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Perioperative care of cannabis users: A comprehensive review of pharmacological and anesthetic considerations

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ABSTRACT

According to the 2015 National Survey on Drug Use and Health, marijuana continues to be the most common illicit recreational drug used in the US. Cannabis is associated with systemic reactions that potentially affect perioperative outcomes. We have reviewed the most important pharmacological aspects and pathophysiological effects that should be considered during the perioperative management of chronic cannabis/cannabinoids users. The synthetic analogues provide higher potency with increased risk for complications. High cannabinoid liposolubility favors rapid accumulation in fatty tissue which prolongs its elimination up to several days after exposure. The multi-systemic effects of cannabinoids and their pharmacological interactions with anesthetic agents may lead to serious consequences. Low doses of cannabinoids have been associated with increased sympathetic response (tachycardia, hypertension and increased contractility) with high levels of norepinephrine detected 30 min after use. High doses enhance parasympathetic tone leading to dose-dependent bradycardia and hypotension. Severe vascular complications associated with cannabis exposure may include malignant arrhythmias, coronary spasm, sudden death, cerebral hypoperfusion and stroke. Bronchial hyperreactivity and upper airway obstruction are commonly reported in cannabis users. Postoperative hypothermia, shivering and increased platelet aggregation have been also documented.

1. Introduction

The perioperative management of patients using cannabis, either for recreational or medical purposes, remains a challenge for the anesthesiologist due to its multi-organ side effects. However, the interactions between cannabinoids and general anesthetic agents, as well as the impact on intraoperative patient care are not yet fully understood.

Our review intends to highlight the most important pharmacological aspects and pathophysiological effects that should be considered by the anesthesiologists during the perioperative management of chronic cannabis/cannabinoids users.

2. Materials and methods

A literature search on Google Scholar, PubMed, Web of Science, Embase databases and Cochrane Library was carried out in order to identify reports published between 1970 and 2018 discussing cannabis pharmacology and perioperative considerations for naïve and chronic users. Our search was initiated by combining the following keywords: “cannabis”, “marijuana”, “acute postoperative pain”, “cannabinoids”, “synthetic cannabinoids”, “phytocannabinoids”, “perioperative care” and “cannabinoid pharmacology”. We limited available literature to studies published in English language, case reports, clinical trials, meta-analysis, reviews and systematic reviews. Likewise, preclinical studies were included when clinical data was not available or to support a specific clinical finding. Conference abstracts, no full-text or methodology available and manuscripts out of scope of this review were excluded.

3. Results

Initial search identified 773 articles. 369 were duplicated and a total of 257 manuscripts were excluded due to different reasons: manuscripts outside the perioperative scope of this review (n = 152), conferences

