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Research Article

Postoperative Healing Assessment Using Cannabinoids in Oral Surgery

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Abstract

Objective: To ascertain and compare postoperative healing appearance after third-molar extraction when using antibiotics versus cannabinoids.

Materials and Methods: Sixty randomly selected patients were included in the study and performed teeth removal followed the needed protocols. Post-operative healing assessment were divided into two groups: thirty patients were instructed to use antibiotics intraorally while another group used system of phytocannabinoid-cannabidiol substance intra- and extraorally. All research participants were followed daily for seven days. Objective intraoral estimation along with patients and doctor's overall satisfaction of the healing process were recorded.

Results: Observations of the pain, swelling, tolerance and overall assessment had no significant difference comparing two post-healing medications when only significant factor was time duration after surgery ($p < .0001$). Additionally, five patients who used phytocannabinoid-cannabidiol substance were followed until the tenth day when alveolitis presence fully disappeared.

Conclusions: Antibiotics and phytocannabinoids shows the same implication regard to swelling, pain intensity, patient's and doctor's tolerance, overall assessment and similar results to alveolitis appearance which should be more explored in the further research.

Practical Implications: The study revealed that cannabinoids have a positive potential to be used in dental clinic practice for oral diseases and wound healing prophylaxis.

Keywords: *Cannabinoids; Cannabidiol; Postoperative Healing; Pain Management*

Introduction

Third-molar tooth extraction for various reasons is a standard surgical procedure performed in daily dental practice, which can cause multiple complications [1]. To prevent undesirable consequences, antibiotic therapy is universally acceptable protocol against infections caused by clinically relevant bacteria [2]. Frequent use of antibiotics become a public health problem globally due to its multidrug resistance in methicillin-resistant *Staphylococcus aureus* strains and other pathogenic bacteria [3]. This issue has enormous clinical implications which induced researchers to find alternatives for antibiotics replacement. Cannabinoids for medical purposes might be one of the options which have to be more explored.

The plant Cannabis Sativa produces more than 421 chemical compounds, including about 80 terpeno-phenol compounds named phytocannabinoids which have not been detected in any other plant and exhibit a wide range of biological activity [4-7]. It can be administered topically, orally or sublingually; can be supplied in herbal form, extracted naturally from the plant, gained by isomerization of cannabidiol,

or manufactured synthetically [8]. Cannabinoids and cannabinoid receptors are potential targets for reducing pain and inflammation [9]. The most common cannabinoids are *Δ9-Tetrahydrocannabinol* (THC), *Cannabidiol* (CBD), *Cannabigerol* (CBG), *Cannabichromene* (CBC), and *Cannabinol* (CBN) [10,11]. CBD, structurally similar to THC, is a non-psychoactive cannabinoid, which has positive potential for the treatment of neuropathic pain, multiple sclerosis and inflammation [12]. Evidence shows that CBD acts as an immunomodulator [4] and exhibits a wide range of anti-inflammatory properties including the inhibition of IL-6 and the activation of anti-inflammatory pathways in microglial cells [13]. CBD has been shown to induce apoptosis of microglial cells through lipid raft involvement [14]. Cannabinoid receptors (CB1 and CB2) are located throughout the body in the central and peripheral nervous system [15]. Endocannabinoid system is active peripherally where receptor CB1 stimulation reduces pain, inflammation and hyperalgesia. Receptor type 2 has been localized primarily to cells of the immune system [16], mainly expressed on monocytes, T-cells, macrophages and B-cells. These observations lead to the hypothesis that cannabinoids can partially replace antibiotics regarding inflammation reduction and pain control.

Purpose of the Study

The purpose of this *in vivo* study is to ascertain and compare postoperative healing appearance after third-molar extraction when using antibiotics versus cannabinoids.

