Systematic Review Protocol

The cannabinoids – cannabis and its related compounds – and implications for anaesthesia

Genevieve Tait BCA (Hons I)¹
Rouzanna Aganesova BBiomedSc¹
Nicole Sheridan MBBS FANZCA²
Ann M Møller MD PhD²,³
Georgina Imberger MBBS PhD FANZCA⁴ *

1. Medical student. Department of Anaesthesia and Pain Medicine, Western Health, Footscray, Australia
2. Department of Anaesthesia and Pain Medicine, Western Health, Footscray, Australia.
3. Department of Anaesthesiology and Intensive Care, Herlev Hospital, Copenhagen, Denmark.
4. Cochrane Anaesthesia, Critical and Emergency Care, Herlev Hospital, Copenhagen, Denmark

* Corresponding author: georgina.imberger@wh.org.au
Introduction

Rationale

Cannabis is the most widely used recreational drug worldwide with a 2.5% annual prevalence.\(^1\) As nations such as the Netherlands and an increasing number of US states continue to decriminalize recreational cannabis consumption and permit the medical use of marijuana, cannabis use may increase further.\(^2\) The physiological effects of cannabis are diverse and the base of consumers is set to grow. It is foreseeable that the number of cannabis users undergoing surgery will rise and the impact of cannabis on perioperative risk may become increasingly significant.

The term ‘cannabis’ refers to preparations of the plant *Cannabis sativa* that contain psychoactive levels of Δ-9 tetrahydrocannabinol (THC).\(^3\) Cannabis comes in three main forms that vary in THC concentration – marijuana (dried leaves and flowers), hashish (compressed resin) and hash oil.\(^4\) Cannabis can be either inhaled through smoke or ingested orally.\(^5\) Smoking cannabis is the most common route of administration.\(^6\) Synthetic cannabinoids used medicinally and recreationally are compounds that are structurally similar to the THC of cannabis.\(^7\) In this review we will use the term ‘cannabinoid’ to refer to both cannabis and synthetic cannabinoids.

Cannabinoids have a long history in the evolution of medicine. The analgesic properties of cannabis were discussed by the Chinese physician Hoa-tho in 200AD and became a part of Western medical practice during the Nineteenth Century where is was used in the treatment of pain, chronic cough and muscle spasm.\(^6\) In more recent times, endocannabinoid agonists have been considered for use in a range of conditions including chronic pain, nausea and vomiting, epilepsy, the neuropathic pain of HIV, and for the symptoms of Multiple Sclerosis and Tourette’s syndrome.\(^8\)

Cannabinoids are pharmacologically active at the CB1 and CB2 receptors of the endocannabinoid system.\(^9\) This system modulates inhibitory and excitatory synapses that regulate many functions such as pain, emotion, motivation and cognition.\(^10\) Endocannabinoid receptors are spread throughout the body with CB1 receptors found primarily in the brain and spinal cord and CB2 receptors found in immune system tissues.\(^11\) Effects of cannabinoids include labile blood pressure and heart rate, immunosuppression, decreased conscious state, and other centrally mediated effects.\(^12\) Inhalation of cannabinoids can result in bronchodilation, bronchospasm, airway inflammation, and long-term obstructive airway disease.\(^13\) In the context of perioperative care, physiological and pathological consequences of cannabinoid use may affect important clinical outcomes.

Due to unpredictable reporting of use and a lack of research, the prevalence of exposure to cannabinoids in patients presenting for surgery is unclear. Given the high rate of recreational cannabis use, potential increase in use due to the changing legal landscape, and the pharmaceutical development of cannabinoid agonists, the prevalence is likely to be high enough to warrant attention. Potential implications of cannabinoid use for anaesthesia relate to the physiological effects of acute and chronic activation of endocannabinoid receptors, to the respiratory effects of smoking the drug, and to the interaction of cannabinoids with other anaesthetic drugs. Particular concerns include potential interactions with hypnotic agents,\(^14\) potential effects on perioperative cardiac functioning,\(^15\) and respiratory and airway complications associated with recreational inhalation of cannabis.\(^16\)

In this systematic review, we will review the pharmacology of cannabinoids, consider the potential implications for anaesthesia, and provide a summary of the current evidence relevant to perioperative care of a patient who has used cannabinoids as either a recreational or therapeutic agent.