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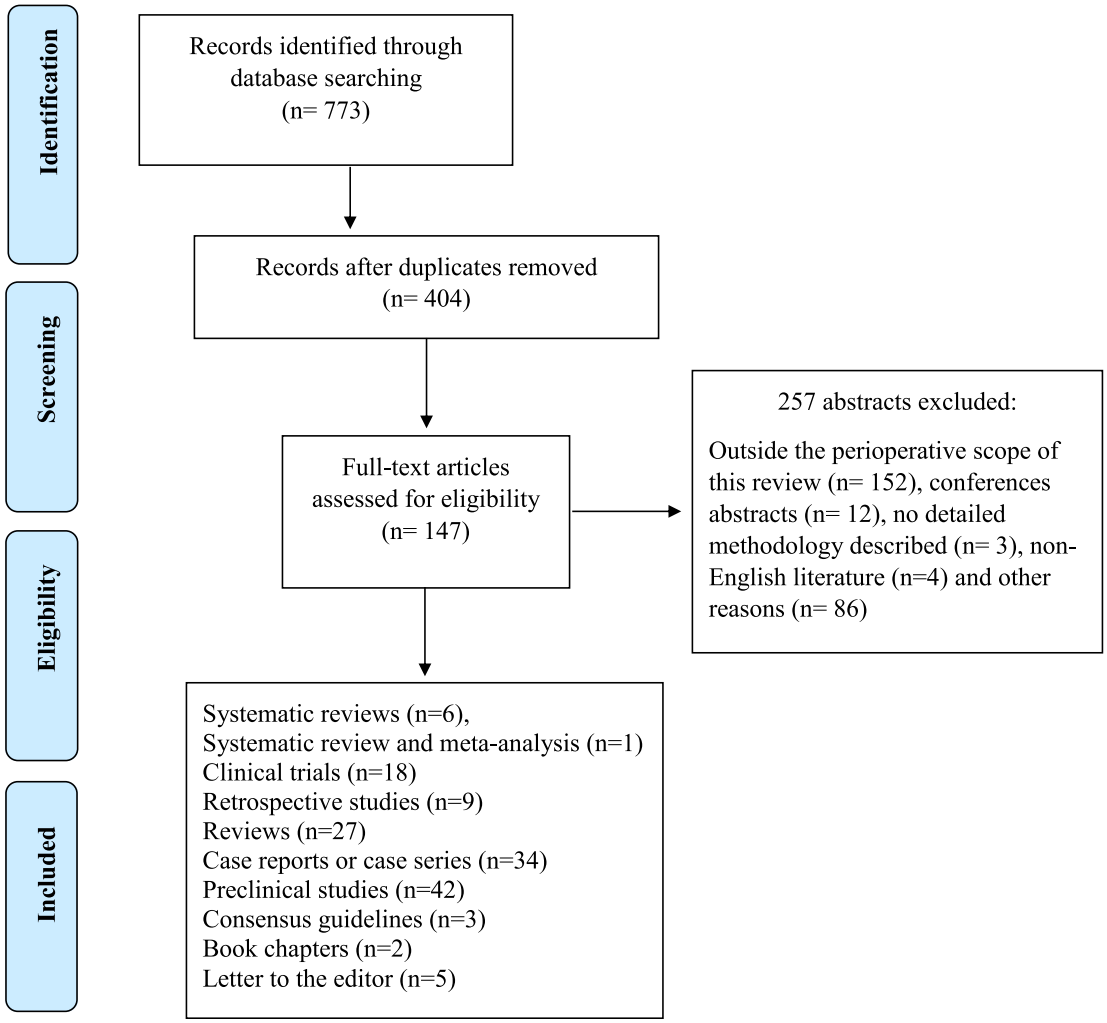

Fig. 1. PRISMA diagram.

abstracts (n = 12), no detailed methodology described (n = 3), non-English literature (n = 4), and other reasons (n = 86). Therefore, only 147 manuscripts were included in our review: systematic reviews (n = 6), systematic review and meta-analysis (n = 1), clinical trials (n = 18), retrospective studies (n = 9), reviews (n = 27), case reports or case series (n = 34), preclinical studies (n = 42), consensus guidelines (n = 3), book chapters (n = 2) and letter to the editor (n = 5) (Fig. 1: PRISMA Diagram [1]).

4. Discussion

4.1. Pharmacological considerations

4.1.1. The Endocannabinoid System

The Endocannabinoid System (ECS) is a biological system consisting of specific ligands, G protein-coupled cannabinoid receptors (CB-R), neurotransmitters and enzymes mediating the endocannabinoids synthesis and metabolism [2,3]. N-arachidonoyl-ethanolamine (AEA; anandamide) and 2-arachidonoylglycerol (2-AG) are endocannabinoids (ECBs) synthetized from phospholipids of the cellular membrane [4] after physiological or pathological stimuli [5–7].

Cannabinol (CBN) and Δ^8-tetrahydrocannabinol (D8-THC) are the main cannabinoid type 1 (CB1-R) and type 2 (CB2-R) receptor agonists. These molecules are classified as phytocannabinoids because they were first identified in the cannabis plant [8]. The CB1-R and CB2-R are part of the family of rhodopsin-like G protein-coupled ($G_{i/o}$-protein) receptors (GPR) that bind to phytocannabinoids, endocannabinoids and synthetic cannabinoids. These ligands are highly lipophilic compounds and their effects are mediated by inhibiting the adenylyl cyclase pathway [4,6]. Additionally, the GPR55 (also known as CB3-R) has been also identified as a cannabinoid receptor present in the human brain and liver [9].

The administration of THC produces an increase in heart rate with long-lasting conjunctival congestion followed by euphoria, drowsiness, short-term memory and concentration impairment, and reduced cognitive skills [10]. Table A summarizes the main physiologic effects of cannabinoids by system.

4.2. Physiological and perioperative considerations in cannabis users

4.2.1. Cardiovascular effects

The spectrum of the cardiovascular effects of cannabis intake are mainly mediated by CB1-R stimulation and controlled by two main physiologic events: the activation of the sympathetic nervous system (SNS) and the inhibition of the parasympathetic nervous system (PSNS) [11]. However, the onset and intensity of these responses may depend on the time of cannabis consumption [11–14]. A dose-dependent increase in heart rate and systolic blood pressure have been reported in naïve cannabis users immediately after beginning to smoke. THC peak plasma concentration has been linked to a 20% to 100% increase in systolic blood pressure when compared to baseline values, which may last up to 60 min after smoking cessation [11,12].

