and acetaminophen /pethidine. Since these two pharmacologic regimens of analgesics appear to be equivalent in efficacy, the combination of acetaminophen and parecoxib might be preferable over acetaminophen and pethidine to reduce opioid consumption and associated adverse events. Both combinations of postoperative analgesics outweigh the paracetamol monotherapy and should be therefore preferred. This study did exclude patients with breakthrough pain, which was not defined, but was reported as patients asking for additional pain medications. This could also be a limiting factor to this study.

The PROSPECT (Procedure Specific Postoperative Pain Management) working group is a collaboration of surgeons and anesthetists working to formulate specific recommendations for pain management after common but potentially painful operations. The recommendations are based on procedure-specific literature review of systematic reviews and randomized control studies. The methodology considers clinical practice, efficacy, and adverse effects of analgesic techniques. These studies are also grouped together based upon the analgesic technique and drug class. Within each analgesic group, the studies were further placed into subgroups of preoperative, intraoperative, and postoperative interventions. Recommendations for optimal pain relief are graded A–D according to the overall level of evidence, as determined by the quality of studies, consistency of evidence and source of evidence. A total of 200 studies were used to justify their recommendations.

Two of the studies reviewed showed significant reduction in pain scores within the first 2 hours after operation when an IV paracetamol infusion was administered prior to surgery ($P<0.05$) (Barazanchi, 2018). However, when IV paracetamol was compared with oral administration before operation, there was no significant difference in pain scores in an RCT of 60 subjects. The previously published review recommended the use of NSAIDs (including COX-2 inhibitors) before operation (GRADE B) (Barazanchi, 2018). Seven papers examined the use of preoperative NSAIDs showing either reduced pain, analgesic requirement, or both. One study comparison showed no difference between preoperative IV paracetamol and ketorolac but had no control group.

Preoperative use of oral paracetamol and NSAID or COX-2 inhibitor is recommended based on several studies in this and the previous review (GRADE A) (Barazanchi, 2018). If paracetamol or NSAID was not administered before surgery, then they can be given IV during

the procedure (GRADES A and B, respectively). Paracetamol and NSAID are recommended to be continued after the completion of the operation (GRADE A) (Barazanchi, 2018). The previous review recommended only postoperative paracetamol and NSAID, but this review extends this recommendation to the pre-/intraoperative period.

Efficacy of systemic non-steroids anti-inflammatory

Nonsteroidal anti-inflammatory drugs (NSAIDs) are becoming a common treatment option for preventing postsurgical pain. However, concerns remain regarding the use of non-selective NSAIDs, like ketorolac due to blockade of prostaglandin synthesis at the cyclooxygenase-1 (COX-1) receptor. Caution has been used during the perioperative period because of the risk of operative site infection and gastrointestinal mucosal bleeding. COX-2 selective inhibitors have demonstrated that they can improve pain control after a wide variety of ambulatory surgery procedures (White, 2007). When studied previously, parecoxib followed by short-term postoperative valdecoxib improved recovery after laparoscopic cholecystectomy procedures (White, 2007). However, when studied with other procedures, such as cardiac surgery, it was found to increase infection and complications.

The use of COX-2 selective inhibitors has become increasingly controversial following the withdrawal of rofecoxib and valdecoxib from the market due to concerns for patient's safety, even when used in the short term such as postsurgical pain. A randomized, double-blinded, placebo-controlled clinical study conducted by White et al. (2007), utilized 80 patients to assess the effectiveness of celecoxib. The initial dose of medication was administered by mouth 10–20 minutes after patients arrived in the PACU, either two celecoxib 200 mg or two placebo capsules. The patients were then instructed to take one capsule twice a day for the next 3 days. The patients, observers, and anesthesiologists directly involved in the patients' care were all

