Cannabinoid Antagonism for Mitigation of Intraoperative Cardiovascular Instability

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Cannabinoid antagonism may **mitigate** intraoperative risk for **cardiovascular instability**

INTRODUCTION

- Cannabis (CB) is the most widely cultivated, trafficked, and abused drug used by 2.5% of world population, which is roughly 147 million people. (A stark comparison to 0.2% of the world population consuming opiates and 0.2% consuming cocaine.)[1]
- Use in the United States has increased in recent years following the legalization of use for medical and/or recreational use.[1,2]
- Tetrahydrocannabinol (THC) is the major psychoactive constituent in cannabis. It is an agonist at both CB-1 and CB-2 receptors; with greater affinity for CB-1 than CB-2.[3-9]
- CB-1 is expressed throughout the body, highly in the central nervous system whereas CB-2 is mainly expressed in the immune system.[5] Both share localization in cell types (eg, cardiomyocytes) platelets, endothelial cells).[5]
- CB-1 is conventionally recognized as a "central receptor" and CB-2 as a "peripheral receptor."[5]
- Synthetic cannabis (SC) use is also increasing due to cheaper cost and negative toxicological screening.[3-4]
- SC is a full CB-1 agonist with 10-200x greater potency and 2-4x higher affinity for CB-1 compared to THC.[3,8]
- The inevitable increase in use underlines the importance of exploring the cardiovascular implications associated with cannabis and anesthesia management. IRB/IACUC approval does not apply to this evidence-based project.
- **PICO:** (P) In patients intoxicated with cannabinoids undergoing non-elective surgery, (I) is cannabinoid antagonist therapy compared to (C) no cannabinoid antagonist therapy (O) efficacious in mitigating the risk for cardiovascular instability?

METHODS

- Systematic search of EMBASE and PubMed
- Search terms: *Cannabis, marijuana, heart infarction, perioperative period.*
- Limitations: Research within 10 years, English
- Search yielded 34 results. Highest level evidence meeting including criteria were 6 articles: 5 systematic reviews, and 1 cohort study

Author	Study, Design	Population, Setting	Key Findings
Goel et al, 2020	Retrospective cohort study	Elective surgery in the US hospitalized ≥1 day, 18-65 years *N*=26,706; chronic CB use vs none	Chronic cannabis users 1.88x more likely to have a postoperative MI
Skolnick P et al, 2019	Systematic review of descriptive studies	Evidence review on CB-1 antagonists to treat acute cannabinoid overdose	CB-1 antagonists block and reverse actions of THC and SC
Alexander et al, 2023	Systematic review	Current evidence on marijuana influence on anesthesia perioperative care	CB-1 promotes cardiovascular disease pathology CB-2 exerts anti-inflammatory effects
Patel et al, 2018	Systematic review	Case reports with acute MI following CB use *N*=62; patients with acute MI and marijuana use; mean age 27.7 (±10.3 years)	THC induces endothelial dysfunction; 14 cases acute MI within 5 hours of CB use; 30 cases with LAD/RCA occlusion
Pacher et al, 2018	Systematic review	Care reports and clinical studies	CB-1 mediates acute hemodynamic effects; contributes to cardiovascular disease pathology
Tang et al, 2021	Systematic review	Evidence involving CB receptors and myocardial injuries	CB-1 negative inotropy, aggravates cardiac ischemia, pro-hypertrophy and fibrogenesis; inhibition was cardioprotective CB-2 positive inotropy, activation was cardioprotective

RECOMMENDATIONS for PRACTICE / CONCLUSIONS

- Thorough preoperative evaluation with extra vigilance to various methods of cannabis use. Inquire about the type of cannabis product used, overall duration, and frequency of use to gauge the potential for acute intoxication, tolerance, and withdrawal.
- When patients present with altered sensorium, have high index of suspicion and consider cannabis intoxication in differential diagnosis.
- **With cannabis and synthetic cannabis use on the rise, the role of CB-1 receptors in cardiovascular disease pathology and emerging evidence of CB-1 antagonist benefits underlines the value of conducting more research on the possibility of parenteral CB-1 rescue agents.**

REVIEW of LITERATURE / CRITICAL APPRAISAL

- All articles examined the physiological effects and complications that followed the use of cannabis and cannabis-related products.[3-8]
- All suggested links between cannabis and cardiovascular instability. [3-8]
- Postoperative myocardial infarction (MI) incidence 1.88x higher ($P<0.001$) with cannabis use disorder (CUD) vs. no CUD ($P<0.001$)[8]
- Acute MI symptoms were noted within 5 hours of last marijuana use in 23% of CUD patients.[4]
- CB-1 receptor activation is implicated in cardiovascular pathologies, including negative inotropy, ischemia, pro-hypertrophy, and fibrogenesis[3,5,8-9]
- CB-1 antagonists have demonstrated the ability to both block and reverse the pharmacological effects of THC and SCs in vitro and in vivo in non-human primates.[5,8]
- A double-blind, placebo-controlled study demonstrated substantially reduced THC-induced changes (eg, tachycardia) in healthy human male subjects with oral CB-1 antagonist.[4]
- CB-1 antagonists have demonstrated the ability to improve survival rate and restrict infarct size in rodents.[5]
- Rimonabant, a CB-1 antagonist marketed for anti-obesity therapeutics, was administered orally and removed from the market due to adverse psychological effects.[5,8]
- Rimonabant-induced MI protection possibly resulted from peripheral metabolism modulation vs. direct heart effects.[5]
- CB-2 dubbed CB-1's "rival" since signaling causes positive inotropic effects, mitigates cardiac ischemic injuries, has anti-hypertrophic properties, and is generally cardioprotective.[5]
- CB-1 is a crucial mediator of doxorubin-induced cardiotoxicity while CB-2 had no effect.[5]

GAPS IN KNOWLEDGE

- Lack of formal studies for cannabis-related morbidity or mortality; more thorough publications with animal studies.
- Most data with humans are anecdotal case reports.
- Drug Enforcement Agency categorizes cannabis as a schedule I substance, creating a barrier to conducting clinical trials.
- No parenteral CB-1 antagonist is currently available.
- Research limited by patient self-reporting of use.
- SC use difficult to examine due to inability to detect
- Provider should take caution in extrapolating data due to interspecies differences before changing practice

REFERENCES: