

Learning Objectives

- 1) Understand the mechanism of how Cannabis can decrease PONV, pain and opioid requirements during the perioperative period.
- 2) Know the various methods of Cannabis administration and bioavailability
- 3) Understand the possible side effects and anesthetic effects of Cannabis use.

Introduction

Mechanism

Cannabis exerts its effect and works synergistically with opioids because of its CB1 and CB2 G-protein cannabinoid receptors. CB1 receptors are located primarily in the brain and periphery which manages neuronal activity, the CB2 receptors are in immune and hematopoietic systems and they manage immune response (1). Both are present in primary afferent pain pathways and stimulate opioid receptors in this same pathway due to similar endogenous ligands meaning this mechanism may enhance opioid analgesia, seen in Figure 1 below (1,2). Opioids exert their effects on mu, kappa and delta receptors, some studies suggest this is how THC enhances the effects of opioids by activation of kappa and delta receptors (3). They also produce effects such as psychomotor depression, hypotension, hypothermia and antinociception like cannabinoids (3). This endocannabinoid system synergy is an ideal area for target study because it can lower perioperative doses needed for opioids to reduce pain. Some of side effects of cannabis include drowsiness, sleepiness and dry mouth which are also beneficial during surgery especially MAC anesthesia (4). The primary compounds found in cannabis are delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabivarin with the main psychoactive compound being THC at 20% of its composition (3). Synthetic Dronabinol is available containing 100% THC. For PONV it is shown that the endocannabinoid system is responsible for decreasing intestinal motility via the CB1 receptors and centrally attenuating emesis (5,6). The nucleus of the solitary tract (NTS) located in the Dorsal vagal complex (DVC) in animal studies have CB1 receptors which are activated by THC producing antiemetic effects but there is evidence that peripherally at higher doses it acts against 5-HT receptors suppressing the emetic response. (7).

Bioavailability and Routes of Administration

- First pass metabolism involves digestion and then traveling to the liver to become metabolized. Cannabis has various delivery methods some which avoid first pass metabolism. Smoking is an efficient method but it involves inhaling carcinogenic smoke posing health risks but there are other methods such as oral and sublingual routes, rectal, vapor and nebulizing although difficult due to its oily content. (8).
- Bioavailability is 25% for smoking, oral route is 5-25%, IV administration is similar (3).
- Half-Life distribution of Cannabis is 30 minutes and elimination is 30 hours because its highly lipophilic. (3).

Methods and Materials Continued

Side effects and Anesthetic Effects

- Ware et al. conducted a clinical study and were primarily concerned with the safety of Cannabis use and effectiveness on chronic pain, intensity and quality of life, they had a control group of 216 patients with chronic pain but no current cannabis use 66% were using opioids, then a cannabis group of 141 current users and 58 ex-users, 55% were using opioids from 7 different clinics (12). This was a large clinical trial that span the course of a year, they allowed the participants to choose their route of administration which included: 7% smoking only, 61% used a combination of smoking, oral and vaporization, 8% consumed cannabis orally only (12). Patients were contacted by either telephone interviews or in a clinical visit as follow-up during the course of the 1 year study.
- Echeverria-Villalobos et al. performed a comprehensive review of the pharmacological aspects and pathophysiological effects and anesthetic considerations that should be considered perioperatively for the cannabis patient (13).

