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Journal

Cannabis and Cannabinoid Research, 7(3)

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Publication Date

2022-06-01

DOI

10.1089/can.2021.0009

Cannabis Exposure Decreases Need for Blood Pressure Support During General Anesthesia in Orthopedic Trauma Surgery

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Abstract

Introduction: As cannabis use continues to increase in popularity, it is important to investigate how it impacts public health in all sectors of the population, including patients undergoing anesthetic management. This retrospective study focuses on the orthopedic trauma population presenting through an emergency department (ED) and receiving a urine drug screen (UDS) with subsequent urgent surgical intervention. We aimed to evaluate differences in response to general anesthesia in patients with exposure to THC, a major cannabinoid, compared to controls that screened negative for THC.

Materials and Methods: All ED visits at UC Irvine, a level 1 trauma center between November 4, 2017 and January 7, 2020, were evaluated in this study. Only adult patients who received a UDS and underwent urgent orthopedic trauma surgery within 48 h of ED visit were included in this study. Additional inclusion criteria required an anesthesia time greater than 1 h as well as anesthesia induction and intubation while in the operating room. Overall, we analyzed a total of 221 adult patients.

Discussion: When adjusting for demographic variability, there were statistically significant differences in response to general anesthesia between these two groups. The THC-positive (THC(+)) group was less likely to receive intraoperative vasopressors, had higher mean arterial blood pressure and mean diastolic blood pressure, needed less total fluid input and had a lower overall fluid balance. Chronic exposure to THC has been shown to downregulate cannabinoid 1 receptors and cause alterations in endocannabinoid tone. These are two potential mechanisms by which the THC(+) group in our study may have become more resistant to the typically observed hypotensive effects of general anesthesia.

Conclusion: The present study suggests that prior use of cannabis, objectively assessed by urinalysis, results in a decreased need for blood pressure support during general anesthesia. The physiological basis for this phenomenon is unclear, but possible causes might include the downregulation of vascular cannabinoid receptor 1 and/or altered endocannabinoid levels after exposure to cannabis.

Keywords: blood pressure; cannabis; general anesthesia; orthopedic trauma, tetrahydrocannabinol

Introduction

In the past two decades, cannabis use has become increasingly prevalent[1] despite persistence of its illegal designation, which was federally mandated in 1970. The surge in cannabis use is due, in part, to confrontation of this federal illicit status by state governments, the first of which was California's, which passed legislation permitting medicinal use of cannabis in 1996. Many states have followed suit and now a majority permit legal use of cannabis in some capacity[1,2] with 15 states permitting recreational use and 36 states permitting medicinal use. Based on the National Survey on

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Drug Use and Health, the change in legal landscape has coincided with an increasingly positive perception of cannabis among adults.[1] As cannabis use continues to increase in popularity and is encountered in patients undergoing surgery, it is important to consider the effect it may have on anesthetic management.[3]

Studies have highlighted the challenge for anesthesiologists and the need for further studies to inform national recommendations for perioperative care of patients who use cannabis.[4,5] A recent study demonstrated no increase in intraoperative anesthetic complications in trauma patients with urine samples that screened positive for recreational substances.[6] Although cannabis has not been shown to increase perioperative morbidity and mortality, cannabis users do have an increased risk of perioperative myocardial infarction compared to nonusers, with an adjusted odds ratio of 1.88.[7] Oral THC has not been shown to improve postoperative analgesia[8] and use of other cannabinoids have not shown a benefit in acute pain.[9] A 2009 prospective, randomized, single-blinded study showed increased propofol doses were needed in cannabis users to achieve sufficient depth of anesthesia to successfully place a laryngeal mask airway.[10] More recent retrospective studies demonstrated that consistent cannabis users had increased intravenous sedative medication requirements during endoscopic procedures[11] and increased requirement for inhaled anesthetic gas in orthopedic surgery.[12] Preclinical and clinical studies have also reported varying effects on blood pressure from cannabis use.[13] For example, Malinowska et al. report a triphasic effect on blood pressure from cannabinoids in animal studies.[14] In addition, it has been observed that acute cannabis use can lead to increased blood pressure.[14] Most existing studies relied on patient reported use of cannabis, which is subject to recall bias, nondisclosure due to concern for stigma, and inability to accurately quantify use. Impact of cannabis on intraoperative anesthetic management has not been fully elucidated and the effect of objectively assessed cannabis exposure on intraoperative blood pressure management has not been previously investigated.

