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ORIGINAL ARTICLE

Oral paracetamol: Evaluation of its effects on intraocular pressure, anterior segment parameters, and axial length

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Abstract

Purpose: The purpose of the study is to evaluate the effect of oral paracetamol on the intraocular pressure (IOP) and the anterior segment parameters and axial length (AL) in participants without glaucoma.

Methods: The study involved and evaluated two groups of participants: Group 1, which received oral paracetamol (1 g/day) for 14 days, and Group 2, which received topical brinzolamide (1%, bid) for the same duration. The IOP was measured with a Goldmann applanation tonometer. The central corneal thickness (CCT) and anterior chamber angle (ACA) measurements were performed using a Scheimpflug camera–Placido disc device (Sirius, CSO, Italy). The anterior chamber depth (ACD) and AL measurements were performed using the IOL Master 500 (Carl Zeiss Meditec, Jena, Germany). Measurements were taken before the beginning of oral paracetamol and topical brinzolamide therapy, and 7 and 14 days after the beginning of therapy.

Results: A significant decrease in IOP was observed in both groups at the end of the 1st week (3.5±0.44 mmHg and 3.5±0.39 mmHg in groups 1 and 2, respectively), and no significant difference was found between the groups (p=0.798). The decrease in IOP persisted in the 2nd week, but the reduction was significantly greater in Group 2 (p<0.001). While Group 1 demonstrated a significant decrease in ACD at the end of the 1st week (p=0.005), no significant difference was found at the 2nd week (p=0.101). The AL, ACA, and CCT measurements did not show any significant changes from baseline in both groups (p>0.05, for all comparisons).

Conclusion: The findings of this study suggest that paracetamol treatment may have a lowering effect on IOP, although its efficacy may diminish over the weeks. However, further research enrolling glaucoma patients and employing a prolonged treatment period is necessary to delineate the potential role of paracetamol in glaucoma management.

Keywords: Anterior chamber depth; axial length; glaucoma; brinzolamide; intraocular pressure; paracetamol.

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Glaucoma is one of the leading causes of permanent visual loss worldwide.[1,2] Its prevalence is reported to be 3.54% for people over 40 years of age.[3] It is an optic neuropathy characterized by loss of ganglion cells and associated visual field loss. Increased intraocular pressure (IOP) is a major factor in the pathogenesis of glaucoma, and currently, the treatment is mostly focused on decreasing IOP to stop the progression of the disease.[4,5] Medical treatments using topical antiglaucomatous drugs are the most preferred choice in the initial treatment of glaucoma.[6] There are several drug molecule options available for glaucoma patients, while many patients need more than one drug to control IOP.[7] Although these medications provide a significant reduction in IOP, their range of side effects is broad.[7] Besides, a substantial portion of patients require surgery if the IOP cannot be controlled by medical treatment.

There is continuous research to find more efficient drugs with less adverse effects to treat glaucoma. Cannabinoids have also been suggested as a potential drug for glaucoma management.[8,9] Cannabinoids show their effect by interacting with cannabinoid receptors 1 and 2, which are located in the trabecular meshwork, Schlemm's canal, ciliary body, and retina.[10,11] These molecules were reported to exert both an IOP-lowering effect and a neuroprotective effect.[9] The exact mechanism of action of these molecules is still not fully understood.[12] However, systemic side effects, development of tolerance, and their short-lasting effect on IOP limit their usage in glaucoma.[9] Several studies have also indicated that paracetamol, a commonly used analgesic, exerts its analgesic action through the cannabinoid receptors by its conversion to N-arachidonoylphenolamine (AM404), which is an endogenous cannabinoid.[13,14] It is a well-known drug and has a known safety profile when taken in the appropriate doses. These findings led to studies that investigate the effect of paracetamol on IOP. The results were conflicting. While some of the studies reported favorable effects on IOP with both the oral and intravenous forms of the drug, other studies did not show this effect.[11,15,16] In this study, we investigated the effect of oral paracetamol on the IOP in patients without glaucoma. We chose not to include glaucoma patients because we could not predict how their routine treatments and ideal IOPs would be affected by paracetamol in this study group. We also investigated the anterior segment parameters to see the possible effects of oral paracetamol on the structures.

Materials and Methods

The study protocol received ethical approval from the Local Ethics Committee (2024/63) and was performed in accordance with the tenets of the Declaration of Helsinki. Following a detailed explanation of the study protocol, procedures, and planned measurements, written and verbal informed consent were obtained from all participants. This prospective study recruited participants from patients admitted to the department of physical medicine and rehabilitation and the department of ophthalmology who volunteered and met the inclusion criteria.

A prospective, comparative, controlled, and single-center study was conducted with two groups. Group 1 comprised individuals with upper extremity soft-tissue trauma or osteoarthritis who received oral paracetamol at a dosage of 1 g/day, administered in two divided doses (one at 9:00 a.m. and another at 9:00 p.m.) for a treatment period of 2 weeks. These participants were referred to the ophthalmology department for an ophthalmologic examination before the beginning of oral paracetamol therapy and 7 and 14 days after the beginning of therapy. Group 2 consisted of patients with unilateral acute or active central serous chorioretinopathy (CSCR) treated only with topical brinzolamide 1% bid for at least 2 weeks at the same time points as the paracetamol group. Similarly, participants in Group 2 were assessed before the initiation of topical brinzolamide and at the end of the 1st and 2nd weeks of treatment. Patients were studied between May 2024 and December 2024. A detailed eye examination was performed on all participants in three visits, including the measurement of best-corrected visual acuity, spherical equivalent, anterior segment examination using slit-lamp biomicroscopy, IOP measurement using Goldmann applanation tonometry, central corneal thickness (CCT), anterior chamber depth (ACD), anterior chamber angle (ACA), and axial length (AL) measurements. Visual field assessments, utilizing the Humphrey Field Analyzer 24:2 program, were conducted at the initiation and termination of the study. The CCT and ACA measurements were performed using a Scheimpflug camera–Placido disk device (Sirius, CSO, Italy). The ACD and AL measurements were performed using the IOL Master 500 (Carl Zeiss Meditec, Jena, Germany). Optical coherence tomography examinations of participants were performed using the Cirrus HD-OCT device (Carl Zeiss Meditec Inc., Dublin, CA, USA). Gonioscopy and dilated fundoscopic evaluations were restricted to the baseline visit, after the completion of other evaluation procedures.

The IOP measurements were taken at the same time of the day (10:00 a.m.) by two experienced observers. The observers were masked to all participants' treatment regimens and to the treated eye in Group 2. The IOP was assessed in both eyes of participants by performing duplicate measurements at each visit. If the initial two measurements differ by 2 mmHg or less, the mean value was adopted as the IOP. However, in cases where the initial measurements exhibited a discrepancy exceeding 2 mmHg, a third measurement was obtained. Subsequently, the median value of all three measurements was recorded as the final IOP per observer. Finally, the data from the two observers were averaged, and the results obtained were evaluated. In Group 1, the study eye was randomly selected (using Excel [Office 365, Microsoft, Redmond, WA, USA]) during the initial examination, and measurements from this eye were included in the study at subsequent visits. The eye diagnosed with CSCR was included in Group 2 for this study. In addition, peripheral venous blood samples were collected from the participants in Group 1 during the 1st and 2nd weeks to assess potential liver toxicity. All participants were contacted daily by an independent researcher to remind them to take their medication. Compliance was evaluated by this researcher, who quantified the number of unused capsules returned in supplement containers by paracetamol users. To be included in the data analysis, participants were required to have consumed at least 75% of the capsules provided, as determined by this count.

The exclusion criteria were a history of normal-tension glaucoma, ocular hypertension, eye surgery or trauma, refractive error of >±6 spherical or ±3 cylindrical diopters, abnormal corneal topography (e.g., keratoconus), ocular surface disease, IOP above 21 mmHg, or the presence of optic disk pathology, dry eye, cataract, retinal laser treatment, narrow ACAs, or secondary mechanisms of IOP elevation, including pigment dispersion or exfoliation. The ALs of the participants fell within the range of 22–24 mm. In addition, participants who were using systemic medications other than paracetamol and had a history of hepatic disease were also excluded from the study.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0, for Windows (IBM Corporation, Armonk, NY). Descriptive statistics were presented as numbers, mean, standard deviation, minimum, and maximum was used for numerical variables. Quantitative data were expressed as the means±standard deviations, and qualitative data were expressed as proportions (%). Normality assumptions were examined according to the Shapiro–Wilk test results. Repeated analysis of variance was used to test significant differences between the measured variables over time. Sphericity was assumed (Mauchly's sphericity test), and post hoc tests were used to determine significant differences in pairs of values. Pearson correlation was applied to test the correlation between the IOP measurements and the anterior segment parameters and AXL. Inter-observer agreement for IOP measurements was evaluated using the intraclass correlation coefficient (ICC) within a two-way random effects model, with a 95% confidence interval. Statistical significance was set at $p<0.05$.

Results

Of the 32 participants in the paracetamol group, six were excluded due to non-compliance with medication or control visits. Similarly, two out of 23 participants in Group 2 were excluded for non-adherence to the medication regimen. Twenty-six participants with a mean age of 51.7±9.1 were included in Group 1. Group 2 consisted of 21 participants with a mean age of 49.1±10.2. There was no significant difference between the groups in terms of age distribution ($p=0.089$). A statistically significant difference in gender distribution was observed between the two groups, with a higher proportion of males in Group 2 (71.4%) than in Group 1 (65.3%) ($p=0.048$). Baseline demographic and ocular characteristics are summarized in Table 1.

The mean values and standard deviations of IOP, CCT, AL, ACA, and ACD measurements are presented in Table 2. Baseline CCT, AL, ACA, and ACD measurements did not exhibit any significant differences between the groups ($p>0.05$ for all comparisons). Pre-treatment IOP measurements indicated

Table 1. Demographic and baseline ocular characteristics of the participants

	Group 1 (n=26) Mean±SD	Group 2 (n=21) Mean±SD	p
Gender (M/F)	18/8	15/6	**0.048**
Age (years)	51.7±9.1	49.1±10.2	0.089
Average RNFL thickness (µm)	101.3±8.72	102.4±9.46	0.221
Vertical cup to disk ratio	0.33±0.15	0.36±0.11	0.199
Spherical equivalent (diopter)	–0.53±0.98	1.01±0.77	**<0.001**
BCVA (logMAR)	0.02±0.39	0.18±0.42	**0.038**

Bold values are statically significant; SD: Standard deviation; RNFL: Retinal nerve fiber layer; BCVA: Best-corrected visual acuity.v

Table 2. Intraocular pressure, anterior segment parameter, and axial length changes by oral paracetamol and topical brinzolamide therapy

	Group 1 n=26 Mean±SD				Group 2 n=21 Mean±SD			
	Baseline	**Week 1**	**Week 2**	**p**	**Baseline**	**Week 1**	**Week 2**	**p**
Intraocular pressure (mmHg)	17.6±2.1	14.1±2.4	16.2±1.9	**<0.001[a]** **0.036[b]** **0.002[c]**	16.9±2.4	13.4±2.2	13.3±2.4	**<0.001[a]** **<0.001[b]** 0.207[c]
Axial length (mm)	23.29±0.77	23.25±0.71	23.26±0.69	**0.062[a]** **0.071[b]** 0.288[c]	23.44±0.71	23.46±0.68	23.45±0.66	0.124[a] 0342[b] 0.517[c]
Anterior chamber depth (mm)	3.21±0.25	3.15±0.21	3.20±0.24	**0.005[a]** 0.101[b] **0.032[c]**	3.19±0.22	3.18±0.20	3.19±0.21	0.091[a] 0.118[b] 0.193[c]
Anterior chamber angle (o)	23.6±3.59	23.69±3.31	23.63±3.44	0.198[a] 0.241[b] 0.321[c]	23.55±3.51	23.51±3.44	23.54±3.48	0.111[a] 0.229[b] 0.179[c]
Central corneal thickness (µm)	542.6±39.9	541.1±44.2	543.4±43.3	0.376[a] 0.843[b] 0.422[c]	547.1±41.4	545.8±44.1	546.4±42.8	0.074[a] 0.201[b] 0.144[c]

SD: Standard deviation, *: The repeated analysis of variance test, Post hoc tests: a: Baseline versus week 1, b: Baseline versus week 2, c: week 1 versus week 2, Bold font indicates statistical significance

a mean of 17.6±2.1 mmHg in Group 1 and 16.9±2.4 mmHg in Group 2. There was no statistically significant difference between the groups in terms of baseline IOP measurements (p=0.102). In Group 1, the IOP values were significantly lower after 7-day (14.1±2.4 mmHg) and 14-day (16.1±1.9 mmHg) oral paracetamol therapies compared to baseline IOP measurements (p<0.001 and p=0.036, respectively) (Fig. 1). A decrease in AL measurements was observed at both the 1-week and 2-week post-paracetamol treatment periods compared to baseline. However, these reductions were not statistically significant (p=0.066 and p=0.113, respectively). In Group 1, ACD measurements showed a statistically significant decrease in the 1st week compared to baseline measurements (p=0.005), while there was no significant difference in the measurements obtained in the 2nd week (p=0.101). The CCT and ACA measurements did not reveal any statistically significant differences among the baseline, day 7, and day 14 measurements (p>0.05 for all comparisons) in Group 1.

In Group 2, IOP measurements after brinzolamide treatment were 13.4±2.2 and 13.3±2.4 in the 1st and 2nd weeks, respectively. Both measurements were significantly lower compared to the pre-treatment period (p<0.001 for both comparisons). Group 2 participants demonstrated a significantly greater reduction in IOP at the 2-week follow-up compared to participants in Group 1 (21% vs. 8%) (p<0.001). The AL, ACD, CCT, and ACA measurements did not show significant changes at any visit (P > 0.05, for all comparisons). In addition, the intra-class correlation value for inter-observer agreement (95% CI) was calculated as 0.91 (0.90–0.92) (p<0.001) for IOP measurements.

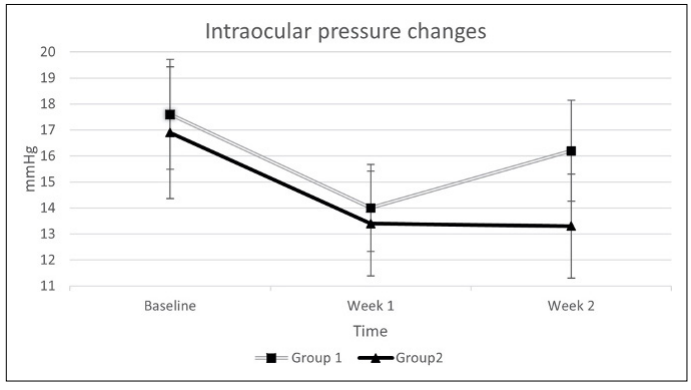

Fig. 1. Changes in intraocular pressure with oral paracetamol and topical brinzolamide administration.

Serum markers of liver injury, including alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TB), and alkaline phosphatase (ALP), remained within the normal reference range during the treatment. Hepatotoxicity was defined according to established criteria, with a threshold of serum ALT or AST exceeding

1000 IU/L, and the DILI Network criteria were employed to identify potential cases of drug-induced liver injury.[17]

The decreases in IOP in the 7th and 14th days with the paracetamol treatment had a significant positive correlation with the changes in AL and ACD measurements (r=0.502, p=0.001, and r=0.587, p<0.001, respectively). In addition, in Group 1, AL and ACD measurements in the three visits were positively correlated with each other (r=0.449, p=0.002). There was no significant correlation among the CCT, ACA, and IOP measurements (P > 0.05 for all comparisons).

Discussion

In this study, a 2-week oral paracetamol treatment significantly reduced the IOP in a group of participants without glaucoma or ocular hypertension. Furthermore, the ACD of the paracetamol users was significantly lower after 7 days of treatment, whereas this measurement obtained in the 2nd week was not significantly different compared to baseline values. A significant reduction in IOP was also observed in the brinzolamide group in the 1st and 2nd weeks; however, no significant changes were found in ACD and AL measurements. There were no significant changes in the CCT or ACA values among the baseline, 7th, and 14th day measurements in both groups.

Paracetamol, a widely used and well-characterized analgesic, exhibits a favorable safety profile when administered at recommended doses.[13] Notably, it demonstrates even distribution across various body fluids, readily crosses the blood–brain barrier, and possesses well-defined drug interactions and toxicity profiles.[13] Within the field of ophthalmology, there exists a continuous pursuit for novel therapeutic strategies and mechanisms of action to combat glaucoma. In this context, recent advancements in understanding paracetamol's mechanism of action provide a robust scientific foundation for both clinicians and researchers to evaluate its potential as a procannabinomimetic agent for regulating IOP.

Apart from its well-known role in inhibiting the cyclooxygenase pathway, the therapeutic effects of paracetamol are also mediated through cannabinoid receptors.[11,14] The cannabinoid agonists demonstrated ocular hypotensive and neuroprotective effects on retinal ganglion cells in experimental studies.[12] These findings suggest a possible role for paracetamol in glaucoma treatment. There are a limited number of studies investigating the effect of paracetamol on IOP, and the results of these studies are conflicting. Mohamed et al. [11] investigated the effect of oral paracetamol in a 2-week prospective, randomized, controlled study in which they compared the effect of paracetamol with levobunolol. Their study included patients with open-angle glaucoma, and their participants used paracetamol 1000 mg qid for 2 weeks. In this study, paracetamol showed a comparable effect to levobunolol and significantly decreased IOP on days 7 and 14. In another study by Heever et al. [15] the short-term effect of intravenous paracetamol on IOP was investigated. Their study participants were not glaucoma patients, and they compared the effects of intravenous paracetamol with those of oral acetazolamide and topical timolol. Although the effect was lower than that of timolol and acetazolamide, paracetamol significantly decreased IOP compared to the control group within the first 6 h after the administration. A commentary on the results of this study stated that the IV paracetamol formulations contain mannitol, and this may at least partially contribute to the IOP-lowering effect of IV paracetamol.[18] Another study by Jampel et al. [16] investigated the effect of oral paracetamol on patients with increased IOP. In their study, the IOP did not change significantly after 1 week of 650 mg qid paracetamol use. The use of different doses, different intervals, and other differences in study protocols makes direct comparison difficult. In our study, we showed a reduction in IOP with oral paracetamol use, like the findings of the study by Mohamed et al.[11] Unlike their study, we used a lower dose (500 mg bid) of paracetamol, and our study group did not include glaucoma patients or participants with increased IOP values. Our findings diverge from those reported by Jampel et al.,[16] who did not observe a significant decrease in IOP following oral paracetamol administration.

In Group 1, we observed a statistically significant reduction in IOP compared to baseline measurements in both the 1st and 2nd weeks. Specifically, the IOP reduction in the 1st week was 20%, while this value decreased to around 8% by the 2nd week. Compared to pre-treatment measurements, IOP values were significantly lower in the 2nd week, but the decrease was not as pronounced as in the 1st week. The brinzolamide group exhibited a consistent and significant IOP reduction of 20.7% and 21.3% in weeks 1 and 2, respectively, demonstrating a more stable treatment response compared to the paracetamol group. The observed pattern of IOP reduction in the paracetamol group could potentially be attributed to desensitization of cannabinoid receptors to the cannabinomimetic metabolic products of paracetamol.[11] In the study by Mohamed and Meyer, a similar pattern of IOP reduction was observed, with a greater decrease in the 1st week compared to the 2nd week (29% and 20%, respectively).[11] Notably,

the magnitude of IOP reduction in their study was also higher than in our findings. However, it is important to consider that their study involved glaucoma patients, who inherently have higher baseline IOP values. This situation may suggest that paracetamol's IOP-lowering effect might be particularly pronounced in eyes with elevated pressure, especially during the initial treatment phase.

The effect of paracetamol on the anterior segment parameters and AL was not investigated in other studies. In addition to IOP measurements, we also found that the ACD values of the participants were significantly lower after 1 week of paracetamol treatment. However, this change was not significant in the 2nd week compared to baseline measurements. There are studies reporting that IOP variations affect the AL, with increased IOP associated with increased AL. [19,20] Since we had lower IOP after paracetamol use in our study, this may explain the decreased AL measurement obtained in our study. It has been found that the diurnal rhythm changes observed in AL may be caused by changes in IOP, and these changes in IOP may cause changes in AL by causing expansion and contraction of the globe.[19] Saeedi et al. [21] found a significant decrease in AL in parallel with the decrease in IOP after trabeculectomy. Hata et al. [22] reported an increase in AL correlated with increased IOP in primary angle closure. In a study by Yin et al., [23] they found that corneal thickness and ACD were positively correlated with AL, but they did not find a relationship between IOP and AL. Hosny et al. [24] also reported that ACD and AL were positively correlated. Mauger et al. [25] have monitored changes in IOP, AL, and ACD after mannitol and found no change in AL and ACD. They explained the lack of expected reduction in ACD by a centrally mediated mechanism of IOP reduction and the inability to detect small changes in the measurement techniques they used. In a population-based study, it is reported that the ACD values were not associated with changes in IOP.[20] We had lower ACD measurements after the 1-week paracetamol treatment. The downward trend in IOP observed during the 1st week of paracetamol treatment was not sustained by the 2nd week. This observation, coupled with the potential adaptation of the globe to relatively lower pressure, may result in ACD and AL values after 2 weeks of treatment that were not statistically different from baseline measurements. Leydolt et al. [26] investigated the effect of IOP changes on ACD and reported that while an increase in IOP did not result in significant changes in ACD, a decrease in IOP significantly increased ACD. However, in their study, IOP was first increased to 10 mm Hg through mechanical pressure, and then ACD measurements were taken after the pressure was released. In our study, we observed a deepening of ACD with relatively smaller decreases in IOP, suggesting that even minor IOP changes in a healthy eye, not subjected to abnormally high pressure, could alter lens position or affect scleral compliance. Further studies on the effect of paracetamol on anterior chamber parameters and AL are necessary.

