Three IOP readings were taken at each time point from each subject and the average of these readings was obtained for each time point. The IOP was normally distributed. For each group, a paired t-test was conducted to test for statistical difference at each time point compared with baseline.

In the treatment group, the IOP reduction was statistically significant at all time points after treatment, up to and including the 4-hour post treatment. There was also a significantly lowered IOP in the placebo group, but this was only seen at variable intervals: at the 80-minute, 3-hour, and 5-hour time points. There were no statistically significant differences in the IOP-lowering observed between the placebo and treatment groups.

<1>Discussion

The results of this study indicate that in healthy adult subjects, inhaled cannabis significantly lowers IOP, and that this effect is detected within 40 minutes of inhalation. This IOP lowering of about 15% slowly drifted back towards baseline, but the effects were still significant at 4 hours post treatment dosing (*Figure 1*). Interestingly, the placebo group also saw a reduction in IOP after dosing; however, the IOP effect was less dramatic, and more labile. There are several reasons for this.

First, there was a very small sample of participants in the placebo group, leading to less robust powering of the placebo arm. Second, the baseline IOP was lower in the treatment group (17.5 mmHg) compared to baseline IOP in the placebo group (18.4 mmHg). Starting at a lower IOP limits the potential for further IOP reduction and skews the data such that a significant difference is more difficult to establish. There may be also have been an additional effect of relaxation imparted to the placebo group, as the treatment was self-administered in a quiet room without interruptions. It has been shown that endocannabinoid system can elicit a strong placebo effect which can be activated by the smell of cannabis and visual cues associated with smoking cannabis, such as the cigarette itself, the smoke, or the lighter.[13] It can be assumed that when smoking what the subject understands might contain cannabis, that a certain degree of

expectation and relaxation is imparted, activating the endocannabinoid system, in turn, eliciting the placebo effect on IOP.

Additionally, a recent study by Dada et al. concluded that a 21-day practice of relaxation and mindful meditation can lower IOP by 25%.[14] Lastly, and perhaps most importantly, there is a known effect of placebo on IOP.[15] A recent article by Sharpe et al. reviewed the placebo-group IOP data from 23 clinical trials and found that in 22 of the trials, there was a significant effect of placebo on IOP, sometimes as much as 2 mmHg, similar to our findings, as summarized in *Figure 2*. Another meta-analysis of phase I/II glaucoma clinical trials investigating the placebo effect on IOP, found that IOP reduction from baseline was less pronounced in the treatment group than in the placebo group in all 50 studies reviewed. The authors concluded that in early-phase clinical trials, the reduction from baseline better approximates the results of later regulatory and post-commercialization trials than the decrease from placebo.[15]

The specific mechanisms by which cannabis lowers IOP are the subject of active investigation. It is known that there are cannabinoid receptors located throughout the eye, in particular in the ciliary muscle, ciliary epithelium, trabecular meshwork, and Schlemm's canal.[16] These receptors, part of the endocannabinoid system, include CB1, CB2, GPR18, GPR119, and GPR55. It has been shown, in mouse models, that CB1, GPR18, and GPR119 each lower IOP when activated by topical administration of Δ^9-THC.[5] This study also found that CBD blocks THC from lowering IOP, hence the active IOP-lowering component of cannabis is Δ^9-THC, and not CBD.

Studies have found that CB1 activation results in a series of varied changes, such as ciliary body contraction, widening of Schlemm's canal, and activation of matrix metalloproteinase, which enhances outflow of the trabecular meshwork.[17,18] Moreover, cannabinoids not only act through the CB1 pathway, but also activate COX-2, which increases the presence of prostaglandin E2 and metalloproteinases, enhancing the outflow of aqueous humor and thereby reducing IOP.[19,20] It has also been suggested that some cannabinoids lower IOP through a prostaglandin-mediated mechanism, as well as through adrenergic receptors within the eye.[21–23] There is a possibility that

cannabis may enhance ocular blood flow and perhaps perfusion to the optic nerve. This was suggested by a study investigating the effect of oral dronabinol in healthy volunteers, which showed decreased retinal arterio-venous passage time, as measured by fluorescein angiography.[24] Besides any manipulation on ocular blood flow, the potential role of cannabis in neuroprotection has been suggested by many studies, although no clear evidence of neuroprotection in glaucoma has yet been established.[25,26]

Aside from psychotropic effects, another potential limitation to the use of systemically administered cannabis is the purported effect on systemic blood pressure. The cardiovascular effects of cannabis are not well understood as they appear to be variable and heterogenous. Cannabis consumption has been shown to cause an increase in systolic blood pressure, while potentiating orthostatic hypotension and tachycardia.[27] The ultimate effect of cannabis on perfusion pressure to the optic nerve remains unknown at this time. Data from the treatment group in the current study showed no significant effect on systolic blood pressure at any time point, and only one statistically significant diastolic blood pressure reading at the 120-minute post-dose measurement, which is not clinically significant, nor statistically different from placebo (*Figures 3 and 4*). These data did not raise any new concerns with regards to short-term cardiovascular side effects in healthy individuals.