Materials and Methods

The study was conducted among randomly selected patients in Vilnius Implantology Center Clinic (Vilnius, Lithuania) who had indications for mandibular third molar extraction. Inclusion criteria were: (i) generally healthy patient, (ii) no medical contraindication for oral surgery, (iii) partially or fully impacted mandibular wisdom teeth, (iv) no signs of inflammation. Exclusion criteria: (i) poor oral hygiene, (ii) smoking, (iv) diabetes, (v) the use of bisphosphonates or any other medications which can affect healing, (vi) alcoholism.

In total, 60 patients were selected for the clinical study who met the previously mentioned criteria. All participants received similar protocol for third-molar extraction, which has been approved by the Bioethics commission of the Lithuanian University of Health Science, No. BEC-LSMU(R)-05. During surgery procedure, two incisions were made for mucoperiosteal flap elevation under inferior alveolar nerve block anesthesia (4% articaine solution with vasoconstrictor epinephrine (1:100 000) (Ubistesin forte, 3M ESPE)). Bone resection and odontotomy were performed to ensure enough exposure and safe extraction of the third-moral if needed. Alveolar socket following tooth extraction was cleaned, and a blood clot was formed. After tooth removal mucoperiosteal flap was sutured with 4-0 PGA resorbable suturing material (Assucril, Switzerland).

Subsequently, all 60 patients who received the same surgical protocol were divided into two groups regarding different postoperative medications: one group received antibiotics amoxicillin 500 mg three times daily for 7 days; another group-system of phytocannabinoids-cannabidiol in gel form (Phytocannabinoid oil Paste 4200, SatiMed, Lithuania, www.satimed.eu) for 7 days. Both medications have been used intraorally. Previous group of patients used phytocannabinoids-cannabidiol together with extraoral oil gel in the affected area (SATIVERA Deep Tissue Oleogel 600, SatiMed, Lithuania, www.satimed.eu). All participants were instructed to rinse 0,12% chlorhexidine/digluconate (Perio-aid; Dentaid, Spain) solution twice a day for a week as well as informed about personal care requirements.

All 60 patients were invited to the clinic daily for seven days to record patient's satisfaction and doctor's overview of the healing process after surgery. The data was collected by questionnaire of closed-ended questions with one possible answer or Likert's scale. The purpose of the questionnaire was to measure pain intensity (1- none; 4- severe); swelling (1- none; 4- severe); presence of alveolitis (yes; no); patient's tolerance (1- very well tolerated; 4- not tolerated at all); doctor's tolerance (1- very well tolerated; 4- not tolerated at all); patient's overall assessment (1- very satisfied; 4- not satisfied at all) and doctor's overall assessment (1- very satisfied, 4- not satisfied at all).

The descriptive statistics (mean ± SD/mode) and histogram for each follow-up day were presented for doctor's tolerance and overall assessment of the treatment satisfaction and pain, swelling and alveolitis assessments, respectively. The mean differences of pain, swelling and patient's overall assessment of the treatment satisfaction during 7 days follow-up period between treatment groups were assessed

with two-way repeated measures ANOVA. Additionally, two-way ANOVA was performed for alveolitis and patient's tolerance assessment for each follow-up day. A two-tailed p-value less than 0.05 considered to be significant. Statistical analysis was performed using SAS 9.2.

Results

All sixty randomly selected patients who were included in the study had not missed any daily check-ups for seven days. Statistical analysis was measured regarding collected data and assessed by dividing into fields: clinical evaluation (swelling intensity, alveolitis presence) and overall estimation (pain control, tolerance and overall assessment) approach.

Pain control

The collected data revealed that there is no correlation between pain presence and medication type, specifically, antibiotics or cannabinoids. As can be seen in figure 1, the statistically significant result was measured only in the term of time ($p < 0,001$) when the long period after surgery shows a lower presence of pain. Comparison of the different treatment groups with time and medication had no significant difference (p 0,9929) regarding the pain control.