Results

Decrease PONV, Pain and Opioid Requirement

Supporting the synergistic relationship between cannabis and opioids Boehnke et al. saw a self-reported patient decrease of 64% in opioid use when cannabis was added for pain, for that reason there is potential for significant decreases in opioid use perioperatively (10). Results from Boehnke et al. study showed that there was a significant decrease in the different medication classes used from 2.38 to 1.81 from all respondents before and after cannabis use (10). The reduction of opioid use was seen more in the lowest Fibromyalgia (FM) scores which it was expected to be seen in the higher FM scores. Opioid use being reduced in the lower FM scores is a beneficial outcome. It has potential of lowering the chances of addiction to opioids by adding or replacing it with Cannabis at an earlier time during pain management. This decrease in opioids and medications once taking Cannabis correlated with a decrease in side effects from their medications and improvements in quality of life. Narang et al. used oral Dronabinol but perioperatively IV Dronabinol would be a better choice because pain intensity is expected to decrease at an even faster rate, therefore shortening the timeframe to plateau because it will be bypassing first pass metabolism increasing its bioavailability, which is what limits oral pills to 25% bioavailability (4). For pain intensity we can see in Figure 2 from Narang et al. study a gradual decrease over the course of the 4-weeks and it significantly decreased between the 0-2-hour timeframe after administration then plateaued and slowly came back as seen in Figure 3 (4). These results are promising and support the synergy between cannabis and opioids but larger trials should be performed as this study only had 30 participants. PONV study conducted by Meiri et al. showed the efficacy of dronabinol and ondansetron were comparable when used alone and together. There was a 71% with no nausea with dronabinol and 64% with ondansetron and only 15% with placebo but the interesting data was that together they were much more effective (11). In the Operating room we currently use ondansetron for PONV but this study supports at the possibility of using dronabinol instead with a higher percent of relief from PONV in PACU as well as continued treatment at home. A lot of patients experience nausea and vomiting after leaving the hospital setting and this could be a potential continued treatment at home.

Bioavailability and Route of Administration

The Results of Ohlsson et al. study showed that administration of Cannabis by Intravenous injection had little variation in plasma concentrations between individuals and was a smooth curve unlike the Oral route despite the higher dose, it varied a lot between individuals from 60-90minutes to 240-300 minutes (9). Therefore, the plasma levels after oral administration were low, irregular due to slow and erratic absorption and plasma concentrations lagged behind and lasted longer in participants (9).

Side Effects and Anesthetic Effects

In order to determine if Cannabis has potential for use perioperatively its effects in the long run need to be considered. The results from Ware et al. showed that the risks of having at least one serious adverse effect (AE) did not differ significantly between cannabis users and controls although non-serious AE had a higher rate of 4.61 events/person-year in cannabis users compared to 2.85 events/person-year for control group (12). The adverse events were mainly nervous system, gastrointestinal and respiratory disorders. In regard to pain intensity and pain there was significant reduction in average pain intensity over the year compared to the control group and an improvement in both groups in regard to quality of life more so in the cannabis group (12). The interesting part of this study was they also included non-Cannabis users who also had chronic pain, other studies focused solely on participants with previous Cannabis use. Some side effects associated with Cannabis is that it can be psychologically addictive due to euphoria but there is no severe withdrawal system like those seen with opioid use (14). Other possible side effects are hallucinations, disorientation, altered perception, heart and digestive problems as well as vomiting, but they are expected to be mild, mainly sleepiness, dry mouth and confusion. For patients who are users of Cannabis during the pre-anesthesia assessment their level of exposure to cannabis, length and frequency of use as well as time since last use should be evaluated (13). For chronic users the use of synthetic cannabinoids mixtures should also be evaluated as well as past history of hyperemesis, hyperreactive airway, severe shivering and it should be discontinued at least 72 hours before surgery (13). During surgery THC prolongs the action of some barbiturates, ketamine and potentiation of inhaled agents but chronic users required higher doses of propofol and inhaled anesthetics due to the similar modulation of GABA (13). Animals studies also showed a potentiation of NMDB that may differ for larger vertebrates (13).

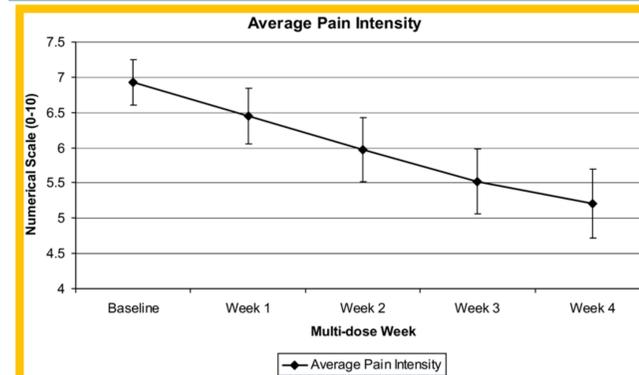


Figure 2. Average pain intensity during a 4 week trial. Reprinted from Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. by Narang et al., 2008, The Journal of Pain, 9(3).