Table A
Main physiologic effects of cannabinoids.

System	CB-R	Physiologic effects	
Cardiovascular	CB1-R	Newly users, naïve, SCB	a) Dose-dependent; initial β-adrenergic effect + parasympathetic inhibition: ↑ HR, ↑ LV contractility, ↑ CO, ↑ SBP, VPCs, AFib, malignant arrhythmias (VTach, VFib, Brugada pattern) b) After 30 min of exposure: Norepinephrine levels peak and stay elevated up to 120 min after cessation
		Chronic and/or heavy-users (THC ≥ 10 mg)	a) Strong parasympathetic response + baroreflexes deregulation: ↓ HR, postural hypotension (not compensated by sympathetic stimulation); cardiac arrest b) Coronary spasm in patients with coronary disease → MI c) MI in young individuals due to an increase in MVO_2, high levels of COHb, and coronary thrombosis
	VR	Heavy users (THC ≥ 10 mg)	Mesenteric vasodilation through release of CGRP
Cerebrovascular	CB1-R	Naïve users or Low-dose THC	Vasodilation and ↑CBF
		Chronic use, heavy "spice" or K2 consumption	Cerebral vasospasm → ischemic stroke (posterior cerebral circulation affected in half of the cases)
Respiratory	CB1-R	Chronic or heavy user	a) ↑ bronchial tone → bronchial hyperreactivity b) Pharyngeal and uvular edema → upper airway obstruction c) Diffuse alveolar hemorrhage and necrotizing bronchiolitis → pulmonary edema d) Pulmonary embolism (more common with SCB)
Temperature	CB1-R	Chronic use, heavy smoking, SCB	Altered central thermoregulation → intraoperative hypothermia → severe postoperative shivering
Coagulation	CB1-R?	Chronic or heavy user	a) Increased clotting time b) Decreased platelet count c) Increased risk of bleeding in patients taking warfarin

CB-R: cannabinoid receptor; CB1-R: cannabinoid receptor type 1; HR: heart rate; LV: left ventricle; CO: cardiac output; SBP: systolic blood pressure; VPCs: ventricular premature contractions; AFib: atrial fibrillation; VTach: ventricular tachycardia; VFib: ventricular fibrillation; THC: tetrahydrocannabinol; MI: myocardial infarction; MVO_2: myocardial oxygen consumption; COHb: carboxyhemoglobin; CGRP: calcitonin gene-related peptide; VR: vanilloid receptor; CBF: cerebral blood flow; SCB: synthetic cannabinoids.

Some reports including echocardiographic evaluations of the cardiac function showed an increased cardiac output and velocity of circumferential fiber shortening (V_{cf}) [12,15]. Likewise, premature ventricular contractions may occur early [16]. Despite an early triggered THC-mediated chronotropic and hypertensive response, norepinephrine plasma level does not reach its maximum concentration until 30 min after starting to smoke marijuana and remains elevated up to 120 min after the end of the exposure [12]. Clinical studies suggest that initial tachycardia observed in these patients may be mediated by the β-adrenergic effect of epinephrine (adrenal stimulation) alongside with parasympathetic nervous system inhibition [11–13]. This principle has been validated by studies indicating that pretreatment with propranolol effectively blocked the THC-mediated increase in heart rate [13,17,18].

Similarly, an increase in heart rate, left ventricular contractility, and cardiac output have been also reported on experienced users after heavy daily marijuana consumption (THC ≥ 10 mg) [15]. These positive chronotropic and inotropic activities are also enhanced when fully CB-R agonists such as synthetic cannabinoids are used and suppressed by the administration of a CB1-R antagonist (i.e. rimonabant) [19,20].

As cannabinoid dosage becomes higher, a strong parasympathetic response is responsible for supine and postural arterial hypotension and bradycardia [21]. Prolonged sympathetic stimulation may not be enough to compensate these postural hemodynamic changes and orthostatic hypotension ensues as a result of peripheral vasodilation and deregulation of baroreflexes [22]. Moreover, anandamide has been linked to vasodilation in other vascular beds (i.e. mesenteric), probably mediated by the activation of vanilloid receptors (TRPV1-R) expressed in sensory nerve terminals with subsequent release of calcitonin gene related peptide (CGRP) [21,23]. Interestingly, decreased heart rate and tolerance to orthostatic hypotension have been reported after controlled administration of high-doses of THC in chronic users [14].