blinded to the content of the study medication. Patients were asked to evaluate their pain and nausea on an 11-point VRS at 30-, 60-, 120- and 240-minute intervals after surgery, as well as immediately prior to receiving any breakthrough pain medication. Patients complaining of moderate-to-severe pain (VRS > 3) were treated with fentanyl 25 mg IV bolus. Those patients requesting analgesic medication with pain scores of 2–3 received a combination of oral hydrocodone (5 mg) and acetaminophen (500 mg). Even though the percentage of the patients requiring rescue analgesics in the PACU was similar in the two treatment groups, the amount of fentanyl administered was less in the celecoxib group compared to the control group ($P < 0.05$). The percentages of patients who required additional analgesic medication at 24, 48, and 72 hours after discharge was significantly reduced in the celecoxib compared to control group ($P < 0.05$).

In conclusion, patients who took oral celecoxib 400 mg daily for four days after laparoscopic surgery had decreased postoperative pain and need for analgesic rescue medication, contributing to improved patient satisfaction and their quality of recovery. The short-term use of the COX-2 inhibitor did not result in any postoperative wound or cardiovascular complications.

Ahiskalioglu, et al. (2017) also conducted a randomized, double-blinded study consisting of 60 patients ages 18 to 65 that were scheduled for laparoscopic cholecystectomy. The control group of 30 patients were administered 100 mL IV saline 30 minutes preoperatively, and the ibuprofen group (30) received 400 mg ibuprofen IV. All patients received 1000 mg IV paracetamol (acetaminophen) before the end of surgery, and this was repeated every 6 hours postoperatively. Patients were attached to a PCA device containing fentanyl after surgery in the recovery room.

Postoperative pain was assessed using a VAS but included assessment at rest and with active movements. Active movement was defined as moving from a lying to a sitting position. Patients with a VAS score of 4 or above, was considered breakthrough pain and received 25 mg meperidine (Demerol), which has the same mechanism of action as morphine, acting as an agonist to the mu-opioid receptor. Pain evaluated at rest and with active movement at 30 minutes and 1, 2, 4, 8, 12, and 24 hours postoperatively were lower in the ibuprofen group ($P < 0.05$).

Fentanyl consumption was lower in the ibuprofen group compared to the placebo group at all time periods ($P < 0.001$). In terms of total fentanyl consumption, 24-hour consumption was lower in the ibuprofen group compared to the placebo group ($P < 0.001$) This study showed that a single preemptive dose of IV ibuprofen reduced 24-hour opioid consumption and was effective in achieving lower pain scores in the postoperative period. This study also helped to evaluate if NSAID use is effective when patients are moving around after surgery. Ambulation after surgery is an important factor to aid in the healing process, returning to activities of daily living and reducing the risk of thromboembolic conditions. Assessing if the agent used for pain management is effective with movement is an important consideration.

Efficacy of Gabapentinoids

Gabapentinoids (gabapentin and pregabalin) were initially approved for the treatment of epileptic conditions, though their use has shown to reduce pain and anxiety as well. Gabapentin, also known by the brand name Neurontin, works by binding to the alpha-2 delta subunit of the presynaptic voltage gated-calcium channels and inhibits calcium release, this prevents the release of excitatory neurotransmitters involved in the pain pathways (Ho, 2006). Another medication in this drug class is pregabalin, also known as Lyrica, which is a structural analog of gamma-

aminobutyric acid (GABA). It acts by presynaptic binding to the α -2-λ subunit of voltage-gated calcium channels that are widely distributed in the spinal cord and brain (Ho, 2006). Pregabalin modulates the release of several excitatory neurotransmitters, such as glutamate, norepinephrine, substance P, and calcitonin gene-related peptide (Ho, 2006). These work to inhibit the overexcitement of neurons caused by tissue damage and decrease pain sensation. Both medications have similar potential side effects including headache, diarrhea, constipation, rash, and shortness of breath. Gabapentin does pose a greater risk for drowsiness and dizziness. One major difference between gabapentin and pregabalin is that the Drug Enforcement Administration (DEA) has classified pregabalin as a controlled substance (schedule V), medications containing gabapentin are not currently scheduled as controlled substances. This means that pregabalin and substances containing pregabalin are considered to have a greater risk for abuse and physiological dependence.