Subretinal fluid accumulation is a hallmark feature of CSCR. [27] While there is no consensus on the optimal treatment for CSCR, therapies such as photodynamic therapy, micropulse laser, anti-vascular endothelial growth factor (VEGF) intravitreal injections, as well as medical treatments including rifampin, mifepristone, and carbonic anhydrase inhibitors, are commonly employed.[27] Therefore, to assess the impact of paracetamol on IOP, we included ocular normotensive individuals, like Group 1 participants, in our study and aimed to compare the effects of paracetamol and brinzolamide on ocular parameters. Despite the significant reduction in IOP at both the 1-week and 2-week follow-up visits in Group 2 participants, no significant differences were observed in anterior segment parameters or AL. Tsai et al.[28] reported no significant changes in ACD and AL following 14 days of dorzolamide treatment in patients with open-angle glaucoma and ocular hypertension.[28] In addition, case reports in the literature have suggested that reduced ACD measurements may be associated with the use or discontinuation of sulfonamide-based medications.[29–31]

Both ACA and CCT values appeared to be unaffected by paracetamol and brinzolamide treatment. In Group 1, while the initial decrease in ACD, particularly during the 1st week, could potentially indicate an ACA change, the overall reduction in AL might have counteracted this effect, resulting in no significant change in ACA. In addition, while the impact of IOP fluctuations on CCT is well established,[23] the lack of meaningful CCT alterations in this study could be attributed to the participants maintaining normal IOP ranges throughout the pre-treatment, treatment, and post-treatment phases.

There are several limitations of this study. First, the sample size was small, and as a result, the difference in gender distribution was statistically significant. In the literature, the relationship between IOP effects on AXL and ACD with gender has not been examined. However, studies indicate that women tend to have a narrower ACD and a more anteriorly positioned crystalline lens.[32] In our study, patients with CSCR also exhibited a male-dominant distribution, consistent with the literature.[27] Second, we included participants without glaucoma or ocular hypertension. Hence, the effect we saw on healthy participants does not indicate that we can achieve similar results in glaucoma patients. The brief follow-up period of

14 days may be inadequate to evaluate gradual structural changes in AL or ACD. In addition, the presence of participants with an AXL between 22 and 24 mm reduces the generalizability of the results. Finally, we used only one dose of paracetamol (500 mg bid) in the study. As a result, studies are necessary to investigate the effect of different doses of paracetamol on glaucoma patients.

In conclusion, the findings of this study suggest that a decrease in IOP can be achieved using paracetamol 500 mg bid, whereas this effect may be transient because of the desensitization of cannabinoid receptors. In parallel with the reduction in IOP, decreases in ACD were observed during the 1st week. However, this correlation was not evident in the 2nd week of paracetamol treatment. Our findings suggest that paracetamol may induce an initial IOP reduction comparable to established antiglaucomatous medications, but this effect appears transient. Although the use of paracetamol as an antiglaucomatous agent may seem counterintuitive, its additional analgesic properties make it a promising candidate for short-term use in patients requiring acute IOP reduction. Moreover, in patients undergoing close IOP monitoring, considering medication changes, or planning for glaucoma surgery, the recent use of paracetamol should be carefully evaluated before making critical decisions. Future studies including glaucoma patients are necessary to determine the potential role of paracetamol in IOP reduction.

Ethics Committee Approval: This study was approved by The Niğde Ömer Halidemir University Ethics Committee (13.06.2024 date; number 2024/69).

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