Objectives

Part 1

To review the pharmacology of cannabinoids with regard to the potential implications for anaesthesia and perioperative risk.

Part 2

To conduct a systematic review investigating:

a) The effect of cannabinoid use on perioperative outcomes

b) Interventions intended to modify perioperative risk in patients exposed to cannabinoids.

Methods

Part 1

We will review the pharmacology of cannabinoids, with regard to the pharmaceutics, pharmacokinetics and pharmacodynamics, and we will consider the potential implications for anaesthesia and perioperative care.

Part 2

We will conduct the systematic review complying with the methodological standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions.\(^17\) We will report our review findings adhering to the standards for the Preferred Reporting Items for Systematic reviews and Meta-Analyses.\(^18\) We will prospectively register our protocol with the International Prospective Register of Systematic Reviews.\(^19\)
Part 2 - Eligibility criteria

We will include all randomized controlled trials, cohort studies, case-control studies, case series and case reports that fulfill the criteria defined in Table 1. We will include all ages. We will include studies irrespective of language and publication status. We will exclude animal studies.

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention/Exposure</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 2a: Perioperative risk in patients exposed to cannabinoids presenting for surgery</td>
<td>All patients presenting for surgery</td>
<td>Exposure to cannabinoids</td>
<td>No exposure to cannabinoids</td>
</tr>
<tr>
<td>Part 2b: Interventions to modify risk in patients exposed to cannabinoids presenting for surgery</td>
<td>All patients presenting for surgery with known exposure to cannabinoids</td>
<td>Any intervention intended to modify perioperative risk caused by cannabinoid exposure</td>
<td>Any comparator</td>
</tr>
</tbody>
</table>

Part 2 - Information sources

We will search for published literature in:
- MEDLINE
- EMBASE (via OVID)
- The Cochrane Central Register of Controlled Trials database (via OVID)
- CINAHL
- Scopus
- Web Of Science
- Science Direct
- Informa Health Care
- Public Library of Science

We will search for current or unpublished trials using ClinicalTrials.gov, ISRCTN Registry and CenterWatch.

We will review the reference lists of all included publications for further possible inclusion in the review.

Search

We will use the search strategy defined in Appendix 1.

Study selection

Two authors (GT and RA) will independently screen all of the abstracts produced by the search. We will retrieve full-text copies of the selected abstracts for full assessment of eligibility. We will document reasons for exclusion. Disagreement regarding inclusion of a publication will be resolved through discussion, and by a third author if required.

Data collection process

Two authors will extract data from each included study (GT and RA). We will extract the following data:
- Study characteristics: first author; year of publication; country of origin; funding source;
- study design and setting; number of participants; outcomes analysed
- Population characteristics: inclusion and exclusion criteria, patient demographics, history of cannabinoid use/abstinence.
- Intervention characteristics: type of cannabinoid used and route of administration; type of intervention undertaken to modify perioperative risk and outcomes of intervention
- Outcomes: all reported outcomes

Risk of bias in individual trials

Two authors (GT and RA) will assess the risk of bias as described in the Cochrane Handbook of Systematic Reviews, for both randomized studies and for non-randomized studies. For non-randomized studies, we will use ACROBAT-NRSI (Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions).
Synthesis of results

We will perform a narrative synthesis of the results, summarizing the finding in the trials that we include. We will not conduct a meta-analysis.

Competing interests

GT, RA, NS, AM and GI declare that they do not have any competing interests.