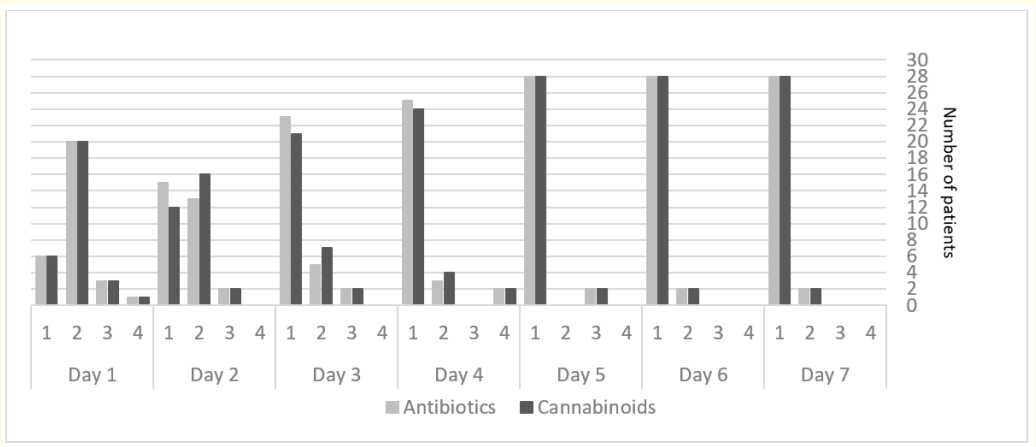

Figure 1: *Pain presence using different medications after surgery (1 - none; 4 - severe).*

Swelling intensity

As well as presence of pain, swelling intensity using different medications after surgery revealed similar results. Only time after surgery ($p < 0,0001$) has a positive correlation with swelling intensity (Figure 2).

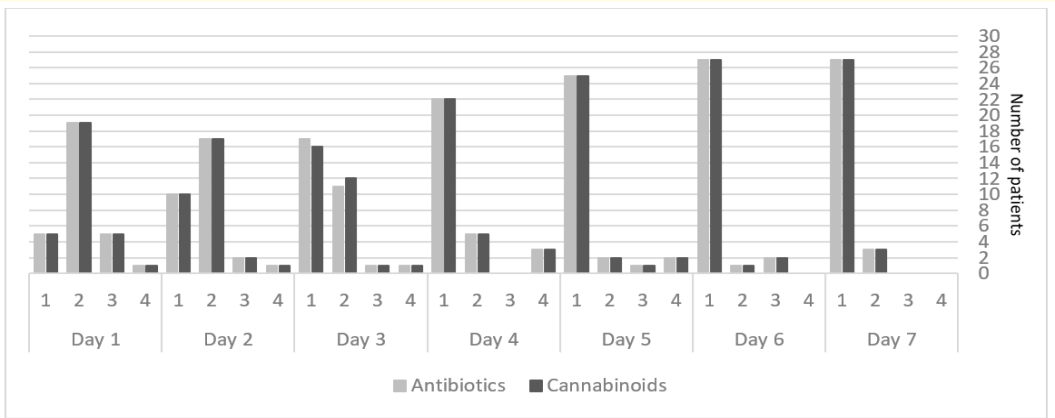

Figure 2: *Swelling intensity using different medications after surgery (1 - none; 4 - severe).*

Alveolitis presence

By measuring alveolitis in the first week after surgery positive recordings were measured in both antibiotic and cannabinoid groups (Figure 3). It was noticed that at the 6rd day patients who used antibiotics had not any presence of alveolitis while at the same day three patients from 30 who used cannabinoids still had the appearance of alveolitis. In the last day of recordings, the previous number got up to 5. These patients were followed until none of them present complications and had no complains. After ten days any patient had not alveolitis appearance. Significant results were observed by comparing alveolitis appearance and time duration after surgery (Table 1). Independent variables of general mode (p 0,0471) and medication type (p 0,0388) were estimated.