This retrospective study focuses on the orthopedic trauma population presenting through an emergency department and requiring urgent surgical intervention. We investigated differences in response to anesthesia of patients with known cannabis exposure by selecting patients who had undergone urine drug screen (UDS) for THC, a major cannabinoid in cannabis, before surgery. Our study, unlike many prior works, distinguishes patients via an objective biological sample and compares the physiologic differences in reaction to anesthesia between the THC-positive (THC($+$)) and THC-negative (THC($-$)) patient groups. This approach identifies preoperative cannabis users and noncannabis users in an objective manner compared to most prior investigations, which have solely relied on patient reports.[10–12] The anesthetic management parameters evaluated include doses of anesthesia induction agents, muscle paralytics, analgesics, vasopressors, fluids, and inhaled volatile anesthetics. The dose of inhaled volatile anesthetic for a patient is measured by the minimum alveolar concentration (MAC) of the volatile agent in the expired gases of the patient into the anesthesia circuit, and this parameter is always adjusted for the age of the patient.[15]

Materials and Methods

This study was conducted at the University of California, Irvine Medical Center in Orange, California. Before any research activities, Institutional Review Board review and approval was obtained (HS# 2019-5415). A retrospective chart review was performed by the research team with assistance from the Department of Clinical Informatics.

Data collection

UC Irvine is a 417-bed tertiary-care level 1 trauma center. All emergency room (ER) visits between November 4, 2017 and January 7, 2020 were included in the study. This timeframe was chosen as our institution introduced a new electronic health record system in November 2017, and therefore, the records from this period could be compared with consistency. We did not analyze records after January 2020 given the widespread changes in anesthetic management practices with the onset of the COVID-19 pandemic. We analyzed adult patients (18–89 years old) undergoing an orthopedic trauma procedure (open reduction and internal fixation, external fixation, intramedullary long bone nail placement, and hip hemiarthroplasty) that was performed within the 48 h after an ER visit. Any cases that did not meet the following criteria were removed from the data set: UDS performed during ER visit, anesthesia time greater than 1 h (defined as time between induction and extubation), and intubation in the operating room (OR). The following data elements were extracted from the electronic medical record system ("EPIC," Verona, WI, USA) by the Department of Clinical Informatics: age, gender, height, weight, body

mass index (BMI), drug screen result, surgical procedure type, intraoperative blood pressure, anesthesia event times (including induction, intubation, and extubation times), intraoperative medications (including anesthetic gases and fluids), intraoperative urine output, and intraoperative blood loss. The research team then performed a manual chart review to extract the following elements: intraoperative fluids (crystalloids, colloids, urine output, total blood loss, and blood products) and all intraoperative medications (induction agents, muscle paralytics, and vasoactive medications).

Data processing

Anesthetic gas use and blood pressure during the middle third of the total anesthetic period were analyzed. The total anesthetic period is defined as commencing at induction of anesthesia and concluding with extubation. This was selected as blood pressure lability and rapid titration of anesthetic gases is common in the initial and concluding phases of the total anesthetic period, whereas patient hemodynamics in the middle third of anesthesia are at a more steady state. End-tidal gas concentrations were collected from the electronic medical record system and subsequently converted to age-adjusted MAC values based on the equations reported by Nickalls and Mapleson.[15] If two or more gas types were reported at the same time, gas use at that time was represented as the sum of the two age-adjusted MAC values, which is the standard in clinical care and research investigations. Blood pressure data were collected from both the noninvasive and invasive monitors when available. As the standard anesthetic practice is to collect blood pressure measurement every 3–5 min, plentiful data were available to assess trends in monitoring this dependent variable. If the noninvasive blood pressure had a sampling frequency of at least one sample every 5 min, then only noninvasive blood pressure measurements were analyzed, as these values are more accurate. If the noninvasive blood pressure sampling frequency was below this threshold, invasive blood pressure readings were included. Blood pressure samples that fell outside the bounds of 10–250 mm Hg mean arterial pressure (MAP) were removed from the data set as these are common inaccuracies in health records due to a nonzeroed or noncalibrated invasive blood pressure monitor.

Statistical analysis

The two groups of interest were the THC(+) group and the THC(−) group. Descriptive statistics were computed to examine differences between the two groups. Mann–Whitney U tests and chi-squared tests were used to compare baseline covariates between the two groups as appropriate. Multiple logistic/linear regression models were used and adjusted for age, gender, BMI, and minutes of anesthesia. All data processing and analysis were performed using Python (Python Software Foundation, Wilmington, DE, USA) and R statistics (www.r-project.org).
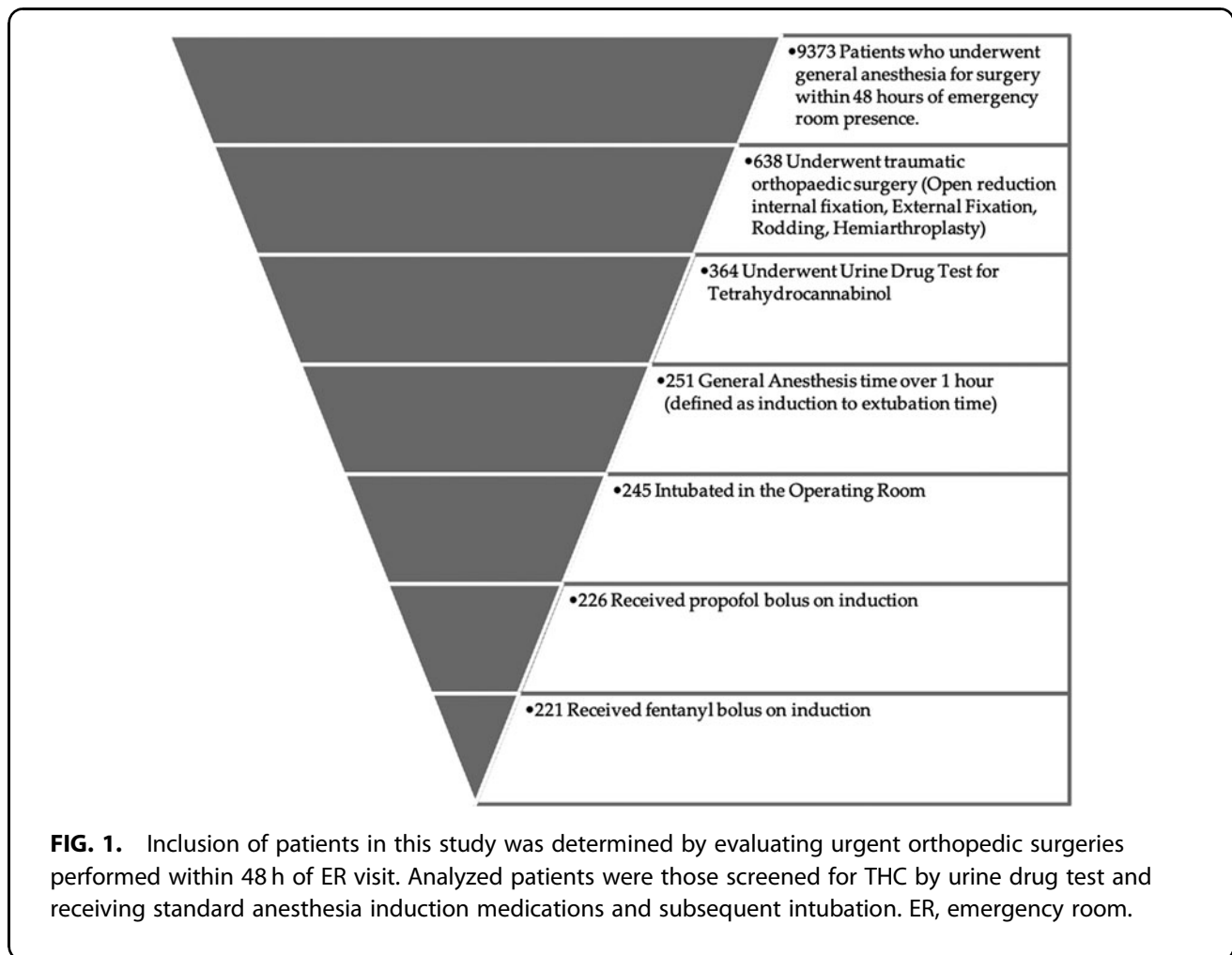
Results

A total of 9373 ER cases with a surgical procedure performed within the subsequent 48 h were identified between November 4, 2017 and January 7, 2020. Of this group, 221 cases were included after filtering by the following criteria: an orthopedic trauma procedure (open reduction and internal fixation, external fixation, intramedullary nail placement, and hip hemiarthroplasty) performed within 48 h of ER visit, urine drug test performed during ER visit, general anesthesia time greater than 1 h (defined as time between induction and extubation), intubation in the OR, received propofol bolus upon induction, and received fentanyl bolus upon induction (Table 1 and Fig. 1). The average time from admission to the ER and entrance into the OR was 20 h with a standard deviation of 10 h. When analyzing baseline demographic data, there were statistically significant differences in age, gender, and height between the two groups. These differences were adjusted for in our analysis (Table 2). There were no statistically significant differences in weight, BMI, minutes of anesthesia, or American Society of Anesthesiologists (ASA) score between the groups.

Table 1. Groupwise Comparisons Between THC-Positive and THC-Negative Patient Populations

	THC-positive (n = 55)	THC-negative (n = 166)	p
Age (years)	29 [25, 40]	46 [30, 62]	<0.05*
Female	7 (13%)	48 (29%)	<0.05*
Male	48 (87%)	118 (71%)	
Height (inches)	69 [67, 71]	67 [64, 70]	<0.05*
Weight (lbs)	176 [149, 212]	170 [147, 200]	0.35
BMI	26 [23, 30]	27 [23, 29]	0.65
Minutes of anesthesia	190 [137, 239]	191 [145, 253]	0.62
ASA score			0.50
1	4 (7%)	12 (7%)	
2	32 (58%)	78 (47%)	
3	17 (31%)	70 (42%)	
4	2 (4%)	6 (4%)	

*Statistical significance.
ASA, American Society of Anesthesiologists; BMI, body mass index.

FIG. 1. Inclusion of patients in this study was determined by evaluating urgent orthopedic surgeries performed within 48 h of ER visit. Analyzed patients were those screened for THC by urine drug test and receiving standard anesthesia induction medications and subsequent intubation. ER, emergency room.

Four areas of anesthetic management were analyzed including the patient's intraoperative medications, intraoperative blood pressure, intraoperative fluids, and the age-adjusted MAC of volatile anesthetic gas. There were statistically significant differences between the THC(+) and THC(−) groups when evaluating intraoperative vasoactive medication use, intraoperative blood pressure, and intraoperative fluid management. Specifically, the THC(+) group was less likely to receive intraoperative vasopressors (Fig. 2), had higher mean arterial blood pressure and mean diastolic blood pressure (Fig. 3), needed less total fluid input and had a lower overall fluid balance (Fig. 4). No significant difference was noted between the two groups when comparing induction doses of propofol or fentanyl, total doses of propofol or fentanyl, and age adjusted MAC of volatile gas during the middle third of cases (Table 2). Therefore, differences in anesthetic management

do not explain the differences in measured blood pressure parameters or interventions to target blood pressure.