Authors’ contributions

Protocol

Conception and design of the review protocol - GT, RA, GI

Approval of the final version of protocol – GT, RA, NS, AM, GI

Plan for review

Search screening, data extraction, assessment of quality of included trials – GT, RA, NS, GI

Resolution of discrepancies – GI, NS

Interpretation of findings – GT, NS, GI

Preparation of manuscript – GT, GI

Development of manuscript – GT, NS, AM, GI

Acknowledgments

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Reference List


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14 Nguyen H. Cannabis (marijuana) and anesthesia. Anesthesiology Rounds 2004;3.


16 Aryana A, Williams M. Marijuana as a trigger of cardiovascular events: Speculation or scientific certainty? Int J Cardiol 2007;118:141-144.

17 Symons I. Cannabis smoking and anaesthesia [Correspondence]. Anaesthesia 2002;57: 1142-43.


Appendix 1

S81  S67 AND S80
S80  S76 NOT S79
S79  S77 NOT S78
S78  (MH "Humans")
S77  (MH "Animals")
S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75
S74  MW dt Groups
S73  Trial
S72  Randomly
S71  Placebo
S70  Randomized
S69  PT controlled clinical trial
S68  PT randomized controlled trial
S67  S38 AND S66
S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65
S65  (MH "Operating Rooms")
S64  operation room*
S63  surgical
S62  surgeon*
S61  surgery OR surgeries
(MH "Preoperative Care") OR (MH "Preoperative Period")
S59  pre-operative
(MH "Intraoperative Neurophysiological Monitoring") OR
(MH "Intraoperative Period") OR (MH "Intraoperative Complications") OR (MH "Monitoring, Intraoperative")
OR (MH "Intraoperative Care") OR (MH "Intraoperative Awareness")
S57  intra-operative
(MH "Postoperative Care") OR (MH "Postoperative Period") OR (MH "Postoperative Complications") OR
(MH "Pain, Postoperative") OR (MH "Postoperative Hemorrhage") OR (MH "Postoperative Nausea and Vomiting")
S56  post-operative
(MH "Perioperative Period") OR (MH "Perioperative Cares") OR (MH "Perioperative Nursing")
S53  peri-operative
S52  (MH "Isoflurane")
S51  (MH "Halothane")
S50  (MH "Propofol")
S49  desflurane*
S48  isoflurane*
S47  halothane*
S46  propofol*
S45  sevofluran*
S44  (MH "Anesthetics, Inhalation")
S43  (MH "Anesthesia, Inhalation")
S42  (MH "Anesthesia")
S41  (MH "Anesthetics, Intravenous")
S40  (MH "Anesthesia, General")
S39  anesthet*
S38  S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S37  delta-9-tetrahydrocannabinol
delta-9-THC
S36  levonantradol
cbd
S35  endocannabinoid*
S34  Sinsemilla
S33  skunk
S32  sativex
tetrahydrocannabinol-cannabinoid
dexanabinol
S28  HU211 or HU 211
cesamet
S26  marinol
S25  marinol
S24  (MH "Dronabinol")
S23  dronabinol
S22  bhang
S21  marijuana
S20  hashish
ganja
S18  hemp
S17  (MH "Cannabinoid Receptor Modulators")
S16  (MH "Cannabinoid")
S15  (MH "Endocannabinoids")
S14  (MH "Receptor, Cannabinoid, CB1")
S13  (MH "Receptor, Cannabinoid, CB2")
S12  (MH "Cannabinoid Receptor Agonists")
S11  (MH "Receptors, Cannabinoid")
S10  (MH "Marijuana Abuse")
S9  (MH "Marijuana Smoking")
S8  (MH "Medical Marijuana")
S7  (MH "Cannabidiol")
S6  (MH "Cannabinoids")
S5  thec
tetrahydrocannabinol*
cannabinoid*
S3  cannabidiol*
S2  Cannabis
marijuana
S1