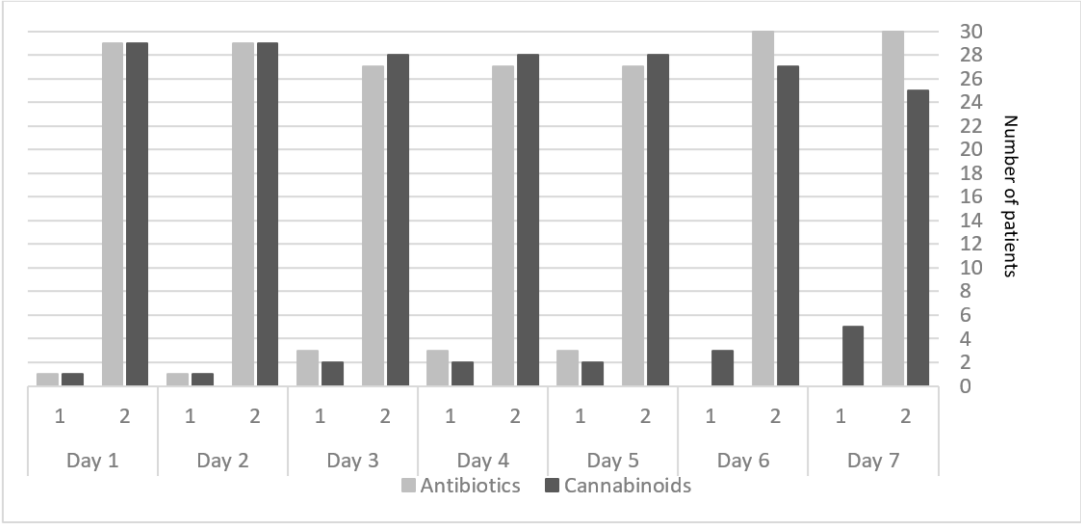

Figure 3: *Alveolitis appearance using different medications after surgery.*

	Dependent variables (p < 0,05) Alveolitis appearance						
Independent variables	**1 day**	**2 day**	**3 day**	**4 day**	**5 day**	**6 day**	**7 day**
General model	0.6477	0.6477	0.6589	0.6589	0.6589	0.3462	0.0471
Medication type	0.7573	0.7573	0.9969	0.9969	0.9969	0.1141	0.0388

Table 1: *Comparison of alveolitis appearance and days after surgery.*

Tolerance

Distribution of doctor's tolerance for each day after surgery in the scale from 1 to 4 was assessed. It was noticed that the doctor's tolerance does not exceed average 1.3 point (max standard deviation (SD) ± 0.66; mode 1) for both medications (Table 2). No significant difference was measured regarding medication and time after treatment according to the tolerance of the doctor.

Table 3 indicates the results of the patient's tolerance according to the day after surgery. A significant difference was measured on the 3rd day ($p < 0.0467$) of the general model.

Time	Antibiotics (±SD/Mode)	Cannabinoids (±SD/Mode)
1 day	1.3 ± 0.60/1	1.3 ± 0.61/1
2 day	1.3 ± 0.64/1	1.3 ± 0.65/1
3 day	1.3 ± 0.65/1	1.3 ± 0.66/1
4 day	1.3 ± 0.64/1	1.3 ± 0.65/1
5 day	1.3 ± 0.64/1	1.3 ± 0.65/1
6 day	1.3 ± 0.64/1	1.3 ± 0.65/1
7 day	1.3 ± 0.64/1	1.3 ± 0.65/1

Table 2: *Distribution of doctor's tolerance for each day after surgery in the scale from (1 - very well tolerated; 4 - not tolerated at all).*

	Dependent variables (p < 0,05) Patient's tolerance						
Independent variables	**1 day**	**2 day**	**3 day**	**4 day**	**5 day**	**6 day**	**7 day**
General model	0.5434	0.1884	0.0467	0.1659	0.7824	0.7824	0.4312
Medication type	0.5277	0.6845	0.8536	0.7308	0.6894	0.6894	0.6910

Table 3: *Comparison of patient's tolerance and days after surgery.*

Overall assessment

The purpose of the overall assessment criteria is to evaluate patient's and doctor's satisfaction with the treatment and post-healing period after surgery. As can be seen from table 4 doctor's overall assessment during the week does not exceed average 1.7 point in the scale of 4 points. From the 5 - 7-day patients who have taken cannabinoids were noted as the best satisfying healing result comparing with antibiotics-1.5 point (Mode 1; SD ± 0.57).