In using gabapentinoids as a multimodal pain management, studies have evaluated its efficiency when administered to the patient at different time frames during the surgical process as well as different dosages. Balaban et al. (2012) conducted a double-blinded, placebo-controlled study using 90 patients randomized to three equal groups; group 1 was the control group and subjects were given an oral placebo one hour before surgery; the second group received 150 mg of pregabalin and group 3 received 300 mg of pregabalin, both one hour before surgery. A VAS score of 5 or more, was considered breakthrough pain and intravenous fentanyl 25 μg was given. Patients were also observed for side effects including nausea, vomiting, pruritus, and urinary retention. If additional doses of medication were required for pain control it was documented. No statistically significant differences were noted in age, gender, body weight, or systemic diseases ($p > 0.05$).

In this study a significant decrease in VAS scores of patients in the 150 mg and 300 mg pregabalin groups versus the placebo group were noted. They found a significant decrease in fentanyl consumption, especially in the patients receiving 300 mg of pregabalin. There were no additional side effects of pregabalin, such as ataxia or confusion, in the patients receiving the drug. These findings support the theory that a single preoperative dose of pregabalin does not affect postoperative recovery of patients but does improve pain relief. The pregabalin 150 mg and 300 mg groups required significantly fewer antiemetics when compared with the placebo group. This is potentially due to the decrease in opioid use. In terms of decreasing post-surgical opioid use, 300 mg of pregabalin was more effective.

As mentioned previously, a major difference between prescribing gabapentin and pregabalin is that pregabalin is a controlled substance. The focus on this research is to decrease the use of potentially addictive medications. Pregabalin has not been classified as an addictive medication. However, does still pose a risk for overdose when taken at the wrong dose or with other medications. Currently, there is not an antidote for an overdose on gabapentinoids. However, most overdoses reported are in conjunction with an additional substance, such as alcohol, benzodiazepines, or narcotics. This should be a consideration with reviewing a patient's social history or prescribing multiple medications for pain management.

Another study by Mohamed et al. (2018) was conducted with 90 patients between the ages of 18- 65 who were all scheduled for a laparoscopic cholecystectomy under general anesthesia. Patients were randomized into 3 equal groups. Group 1 received 150 mg pregabalin, group 2 received 600 mg of gabapentin and group 3 received the placebo. All patients were instructed to take their medication 2 hours prior to the procedure. Patients were administered 1g of paracetamol/acetaminophen and 20 mg of nefopam (non-opioid analgesic) 30 minutes before the

conclusion of the surgery. This regimen was also repeated four times daily over the next 48 hours. Pain intensity was assessed by the VAS ranging from 0 to 10. All patients reported pain when evaluated at the 48-hour mark, specifically shoulder pain. This pain is speculated to be caused by stimulation of the sympathetic nervous system by hypercarbia, and carbon dioxide quickly expanding the abdominal cavity. During laparoscopic surgery the peritoneal cavity is inflated with gas, usually carbon dioxide and causes a pneumoperitoneum. It has been noted that the residual pneumoperitoneum following laparoscopic surgery resolves within 3 days in 81% of patients and within 7 days in 96% of patients (Draper, 1997). This shoulder pain was reported in 51.1% of the surgical patients; 13.3% in the pregabalin group, 12.2% in the gabapentin group, and 25.6% in the control group ($p=0.003$) (Mohamed, 2018). However, there was no significant difference found between the pregabalin group and gabapentin group.

This study evaluated a specific type of pain common for patients undergoing a cholecystectomy. Further studies are needed to evaluate if the doses of pregabalin or gabapentin would alter the outcomes or statistical significance between the two medications. This study was beneficial in analyzing the effectiveness of gabapentin and pregabalin with just one dose prior to surgery. It's important to note, this study used nefopam which is not approved for use in the United States, as it is not approved by the FDA. It is classified as a centrally acting analgesic. In comparison, using a medication such as Tramadol, would be a similar medication classified as a centrally acting oral analgesic. This medication produces a pain reliving effect mainly through central mechanism but has shown local anesthetic properties.