Given the wide range of systemic considerations, the routine use of inhaled or ingested cannabis for glaucoma treatment is not generally feasible. However, novel compounds with improved corneal penetration are being developed for topical administration, thereby mitigating systemic side-effects.[28,29] In addition, non-psychotropic cannabinoids and other CB1 receptor targets are being investigated for potential treatments that avoid systemic effects.[30,31]

There are several limitations to this study. First, the number of subjects in the placebo group was small and may have introduced error into the results from the natural variability in IOP during the diurnal period. Second, the method of obtaining the IOP data was through a non-contact tonometry method in order to facilitate the acquisition of IOP data in contact lens wearers, and

decrease the invasiveness of measurements for this pilot study. Ideally, future studies should use more consistently accurate methods of tonometry. In addition, this study only involved healthy adults, and does not characterize the IOP-lowering effects of cannabis in subjects with glaucoma, ocular hypertension, or in subjects with concomitant IOP-lowering medications.

In conclusion, the current study demonstrates robust IOP reduction with inhaled cannabis in healthy adults that is sustained for up to 4 hours, with no significant effect on cardiovascular parameters. Defining the role of cannabis in glaucoma treatment requires further studies to better characterize these effects in different patient populations.

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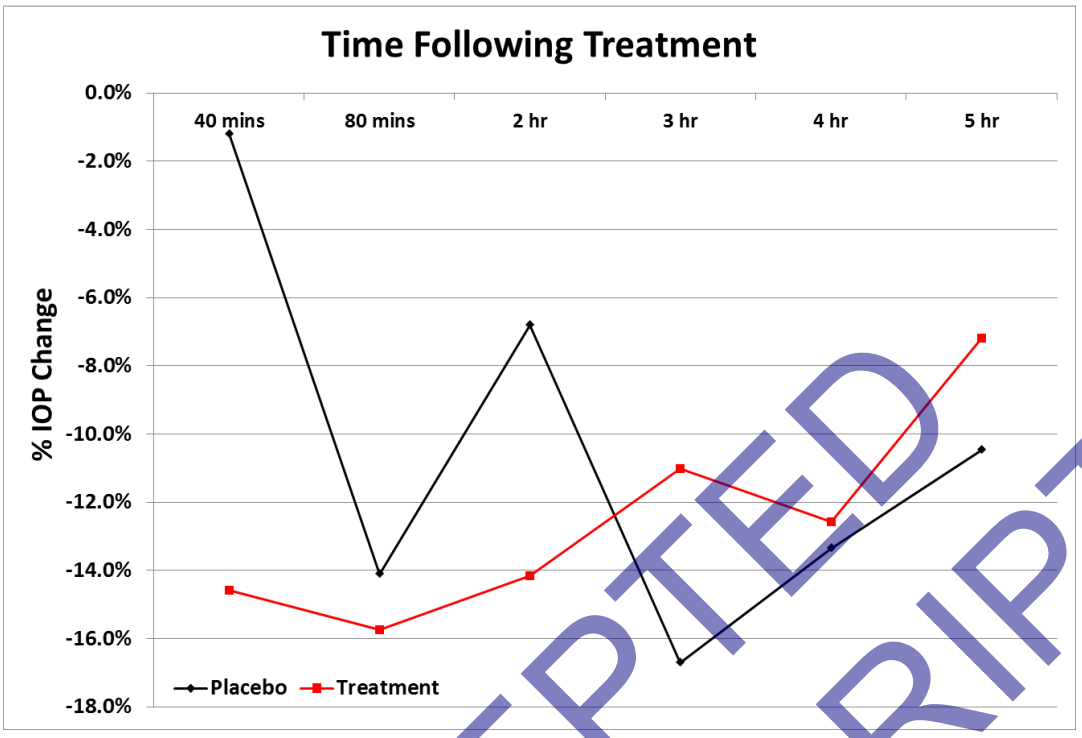
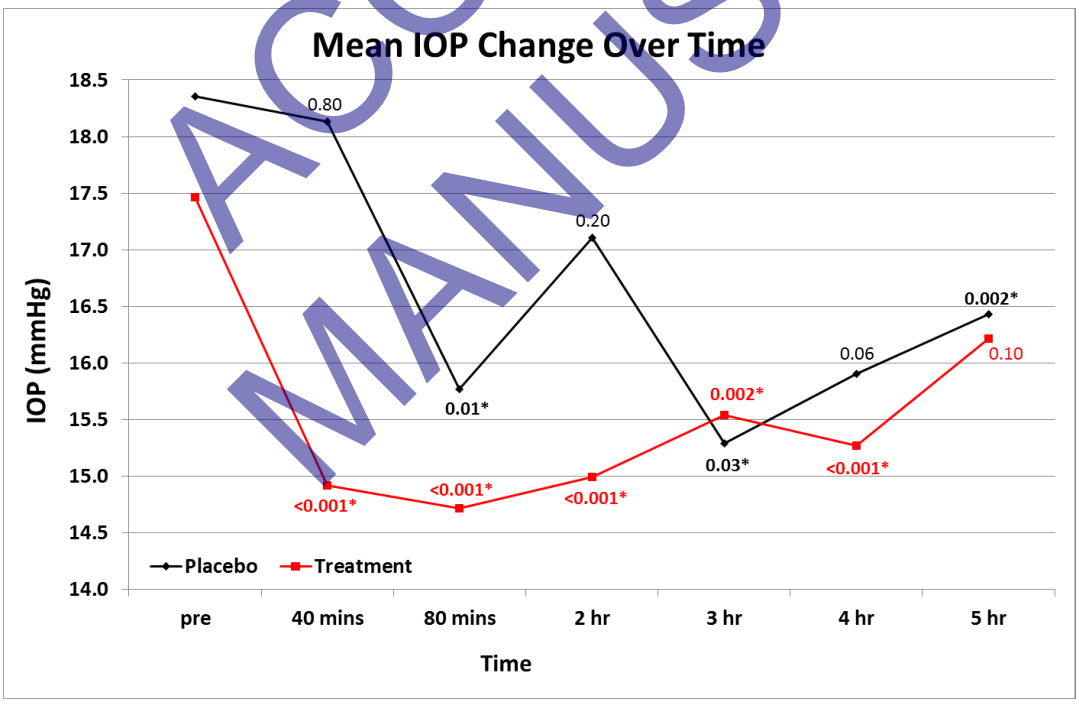
Figure 1: Percentage intraocular pressure reduction over time