Time	Antibiotics (±SD/Mode)	Cannabinoids (±SD/Mode)
1 day	1.7 ± 0.70/2	1.6 ± 0.57/2
2 day	1.7 ± 0.70/2	1.6 ± 0.57/2
3 day	1.7 ± 0.70/2	1.6 ± 0.57/2
4 day	1.7 ± 0.61/2	1.6 ± 0.57/2
5 day	1.6 ± 0.61/2	1.5 ± 0.57/1
6 day	1.6 ± 0.56/2	1.5 ± 0.57/1
7 day	1.6 ± 0.56/2	1.5 ± 0.57/1

Table 4: *Distribution of doctor's overall assessment for each day after surgery in the scale from (1 - very satisfied; 4 - not satisfied at all).*

Taking a note into patient's satisfaction during post-healing period it was noticed that type of medication has no significant difference regarding overall assessment when only significant criteria is time (Table 5).

Patient's overall assessment average differences	P
Time	0.0238
Time and Medication	0.8675

Table 5: *Patients overall assessment differences between treatment groups.*

With a few exceptions, the results showed that medications, particularly, antibiotics or cannabinoids, does not have significant difference ($p > 0.05$) regarding successful healing. The study revealed that those criteria such as pain, swelling or patient's overall assessment are mainly related to time duration after surgery, and both medication expose similar implications.

Discussion

Planned comparison of antibiotics and cannabinoids revealed that both medications have a positive outcome after third-molar surgery, and therefore, our hypothesis can be confirmed. These results might be promising by reducing the use of antibiotics and replacing them by cannabinoids thus leading to lower growth of multidrug resistance caused by pathogenic bacteria.

To our knowledge, no similar *in vivo* research exists addressing the question of phytocannabinoids potential to replace the antibiotics after oral surgeries. For this reason, we can only compare the studies related with cannabinoids in general approach. Angel A Izoo., *et al.* arranged and submitted an overview of different types of cannabinoids with different pharmacological actions [17]. In the article is mentioned, that cannabinoids, particularly cannabidiol, has the affect as an anxiolytic, analgesic, anti-inflammatory, antiepileptic, neuroprotective, vasorelaxant, antispasmodic, anti-ischemic, bone-stimulant and etc. This data positively correlates with our results regarding analgesic, anti-inflammatory response. Observations discussed in the article might lead to the new potential therapeutic interest including not only CBD but other types of cannabinoids as well.

Although the research has reached its aims, there are several limitations. To have a better overview of the efficiency of cannabinoids and antibiotics, it is recommended to add a control group based on placebo approach. By adding previously mentioned group clinical evaluation, as well as overall estimation, could be accurately assessed.

Furthermore, for even higher statistically significant results there is obvious need to add the larger number of patients as a sample size in the study thus providing researchers for reducing the probability of an error and achieving promising significant differences.

In this clinical study, it was estimated the presence of alveolitis which was recorded in the both groups of patients. Because patients were selected with both partially and fully impacted third-molar teeth it may be assumed that different primary clinical situations lead to a broader range of surgery techniques with its different possible complications.

Given the positive primary results of antibiotics and cannabinoids implications after third-molar surgery, the future direction of CBD researches should be improved by adding a placebo group, expanding sample size as well as equalizing the initial clinical situations.

Conclusions

This research underlined the importance of medications replacement thus reducing the use of antibiotics after third-moral surgeries. It was found that antibiotics and phytocannabinoids (CBD and others) have the same or similar implication regarding swelling, pain intensity, alveolitis presence and patient's and doctor's tolerance as well as overall assessment. Despite some limitations, we believe this study might be a starting point for new clinical studies according to the use of cannabinoids in dental practice.

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