Discussion

Understanding the effect of cannabis use on blood pressure during anesthetic management is of paramount importance,[16] and it is also essential to differentiate the effect of acute cannabis intoxication from chronic cannabis use. The impact of physiologically active substances upon general anesthetic management differs markedly if the medication is used chronically versus acutely in an otherwise naive patient.[17] For example, acute cocaine intoxication increases blood pressure, but chronic cocaine use followed by abstinence increases the need for blood pressure support during anesthesia.[18] Our current study highlights the possible impact of prior, but nonacute, cannabis exposure on blood pressure perturbations during anesthetic

Table 2. Regression Models (Adjusting for Age, Gender, Body Mass Index, and Minutes of Anesthesia)

	p	Odds ratio (95% CI)	R^2 (%)
Intraoperative blood pressure			
Systolic mean	0.06	1.34 (0.99–1.82)	10
Systolic median	0.07	1.33 (0.97–1.82)	8
Systolic standard deviation	0.72	1.05 (0.81–1.35)	39
Diastolic mean	<0.05	1.37 (1.01–1.87)	10
Diastolic median	0.06	1.34 (0.98–1.83)	8
Diastolic standard deviation	0.47	1.12 (0.83–1.5)	17
MAP mean	<0.05	1.39 (1.03–1.89)	12
MAP median	0.05	1.36 (1–1.85)	10
MAP standard deviation	0.67	1.06 (0.81–1.39)	30
Intraoperative medications			
Propofol induction dose (mg)	0.91	1.01 (0.78–1.32)	36
Propofol induction dose (mg/kg)	0.89	1.02 (0.77–1.35)	26
Fentanyl induction dose (mcg)	0.56	0.91 (0.66–1.25)	5
Fentanyl induction dose (mcg/kg)	0.70	0.94 (0.70–1.28)	13
Total propofol during case (mg)	0.40	1.14 (0.84–1.53)	17
Total propofol during case (mg/kg)	0.37	1.15 (0.85–1.55)	13
Total fentanyl during case (mcg)	0.19	1.23 (0.91–1.67)	12
Total fentanyl during case (mcg/kg)	0.24	1.2 (0.89–1.61)	16
Vasopressor use (Y/N)	<0.05	0.5 (0.25–0.99)	16
Intraoperative fluids			
Quantified blood loss (mL)	0.66	1.06 (0.82–1.37)	38
Urine output (mL)	0.77	1.04 (0.79–1.39)	24
Total fluid out (mL)	0.65	1.06 (0.83–1.36)	41
Total crystalloid fluids (mL)	0.08	0.8 (0.62–1.03)	39
Total colloid fluids (mL)	0.14	0.8 (0.58–1.08)	10
Total blood products (mL)	0.25	0.84 (0.62–1.13)	16
Total fluid input (mL)	<0.05	0.76 (0.60–0.98)	42
Fluid balance (mL)	<0.05	0.69 (0.51–0.93)	15
MAC			
Age-adjusted MAC average	0.26	1.19 (0.88–1.62)	13
Age-adjusted MAC median	0.19	1.23 (0.90–1.66)	12
Age-adjusted MAC standard deviation	0.23	1.22 (0.88–1.69)	0

CI, confidence interval; MAC, minimum alveolar concentration; MAP, mean arterial pressure.

management. For example, cannabis exposure without acute intoxication was weakly associated with the decreased need for blood pressure support during general anesthetic management. As anesthesia lowers patient blood pressure, the typical role of anesthesiologists is to administer fluids and vasopressors to maintain normotension. However, patients with a THC(+) UDS collected on hospital admission did not require as much blood pressure support as THC(−) patients. Outside of this difference, patient groups were similar in their dose of volatile agents (age-adjusted MAC), dose of induction medications or opioid consumption intraoperatively.

Typically, the pharmacodynamic effects of cannabis resolve 10 h or less after consumption,[19] but detectable levels of THC and its liver first-pass metabolites can be found in urine for up to 24 days.[20,21] Patients in this study experienced an average interval of 20 h between ER visit and entrance into the OR. Therefore, the patients in our study were objectively confirmed to have used cannabis within 24 days of admission and were reliably not acutely intoxicated with the substance at the time of anesthetic management.