Additional research was conducted by Chang et al. (2009) focusing on postoperative shoulder pain. The study consisted of 80 patients who were assigned randomly to two groups, 40 patients received two 150 mg capsules of pregabalin and 40 received the placebo. The

medication was administered orally 1 hour before the start of their procedure. The same surgical team performed all surgical procedures using the same technical principles for the two groups. The patient's pain was evaluated using a VRS with ratings from 0 to 10. In both groups, staff administered ketorolac 30 mg IV as a rescue analgesic. Three patients were considered dropouts after the initial randomization and were therefore not subjected to further statistical analysis. The VRS pain score for surgical pain, cumulative ketorolac consumption, and proportion of patients not requiring rescue analgesia were no lower in the pregabalin group than in the placebo group throughout the study. Of the side effects, only the postoperative 2-hour incidence of oversedation was significantly higher in the pregabalin group than in the placebo group ($P < 0.05$).

This study concluded that perioperative administration of two doses of pregabalin 300 mg 12 hours apart did not decrease the frequency or severity of shoulder pain as well as the severity of surgical pain after laparoscopic cholecystectomy. Rather, it was associated with an increased incidence of undesirable sedation in the early postoperative period. This study provided research into the effectiveness of pregabalin individually to decrease additional pain medication. Interestingly, this study used a nonsteroidal anti-inflammatory for breakthrough pain instead of an opioid.

Eidy, Abdolrahimzadeh, Moravveji & Fazel (2017) acknowledged in their research that the use of gabapentin and pregabalin decreased post-surgical opioid consumption significantly. Their randomized, double-blind clinical study consisted of 108 patients between the ages of 20 and 60. These patients were divided equally in to three groups at random. The patients either received 800 mg of gabapentin, 150 mg of pregabalin or a placebo. As compared to the previous study, this research evaluated a higher dose of gabapentin and the same dose of

pregabalin as the research conducted by Mohamed et al. (2018). The medication for this study was administered one hour before surgery. The study was also blinded to the patient, surgeon, and postoperative pain controller. If the patient felt pain in the recovery room, which was determined to be a pain score greater than 4, they received 25 mg of intravenous pethidine (demerol). Once transferred to the hospital floor, the patient had access to pethidine through a patient-controlled pump.

In analyzing the VAS scores between groups at consecutive times using repeated measurement, tests revealed that the pain intensity differed significantly between groups ($p < 0.001$) (Eidy, 2017). The patients who received gabapentin and pregabalin had lower pain intensity scores than the placebo group. The study also suggested that patients who received pregabalin had a lower pain score over time compared to gabapentin. The grams of pethidine administered was assessed at each time increment (based on a one-way ANOVA test) revealed significant differences between groups. Post-hoc Dunnet's T3 test also revealed that all pairwise comparisons between-groups were significant ($P < 0.05$). The amount of pethidine used in the patients receiving pregabalin vs gabapentin was not significant. This study continued to evaluate different doses of gabapentin and pregabalin and still did not show a significance between the two medications. It does however provide data for the effectiveness of gabapentinoids in reducing the use of narcotics in the post-surgical period. This study had less of a multimodal drug approach as the patients were not administered acetaminophen and Nefopam, in addition to the gabapentinoids.