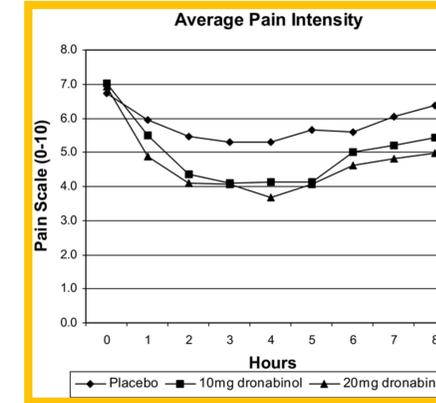


Figure 3. Average pain intensity during visits for Dronabinol administration. Reprinted from Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. by Narang et al., 2008, The Journal of Pain, 9(3).

Discussion/Conclusion

Current studies from Hurd approximate 2.5 million people have been diagnosed with opioid use disorder (OUD), 200 million opioid prescriptions are written each year and 80 people die each day from opioid overdose making it an epidemic (15). Unlike opioids, cannabis has no lethal dose and possibly many of those opioid related deaths could have been prevented had it been used as an adjunct in their pain treatment (14). Cannabis use for asthma, nausea, vomiting and pain is documented over centuries in traditional medicine and currently mainly used for chronic cancer, neuropathic, and acute pain (3,16). There are patients whose pain is so severe that opioid and anti-inflammatory drugs are ineffective (17). This is why research on cannabis is needed, synergism can be beneficial and play a significant role in pain management as a supplement or replacement to opioids perioperatively during this crisis. The purpose of this review is to examine the potential of cannabis use perioperatively in the medical treatment of pain, reducing opioid use as well as PONV. When it comes to cannabis, research is very limited due to its stigma and recreational use. This literature reviews aim is to show it has potential in assisting patients who have pain in which opioids are no longer sufficient alone, as well as those who are just starting to take opioids to avoid needing higher doses, reducing addiction probability. It examines intravenous administration which is good for comparison because of its bioavailability and less plasma variation between patients. This would be ideal in the perioperative setting and is titratable to effect but other methods such as vaporizing and pills are better methods for patients continued care at home, as it would be best to avoid so many IV sticks.

The studies reviewed show a lot of potential for future use of cannabis perioperatively, Narang et al. and Boehnke et al. research showed significant improvement in pain and overall well being with reductions in opioid use and Meiri et al. research showed significant improvement from PONV in her patients with a higher percent relief than ondansetron. Further research should also consider longer and larger studies, as most of the research conducted on cannabis in general and its synergy with opioids are small and short. This review does not take into consideration the patients diagnosis that is causing their pain which should be taken into account for future studies to target a particular population within pain medicine. However, research should also focus on participants who have not been exposed to cannabis as their response to treatment may be different from patients who take or have taken opioids and/or cannabis as a lot of patients getting surgery aren't necessarily on either. The large amount of overdoses, written prescriptions and abuse of opioids has led to a crisis in which cannabis could help us out of. These studies reviewed strengthens the idea that cannabis can be used for this purpose by demonstrating the reduction in opioid use and pain intensity when combined with cannabis, making cannabis a suitable supplementation of choice to aid in this opioid crisis.

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Methods and Materials

Bioavailability and Route of Administration

- To determine the best form of THC administration Ohlsson et al. conducted a study focused on clinical effects and plasma concentration variability using different methods. They administered participants THC 3 ways: Smoking 19mg, Oral in a cookie 20mg, and Intravenous 5mg (9).

Decrease PONV, Pain and Opioid Requirement

- Boehnke et al. in 2016 targeted the question if Cannabis would lower the doses needed for opioids when used in combination, they monitored 244 medical cannabis patients changes in opioid use, quality of life, medication side effects before and after Cannabis use through a 46-question survey and Fibromyalgia (FM) survey (10).
- In a study conducted by Narang et al. they investigated the analgesic effects of adding cannabinoids to participants who have chronic pain and taking opioids to test for synergy (4). Thirty participants were monitored while taking the adjuvant dronabinol I either 10mg or 20mg's with their Opioids to determine if there was a significant improvement in pain, sleep and mood. Narang et al. investigation was a 2-phase double-blind, randomized, placebo-controlled, single and multi-dose study which compared pain relief before and after Cannabis treatment as well as patient satisfaction.
- In a study by Meiri et al. they compared the efficacy of dronabinol and ondansetron both individually and together for PONV in chemotherapy patients over the course of 5 days. Patients received dexamethasone and ondansetron and either a placebo or dronabinol on Day 1 and either Dronabinol, ondansetron alone or together or placebo for the remaining days (11).