Recreational and medical marijuana use have been associated with severe cardiovascular disorders such as malignant arrhythmias, sudden-onset atrial fibrillation, coronary spasm, sudden death, cerebral hypoperfusion and stroke [24–29]. According to the National Inpatient Sample (NIS), the prevalence of arrhythmias doubled in hospitalized cannabis users from 2010 to 2014. Males and patients between 45 and 64 years old were identified at higher risk, atrial fibrillation being the most common arrhythmia reported in all groups [24]. Atrial flutter, second degree atrioventricular block, ventricular tachycardia, ventricular fibrillation, Brugada pattern and asystole are also severe rhythm disturbances linked to marijuana use [25,29–31].

High liposolubility of cannabinoids favors accumulation in fatty tissue, with delayed elimination and drug interaction up to 5 days after exposure. This long-lasting accumulation may be associated with sustained tachycardia experienced by patients receiving general anesthesia within 72 h after cannabis exposure [32]. Acute myocardial infarction has been also associated with previous exposure to "spice" or "K2", a mixture commonly including synthetic cannabinoids [27]. Therefore, cumulative evidence demands a detailed preoperative history of drug use (recreational or medical) including time of use, frequency and last time of exposure. General and regional anesthesia for elective surgery should be avoided at least for 72 h from last exposure [33].

4.2.2. Cerebrovascular effects

Ischemic stroke remains the most common vascular side effect reported in cannabis users [34]. Most of the cells involved in the control of cerebrovascular regulation are able to produce endocannabinoid ligands (anandamide and 2-arachydonylglycerol) and to express CB-Rs [35].

The activation of CB1-Rs leads to the synthesis of endothelial vasodilators which may increase cerebral blood flow (CBF) [36–38]. However, under certain metabolic stress situations (e.g., hypoxia, hypercapnia), CBRs activation actually decreases CBF via inhibition of neuronal metabolic rate and synaptic electrical activity [35].

Recent studies have reported a 2.3 to 2.9 fold incidence of cerebrovascular ischemia in young (25–35 y/o) cannabis users when compared to tobacco smokers [39,40]. A longitudinal cohort analysis done by Hemachandra et al. found a 4.7-fold increase in the risk of ischemic stroke in cannabis users [39]. Nonetheless, other individual predisposing factors may also play an important role in this outcome [41].

Ischemic stroke and transient ischemic attacks (TIA) are more common than hemorrhagic strokes in cannabis users, posterior circulation being the most affected (48%–53%) [42,43]. Cerebral vasospasm and atherosclerosis have been also identified as the main etiologic factors for cannabinoid-related cerebrovascular disease whereas young age (30–50 years), male gender (ratio 3.7:1), and chronic use (86%) have been identified as the main risks factors for cannabis-induced neurovascular toxicity [41,44,45]. Interestingly, one fourth of these patients had significantly increased the consumption of cannabis a few

days before the stroke occurred [46].

Contamination concerns are linked to a recent growing tendency to use cannabis concentrates or "dabs", containing very high amounts of THC, vaporized and inhaled through water pipes [47]. Acute psychosis, seizures, hypertension and myocardial infarction are some of clinical conditions associated with previous exposure to these concentrates [48–50].

4.2.3. Respiratory effects

The effects of cannabis consumption on the respiratory system entail a higher risk of perioperative respiratory complications. Cannabis is commonly smoked in hand-rolled and unfiltered cigarettes ("joints") facilitating the entry of high concentrations of carcinogenic chemicals and irritants (benzopyrene and benzanthracene) into the airways and lungs. Vaping cannabis oil, a new method of cannabis use, also promotes the inhalation of respiratory carcinogens and irritants compounds such as formaldehyde, obtained from the heating of propylene glycol. Exposure to these compounds may result in extensive airspace opacification seen as a centrilobular pattern (also known as "tree in bloom") image that resembles pneumonia [51]. Additionally, particular characteristics of cannabis smoking habit such as prolonged and deep inhalation, a shorter butt and a higher combustion temperature may result in greater carboxyhemoglobin levels and tar retention in the airway [15,52].

Bronchodilation occurs during cannabis smoking and it is probably mediated by the interaction of anandamide with CB1-Rs [53]. Contrarily, increased bronchial tone and risk of hyperreactivity after airway manipulation have been reported in chronic users [54].

Preoperative cannabis smoking has also been associated with postoperative airway obstruction characterized by pharyngeal and uvular edema. For this reason, it is recommended to postpone the operation when the patient has smoked marijuana shortly before an elective surgery. Nevertheless, some practitioners may consider the administration of steroids in order to reduce the risk of uvular edema or uvulitis [55–57].

Diffuse alveolar hemorrhage and necrotizing bronchiolitis have been associated with the inhalation of high doses of THC [58,59]. Ammari et al. reported a case of diffuse alveolar hemorrhage with inflammatory edema and increased capillary permeability aggravated by the antithrombotic effect of THC in a heavy cannabis smoker with THC plasma levels of 163 ng/ml (cutoff levels: 5 ng/ml) [60]. Moreover, recent reports associate the use of synthetic cannabinoids with pulmonary embolism [61–63].

4.2.4. Temperature regulation

Cannabis or cannabinoids exposure has been linked to decreased body temperature. Perioperative hypothermia has been defined as temperature < 36 °C with the shivering threshold usually set on 35.5 °C in non-anesthetized patients. Anecdotally, hypothermia and shivering are frequently observed in cannabis users during the perioperative period. Increased heart rate, hypoxemia, oxygen consumption, oxygen delivery, myocardial ischemia and acidosis are well-known physiologic effects of shivering. Cannabinoid-induced hypothermia seems to be mediated by CB1-Rs activation and it can be reversed administering a CB1-R antagonist such as rimonabant [64].

In a prospective cross-sectional observational trial, Sankar-Maraja et al. studied the frequency of postoperative shivering among chronic marijuana users. The authors analyzed three groups based on the amount of "joints" consumed per week: one group consisted of subjects who consumed > 5 joints/week, a second group with > 10 joints/week and the control group or non-users. The incidence of shivering was comparable between users and non-users (40% vs 33%; $p = 0.609$) [65]. Even though more human studies are required, physicians should consider that concomitant use of inhaled anesthetics shortly after marijuana exposure may potentiate vasodilation, worsening hypothermia and postoperative shivering.

4.2.5. Coagulation

The effects of cannabinoids on coagulation have been widely studied. In-vitro and in-vivo studies have shown both, pro-coagulation effects and anti-coagulation effects of cannabinoids [66–72].

Changes in platelets membrane phospholipids with subsequent decreased platelet count and increased platelet aggregation have been reported in hashish smokers after a high dose of THC [73]. Levy and Livne reported a decreased platelet count in the samples of blood obtained from healthy donors mixed with THC and CBN extract. Authors hypothesized this drop in platelets count resulted from an ADP-induced platelet aggregation [74]. Arterial wall inflammatory response and increased oxidative stress, platelet activation and over-activation of factor VII have been proposed as the main mechanisms for THC-induced platelet aggregation [75]. In addition, cannabinoids may also reduce nitric oxide availability in the vascular beds leading to endothelial dysfunction and platelet activation [76].

Warfarin and cannabinoids are both metabolized by the cytochrome P450. Warfarin is primarily processed by the isoenzymes CYP2C9, CYP3A4 and CYP1A2 [77,78]. Yamreudeewong et al. published a clinical case of a heavy marijuana smoker under warfarin treatment presenting twice with gastrointestinal and nose bleeding. Over-therapeutic INR values of > 10 were reported on this patient. After patient quit smoking marijuana, INR values went back to therapeutic values after 9 months. Authors attributed the impaired coagulation status to the metabolic interaction between cannabis components (THC and cannabidiol) and warfarin [79]. THC is highly bound to lipoproteins whereas cannabidiol is a potent CYP3A4 inhibitor and a weak CYP2C9 inhibitor. These two factors mainly contributed to increase warfarin plasmatic levels on this patient and therefore, the onset of warfarin-related side effects [79,80].

Recently, an outbreak of vitamin-K dependent coagulopathies associated with the consumption of synthetic cannabinoids was reported in the state of Illinois, USA. A total of 155 patients (74% were young males) presented bleeding diathesis with elevated INR (ranging from 5 to 20) after 3 days of cannabinoid use. Four patients (2.6%) died as a result of major bleeding, being hematuria one of the main clinical findings (81% of the patients) [81,82]. Synthetic cannabinoids mixed with *brodifacoum* (a long-acting anticoagulant and warfarin-analog) were identified as the root of this outbreak [81].