Discussion

Preliminary studies have provided significant data supporting the use of acetaminophen as monotherapy or as part of a multimodal approach. The multimodal options researched

included IV Acetaminophen with a narcotic (Demerol) or acetaminophen with an NSAID (Celebrex). The pain scores for the patients only receiving acetaminophen were significantly higher than those in the multimodal groups (P <0.01) (Mulita, 2021). Mulita et al. (2021) reported the combinations of acetaminophen/Demerol and acetaminophen/Celebrex showed a comparable analgesic effectiveness, and they were better than acetaminophen monotherapy for the management of postoperative pain. When considering the potential side effects, avoiding Demerol, and using Celebrex with acetaminophen, patients had less sedation, improved pulmonary function, and decreased constipation. In conclusion, 1000 mg of IV acetaminophen every 8 hours and IV parecoxib (Celebrex) 40 mg every 12 hours was the preferred multimodal treatment for postoperative pain.

Barazanchi et al. (2018) also concluded that pain scores were less when IV acetaminophen was administered prior to surgery (P<0.05). However, when IV acetaminophen was compared with oral (PO) administration before the procedure, there was no significant difference in pain scores in an RCT of 579 subjects (Johnson, 2019). A dosage of 1000 mg PO acetaminophen in addition to Celebrex 200 mg PO could be considered for postsurgical pain control after the patient is discharged home.

Another option for multimodal pain management is incorporating non-steroidal anti-inflammatories (NSAIDs). White et al. (2007) assessed the effectiveness of celecoxib (Celebrex). The patients were given 400 mg PO prior to surgery and then 200 mg twice daily for three days. Initially, the benefits were similar in the two treatment groups, but the amount of fentanyl administered was less in the celecoxib group compared to the control group (P < 0.05). This dosage is effective at decreasing opioid use during the healing phase. Additionally, 800 mg of IV ibuprofen prior to surgery and every 8 hours after the procedure was completed, had significantly

lower pain ratings than the patients who received 1000 mg IV acetaminophen (Ekinci, 2020). Like VAS scores, opioid consumption in patients receiving ibuprofen at all time periods postoperatively was significantly lower than those receiving acetaminophen ($P < 0.05$).

Ahiskalioglu et al. (2017) used both acetaminophen and ibuprofen to decreased post-surgical narcotic use. The recommendation is 400 mg ibuprofen IV and 1000 mg IV acetaminophen before the end of surgery, and this was repeated every 6 hours postoperatively. Fentanyl consumption was lower when both medications were used compared to just acetaminophen at all time periods ($P < 0.001$) (Ahiskalioglu, 2017). These studies concluded that 400 – 800 mg IV ibuprofen prior to surgery in addition to 1000 mg acetaminophen every 6 hours in the post-surgical phase is an effective multimodal pain management regimen to decrease opioid use.

Preoperative gabapentinoids were shown to be effective in reducing pain scores in 10 studies (Barazanchi, 2018). However, five studies were shown to have no significant difference between placebo and preoperative gabapentinoids. Preoperative gabapentinoids are not recommended for routine use but may be considered if basic analgesia is not possible (GRADE D) (Barazanchi, 2018). The research regarding gabapentin is inconsistent, so this recommendation is based only off expert opinion. Additional research is needed to determine optimal dose and to balance analgesic benefits with potential adverse effects such as increased potential for sedation. Although several studies have reported reduced postoperative opioid use, it may not be as effective as acetaminophen or NSAID. Finally, the review reported that opioids should be reserved for rescue analgesia only (GRADE B) (Barazanchi, 2018). This recommendation continues to be consistent across all studies.

Anticipated Results

In the treatment of postoperative pain for patients undergoing a cholecystectomy, it is anticipated that there is a statistical difference in efficacy when using a multimodal approach. It is anticipated that non-opioid analgesics can be used as effective pain management for post cholecystectomy patients. In addition, using non opioid analgesics can decrease the quantity of opioids when needed.

Applicability to Clinical Practice

After review of the research, preoperative use of acetaminophen or NSAIDs should be considered as first line treatment for post-surgical pain to decrease opioid use. Gabapentinoids may be an additional consideration but with conflicting data additional research is needed to determine appropriate dosing recommendations. With the information provided in this literature review, medical providers will be able to make the safest and most efficacious decision for the treatment of postsurgical pain in patients undergoing a cholecystectomy.

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