The primary effects of cannabinoids are facilitated by the endocannabinoid system, which comprised cannabinoid receptor 1 and 2 (CB1R and CB2R) and the endogenous endocannabinoids, anandamide (AEA), and 2-arachidonylglycerol (2-AG). There are also important enzymes involved in this system, fatty acid amide hydrolase, and monoacylglycerol lipase, which degrade the endocannabinoids into
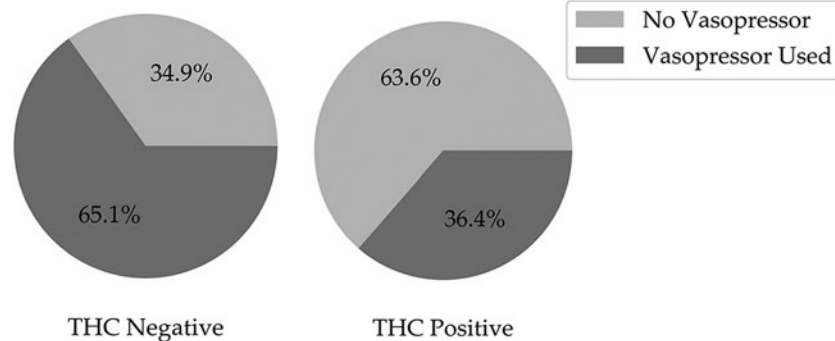

FIG. 2. Vasopressor use in THC(−) and THC(+) patient groups. The THC(+) group required significantly fewer vasoactive medications intraoperatively, which suggests a decreased need for pharmacologic blood pressure support in anesthetic patients who are exposed to cannabis. THC(−), THC-negative; THC(+), THC-positive.
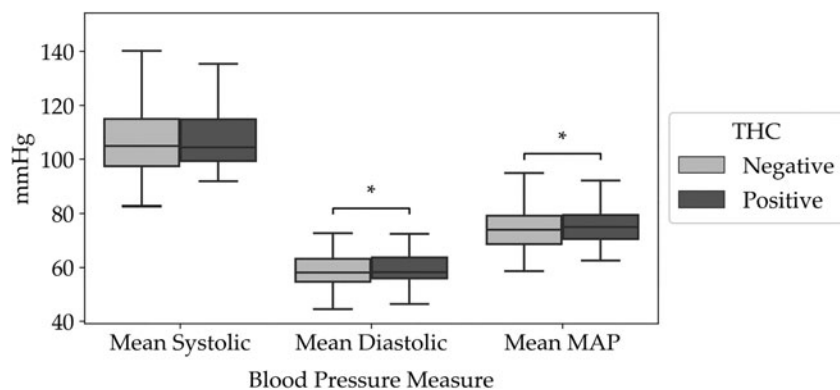
FIG. 3. Mean intraoperative blood pressure in THC(−) and THC(+) groups in mm Hg. Mean arterial pressure and mean diastolic blood pressures were higher in the THC(+) group, suggesting resistance to the hypotensive effects of anesthesia with cannabis exposure. *Statistical significance.

inactive metabolites.[22] The endocannabinoid system plays an important homeostatic role in the cardiovascular system, pain perception, memory, behavior, metabolism, and stress.[9,23–25] These are areas of particular importance when managing a patient undergoing general anesthesia and surgical intervention.

Cardiovascular effects

Cannabis use disorder has not been shown to change morbidity or mortality in the perioperative period, but is associated with an increased risk of perioperative

FIG. 4. Fluid balance in THC(−) and THC(+) patient groups. Overall fluid balance, defined as the net fluid administered to a patient intraoperatively less the urine output and blood loss, was significantly higher in the THC(−) group. This suggests decreased need for blood pressure support during general anesthesia.