4.3. Cannabinoids and anesthetic interaction

One of the most challenging aspects of the pre-anesthesia assessment is to determine the level of exposure to cannabinoids. Therefore, anesthesiologists should first identify patients as new or chronic users and then, determine the time elapsed since last use. If recreational, anesthesiologists should also inquire about potential exposure to cannabis mixtures with synthetic cannabinoids such as "spice" or "K2". Table B summarizes the preoperative considerations in cannabis users.

Table B
Preoperative considerations in cannabis users.

Variable	Comments
Level of exposure	- New users vs chronic/heavy users - Recreational vs medical use - Frequency of dosage or smoking - Time elapsed since last exposure
Chronic users	- Use of "spice" or K2 (if recreational use) - Past medical history of hyperemesis episodes, hyperreactive airway, and severe shivering with previous surgery
Scheduled surgery	Elective surgeries should be avoided for at least 72 h from last exposure

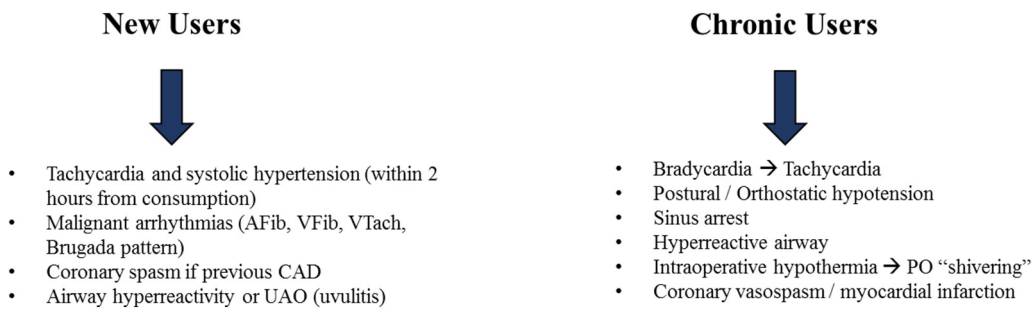

Fig. 2. Major perioperative physiologic findings in cannabinoid users.

4.3.1. Intravenous and inhaled anesthetics

Pharmacological interactions between cannabis/cannabinoids and anesthetics have been mostly reported in preclinical studies [83]. Few case reports explained some unusual clinical perioperative findings in cannabis users [84–87]. Available evidence may vary since the clinical curse of these patients might be unpredictable. Fig. 2 shows the major perioperative physiologic findings in cannabinoid users.

Preclinical studies indicated that THC prolongs the action of some intravenous anesthetics such as pentobarbital, thiopental, ketamine, propanidid and alfaxolone/alfadolone (Althesin®) [88,89]. In contrast, Brand et al. reported a THC dose-dependent antagonist action over the hypnotic effects of thiopental and propofol [90]. Moreover, Patel et al. found that sedating doses of propofol were associated with an increased brain content of anandamide, competitive inhibitor of the fatty acid amide hydrolase, an important enzyme that degrades endocannabinoids [91]. Propofol-induced increase in anandamide has been associated with severe hypotension in anesthetized animals through inhibition of the sympathetic response mediated by the CB1-R and vanilloid receptor-type 1 [92,93]. This interaction may explain one of the mechanisms involved in propofol-induced hypotension. Similarly, several studies have also reported a potentiation of the inhaled agents' effects in animal models after the administration of CBRs agonists [94,95].

In a prospective randomized study, Schelling et al. showed that patients receiving sevoflurane anesthesia had significantly lower blood levels of anandamide whereas no changes were found in those patients receiving propofol anesthesia. Authors concluded that this agent-dependent effect on the endocannabinoid system may potentially mediate the antiemetic properties of propofol and the high incidence of postoperative nausea and vomiting (PONV) after inhaled anesthesia [96].

Iberac et al. studied the effects of nabiximols (Savitex®) premedication on intraoperative bispectral index (BIS) values for patients undergoing general anesthesia. High doses of nabiximols were associated with significantly higher BIS values. Authors considered these outcomes as a cannabis-induced abnormal electroencephalogram (EEG) activity rather than a light anesthetic state [97].

