Placebo effect and its determinants in ocular hypotensive therapy: meta-analysis and multiple meta-regression analysis

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TOPIC: The placebo effect, and its potential determinants, in ocular hypotensive therapy.

CLINICAL RELEVANCE: The placebo effect has been studied and documented within a wide clinical context. It remains unclear whether placebo is effective in glaucoma treatment or, if so, which factors are determinative of effect size.

METHODS: Randomized controlled trials (RCTs) of topical ocular hypotensive therapy for patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) , conducted until June 2, 2022, were included. First, a perceived placebo effect was measured as the overall intraocular pressure (IOP; mmHg) change from the baseline. It was evaluated in terms of the effect size (ES; mean difference between the baseline and the endpoint) and then was compared with the ES as obtained from the untreated control in order to obtain true placebo effect. The primary outcome was ES based on four weeks of treatment. Meta-analysis-based statistical pooling was performed where appropriate, and 95% CIs were used for comparison. Potential placebo effect determinants were scrutinized using a multiple meta-regression model (PROSPERO: CRD42022348098) .

RESULTS: A total of 40 RCTs (7,829 eyes) with 33 placebo groups (2,055 eyes) along with 7 untreated groups (1,184 eyes) were included. Placebo was determined to be effective in lowering IOP (ES -1.30 mmHg, 95% CI, -1.75 to -0.84) . This effect was superior to the effect calculated for the untreated controls by -2.27 mmHg (95% CI, -3.52 to -1.01) . According to the multiple meta-regression model, the active treatment ES was a significant factor to prediction the amount of placebo effect. Placebo additionally lowered IOP by -0.45 mmHg per -1 mmHg of active treatment effect. Add-on study design and larger sample size were also associated with greater amount of placebo effect. No publication bias was evident in either a funnel plot or the Begg and Mazumbar adjusted rank correlation test result (P=0.24) .

CONCLUSION: This meta-analysis indicates that placebo is effective in lowering IOP and is superior to the effect observed for the untreated controls. However, caution is required in interpreting the results, due to the small number of untreated-controlled trials and potential bias from the lack of direct comparison between the placebo and untreated arms.

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