myocardial infarction.[7] The cardiovascular effects of cannabis are primarily regulated by the CB1R, although other receptor systems have also been implicated.[26,27] CB1R are primarily located in the central nervous system, but are also found in presynaptic sympathetic nerve terminals, blood vessels, and the heart.[22,26] Proposed mechanisms for vasodilation that have been investigated in animal models demonstrates that CB1R agonism leads to smooth muscle vasorelaxation through the activation of potassium channels and the inhibition of specific calcium channels.[28] Another involves vasodilation due to CB1R agonism at presynaptic sympathetic nerve terminals inhibiting the release of neurotransmitters such as norepinephrine, leading to vasodilation.[29] CB1R is a G-protein coupled receptor[26] that when agonized in a repeated or prolonged manner undergoes desensitization and downregulation.[13] Chronic exposure to THC has been shown to downregulate CB1R.[30,31] This is one potential mechanism by which the THC(+) group in our study may have become more resistant to the typically observed hypotensive effects of general anesthesia, compared to THC(−) patients. Another potential mechanism is related to cannabis use and endocannabinoid tone. AEA and 2-AG levels may be altered in chronic cannabis users. For example, cerebral spinal fluid AEA levels may be decreased in chronic cannabis use.[32,33] In addition, 2-AG serum levels are known to be elevated in heavy cannabis users.[33] No group to date has investigated the cardiovascular implications of these differences. Further studies are needed as these mechanisms may be responsible for the resistance to hypotension we observed in the THC(+) patients in our present study and
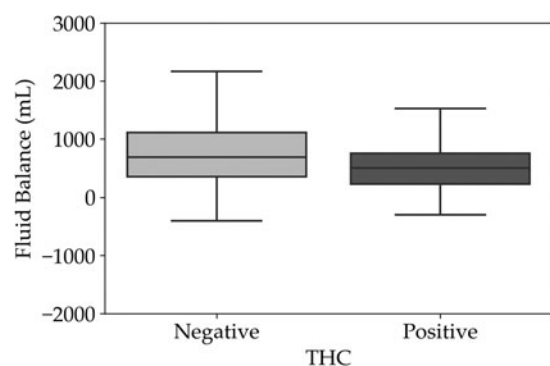
potentially also the source of increased risk of myocardial infarction previously observed in cannabis users undergoing elective surgery.[7]

Limitations

As our study examined a very specific subset of patients undergoing urgent but not emergent orthopedic trauma surgery, this limits generalizability to other patient populations. In addition, this study was carried out as a single-center, retrospective study and has the limitation of a small study population. Future studies should include a larger sample size and other variables such as prior medical history, home medications, and preoperative medications. We are also limited in conclusions as we compared patients with known cannabis exposure to those with insufficient cannabis exposure to result in a positive UDS. We cannot draw conclusions concerning the chronicity or dosing of cannabis in these patients as that data are inconsistently available in our health records. Future directions include comparing and contrasting anesthetic impact of acute intoxication in chronic cannabis users, acute intoxication in naive users, and nonintoxicated chronic cannabis users. In addition, the current study did not examine the effects of other drugs that returned a positive result in the UDS. Future studies are needed to investigate the effect of this.

Conclusions

In the past two decades, cannabis use has become increasingly prevalent and is concomitant with a steadily more positive public perception and more permissive state laws regarding the substance. This trend will likely continue, and anesthesiologists must be prepared to care for cannabis-exposed patients. Analysis of this data suggests that there is a weak but significant association between prior use of cannabis, objectively assessed by urinalysis, and a decreased need for blood pressure support during general anesthesia. As an exploratory study, it is premature to change clinical decision-making at the current state. Additional studies need to be conducted to further understand this topic. The physiological basis for this phenomenon is unclear, but may be due to alterations in endocannabinoid levels or downregulation of vascular CB1R after exposure to cannabis. Further studies are needed to determine if this effect is dose dependent and if acute intoxication causes similar or contrary effects.

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Abbreviations Used

2-AG = 2-arachidonylglycerol
AEA = anandamide
BMI = body mass index
CB1R = cannabinoid receptor 1
ED = emergency department
ER = emergency room
MAC = minimum alveolar concentration
OR = operating room
THC = tetrahydrocannabinol
UDS = urine drug screen