One of the major mechanisms of action shared by general anesthetics and endocannabinoids is the modulation of γ-aminobutyric acid (GABA); therefore, pharmacological interactions may be expected. In a randomized clinical trial by Fleisberg et al., cannabis smokers required significantly higher doses of propofol during the induction of general anesthesia when compared to non-cannabis users (314.0 ± 109.3 vs. 263.2 ± 69.5 mg; $p \leq 0.04$) [98]. Similar higher tolerance to inhaled anesthetics such as isoflurane and sevoflurane was linked to cannabis users [85,87].

4.3.2. Opioids and acute pain management

The effects of cannabis/cannabinoids interaction with opioids remain controversial. In neuropathic pain animal models, THC has been associated with an anti-nociceptive effect that could reach 10-fold the potency of morphine [99,100]. This analgesic effect of THC seems to be partially mediated by delta and kappa opioid-receptors which can explain the synergistic action of cannabinoids and opioids [101–104]. However, an increased incidence of opioid-related side effects has also been reported [45].

Chronic and acute pain response to cannabinoid administration may vary [105]. A systematic review published by Stevens and Higgins analyzed data from patients with acute pain who received either cannabinoids or placebo. Surprisingly, analgesic efficacy was comparable between patients [105]. Moreover, several studies have associated the concomitant use of cannabinoids and opioids with acute pain exacerbation and greater incidence of opioid misuse [86,106–109].

In contrast, cannabinoids effectiveness to treat acute postsoperative pain ws demonstrated in animal models. Activation of CB1-R and CB2-R attenuate the neural transmission of the painful stimulus and subsequent acute pain [110,111]. The antinociceptive mechanisms proposed are mediated by a decreased calcium transmembrane conductance (through the inacticvation of the voltage-activated channels) and an increased potassium conductance [110]. CB1-R activation also inhibits the production of cyclooxygenase, attenuating the inflammatory component of acute pain and the central sensitization at the dorsal horn of the spinal cord [112].

Clinical trials have been unable to translate the synergistic effect between opioids and cannabinoids observed in preclinical studies. Despite anecdotal reports, randomized clinical trials and systematic reviews have shown disapointing results regarding postsurgical pain management [105,113–115].

4.3.3. Neuromuscular blockers

CB1-Rs are also located at the neuromuscular junction in the striated peripheral muscle and in the smooth intestinal muscle (pre-junctional) [116,117].

The effects of cannabinoids on neuromuscular transmission have been mostly studied in small vertebrates such as frogs and lizards in which stimulation of pre-junctional CB1-Rs via CB1-R agonists or ECB ligands (especially 2-arachidonoylglycerol) mediates the inhibition of the neurotransmitter acetylcholine (ACh) through the activation of the presynaptic M_3 muscarinic receptors [118]. Sanchez-Pastor et al. showed that CB1-R agonists administration not only decreased the release of ACh at the neuromuscular junction, but also the frequency and amplitude of miniature end-plate potentials (MEPP) [119].

Based on this premise, some authors inferred that cannabis may potentiate or prolong the effects of non-depolarizing neuromuscular blockers [84]. However, mammalian neuromuscular junction may respond to cannabinoid administration in a different manner. Morsch et al. reported that CB1-R agonists (anandamide, WIN) and fatty acid amide hydrolase enzymatic system inhibitors were associated with an increased volume in presynaptic vesicles. Stimulation of Ach migration resulted in an enhanced neuromuscular synaptic transmission with subsequent increase in postsynaptic action potentials measured with electromyography [120].

The differences observed in neuromuscular transmission of small vertebrates and mammalians correlate with the evolution of cannabinoids signaling processes reported in phylogenetic studies [121,122].

Whether this phenomenon is an adaptive effect rather than a circumstantial element is probably part of the pluralistic hypothesis of the evolutionary changes. Currently, no reports describing the interaction between cannabinoids and non-depolarizing muscle relaxants have been published.

4.3.4. Cannabinoid hyperemesis syndrome

Cannabis and some cannabinoids (Δ8-THC, nabilone, levonantradol and nonabine) act as broad-spectrum antiemetics, especially in chemotherapy-induced nausea and vomiting (CINV), through the activation of CB1-Rs in brainstem and in the enteric nervous system [123]. Nevertheless, a paradoxical hyperemetic effect of cannabis has been reported in some chronic users. This condition resembles the cyclic vomiting syndrome described in children and has been termed cannabinoid hyperemesis syndrome (CHS) [124–126].