IOP = intraocular pressure.

Figure 2: Mean intraocular pressure over time across different groups



IOP = intraocular pressure.

Figure 3: Mean systolic blood pressure over time

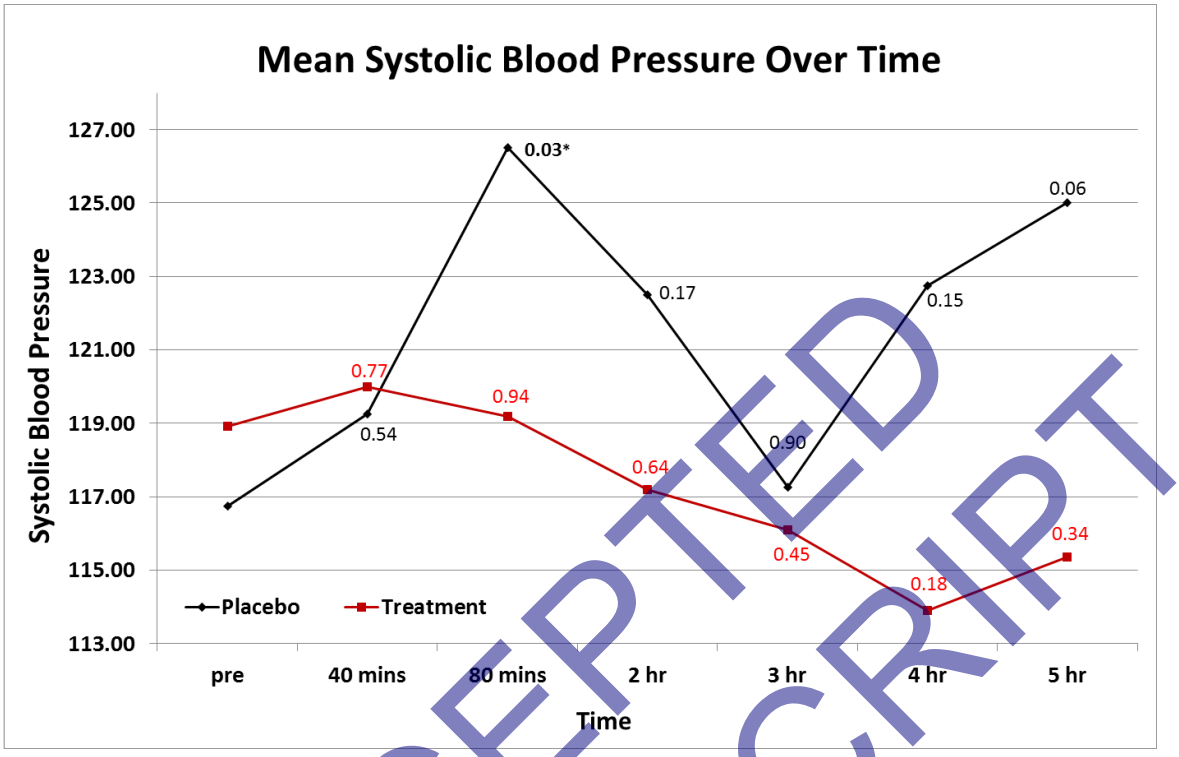


Figure 4: Mean diastolic blood pressure over time