Kim et al. reported an increased incidence of CHS in states where the use of recreational marijuana is legal [127]. CHS is a medical condition that occurs in the setting of chronic cannabis use characterized by a cyclic pattern of severe nausea, vomiting and abdominal pain. These episodes are usually refractory to standard antiemetics and analgesics with rapid improvement observed after cannabis cessation [128]. The pathophysiology is not completely understood. However, most of the symptoms are probably mediated by CB1-Rs activity in the gastrointestinal tract or enteric nervous system. The high lipid solubility of THC is responsible for its long half-life which in combination with pharmacogenetic factors may alter the metabolism of THC and promote the accumulation of emetogenic metabolites [128,129].

Over-expression of CB1-Rs in the preoptical neural area of the anterior hippocampus has been also associated with altered thermoregulation and autonomic dysregulation followed by desensitization of antiemetic CB1-Rs in the brain [117,130–133]. Downregulation of CB1-Rs reduces its functionality turning THC from its natural agonist action, into an antagonist ligand [131,132]. Other authors have hypothesized that reduced CB1-Rs expression may produce gastroparesis and subsequent triggering of hyperemesis [134].

Lapoint et al. recently published a novel diagnostic and therapeutic guideline for CHS management optimization [135]. CHS diagnosis should be considered based on clinical and epidemiologic features. Male patients, chronic or regular cannabis users (over a year), cyclic nausea and vomiting, diffuse abdominal pain and compulsive hot bath (to relieve the symptoms) are some of the main clues for an assertive CHS diagnostic [128,135]. Peripheral vanilloid (capsaicin) receptor-type 1 probably mediates the reported CHS relief after hot baths or showers [135]. Vanilloid receptor-type 1 receptors are activated by heat and regulate the release of substance P, a mediator of nausea and vomiting [117]. Capsaicin binds to vanilloid receptor-type 1 receptors also interacting with CB1-Rs in the central vomiting centers and gastrointestinal tract [136]. Relief of the symptoms with hot water has been explained through a bypass of blood flow from the mesenteric circulation to skin, also known as “cutaneous steal syndrome” [137].

CHS incidence may be underreported, mostly after the current growing recreational use of “spice” or K2 [138–141]. Synthetic cannabinoids are full CB1R-agonist and their toxic effects are certainly more potent than phytocannabinoids [142].

Once identified, certain perioperative consideration must be taken in this patient setting. Synthetic and/or phytocannabinoids cessation is probably the most effective treatment for CHS in conjunction with fluid replacement [128]. Anesthesiologists should avoid the intraoperative use of opioids and consider an opioid-sparing pain management. No satisfactory results have been reported with the administration of conventional antiemetics (antihistamines, 5-HT antagonists, dopamine-receptor antagonist) [128,129]. However, complete symptoms relief has been obtained with the administration of butyrophenones (droperidol, haloperidol) [143,144].

To our knowledge, there is no reporting of the association between past medical history of CHS and the risk of PONV in chronic cannabis users. Therefore, standard recommendations and guidelines for patients at high risk for PONV should be followed in these patients.

4.3.5. Cannabis withdrawal syndrome

The cannabis withdrawal syndrome (CWS) has been validated as a clinical entity. Diagnostic criteria have been included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as well as in the International Classification of Diseases (ICD) [145]. According to DSM-5, CWS diagnosis requires three or more of the following clinical criteria: irritability, anger or aggression, nervousness or anxiety, sleep difficulty (eg, insomnia or vivid dreaming), decreased appetite or weight loss, restlessness, depressed mood, and at least one of the following physical symptoms causing discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills and/or headache [145].

The clinical features of synthetic cannabinoids withdrawal syndrome may differ from the ones observed in patients with THC-induced withdrawal syndrome [146]. Interestingly, cannabis users that are also opioid-dependent hardly ever present with CWS [147]. Amount and potency of cannabis, female gender, enviromental and genetic factors are the main variables determining the severity of the CWS [148]. CWS is clasiffied in 2 types based on the onset and progression of the symptoms. Patients having Type A CWS are those experiencing a peak in symptoms' intensity between day 2 and day 6 after last exposure. On the other hand, patients experiencing a progressive decrease in symptoms' intensity after cannabis cessation are classified under Type B CWS [148].

5. Conclusion

Therapeutic and recreational use of cannabinoids have significantly increased in the United States within the last year. Moreover, cannabinoids have become one of the main alternatives for chronic pain management. However, its efficacy and safety in patients with acute and postoperative pain are still to be determined.

A collaborative effort to report providers' experiences and to promote the design of new protocols aiming to reduce perioperative complications and to improve postoperative functional outcomes in chronic and naïve cannabis users will build a quality body of evidence on this topic.

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