Anti-Glaucoma Medication Use Prior to Anti-VEGF Injections in Lowering Intraocular Pressure: A Systematic Review

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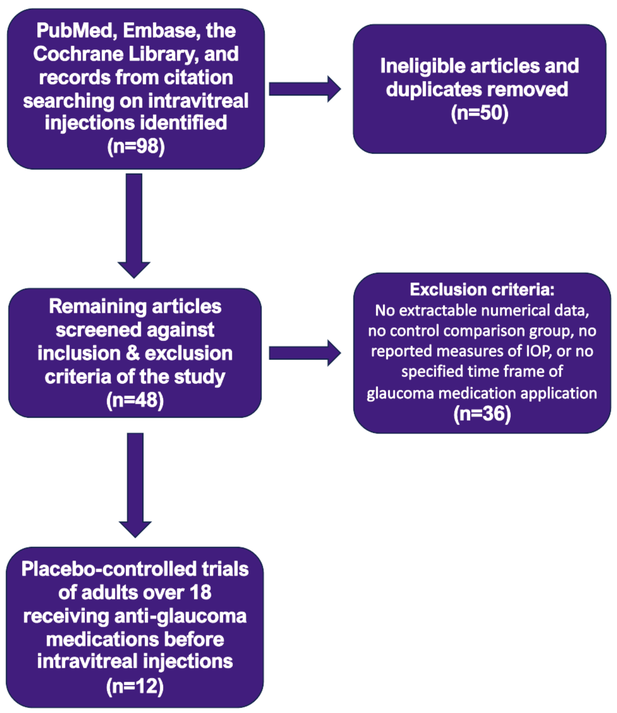
Introduction

- Intravitreal injections (IVI) of anti-VEGF (vascular endothelial growth factor) agents are essential for treating retinal diseases, such as age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion.
- However, IVI of these medications carry risks of acute and chronic intraocular pressure (IOP) elevations.
- Each injection adds 0.05 mL to the eye's 4 mL vitreous volume, a closed system, where volume added increases pressure that pushes against both the optic nerve as well as all blood vessels within it.
- Resulting IOP elevations can lead to can lead to complications such as retinal artery occlusion and loss of the retinal nerve fiber layer, especially in glaucoma patients[1].
- Although various studies have explored the use of prophylactic anti-glaucoma medications to mitigate post-injection IOP spikes[2,3], inconsistencies in research design have created uncertainty regarding best practices.

Methods

Figure 1. Systematic Review using Covidence™



Objective

Through compiling data of the current literature exploring prophylactic treatment with anti-glaucoma agents prior to IVI of anti-VEGF agents, we plan to evaluate status of respective data through conceptual and statistical analysis to make a qualitative assessment on the effectiveness of prophylactic treatment prior to IVI of anti-VEGF inhibitors.

Results

Table 1. IOP at baseline in prophylactic anti-glaucoma groups compared to controls prior to IVI

Study or Subgroup	Anti-Glaucoma Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
Dettoraki 2021	15.1	3.4	31	16.6	2.8	25	4.9%	-1.50 [-3.12 , 0.12]
ElChehab 2013	13.675	5.328625	200	16.7	7.5	50	2.7%	-3.02 [-5.23 , -0.82]
Felfeli 2019	13.8	3.3	58	13.5	3.3	58	9.0%	0.30 [-0.90 , 1.50]
Murray 2014	15.8	4.8	12	15.1	5.5	12	0.8%	0.70 [-3.43 , 4.83]
Pece 2016	15.4	1.750411	100	15.1	1.6	50	41.4%	0.30 [-0.26 , 0.86]
Pokrosvkaya 2018	10.08	3.61	38	13.53	3.66	42	5.1%	-3.45 [-5.04 , -1.86]
Shoeibi 2021	10.141475	3.117743	61	12.3	2.6	13	5.0%	-2.16 [-3.77 , -0.54]
Theoulakis 2010	18	1.6	44	17.7	1.5	44	31.0%	0.30 [-0.35 , 0.95]
Total (95% CI)			**544**			**294**	**100.0%**	**-0.19 [-0.55 , 0.17]**

Heterogeneity: Chi² = 36.55, df = 7 (P < 0.00001); I² = 81%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable

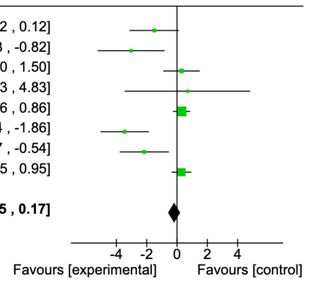
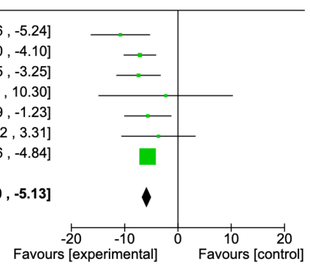


Table 2. IOP decreases in prophylactic anti-glaucoma groups compared to controls following IVI

A. 0-4 minutes after anti-VEGF injection

Study or Subgroup	Anti-Glaucoma Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
Dettoraki 2021	42.6	8.4	31	53.4	12	25	2.0%	-10.80 [-16.36 , -5.24]
ElChehab 2013	39.25	9.119877	200	46.4	10	50	6.6%	-7.15 [-10.20 , -4.10]
Felfeli 2019	34.2	10.8	58	41.6	12	58	3.6%	-7.40 [-11.55 , -3.25]
Murray 2014	42.2	10.2	12	44.5	19.8	12	0.4%	-2.30 [-14.90 , 10.30]
Pokrosvkaya 2018	26.71	10.36	38	32.37	9.79	42	3.1%	-5.66 [-10.09 , -1.23]
Shoeibi 2021	29.753115	17.337271	61	33.41	10	13	1.3%	-3.66 [-10.62 , 3.31]
Theoulakis 2010	28.4	1.1	44	34.1	2.7	44	83.0%	-5.70 [-6.56 , -4.84]
Total (95% CI)			**444**			**244**	**100.0%**	**-5.92 [-6.70 , -5.13]**

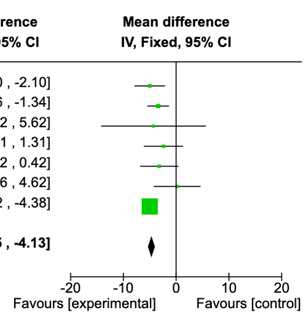
Heterogeneity: Chi² = 5.06, df = 6 (P = 0.54); I² = 0%
Test for overall effect: Z = 14.78 (P < 0.00001)
Test for subgroup differences: Not applicable



B. 5-14 minutes after anti-VEGF injection

Study or Subgroup	Anti-Glaucoma Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
Dettoraki 2021	21.4	5.5	31	26.4	5.5	25	3.8%	-5.00 [-7.90 , -2.10]
Felfeli 2019	18.5	5.7	58	21.9	5.6	58	7.5%	-3.40 [-5.46 , -1.34]
Murray 2014	27.1	10	12	31.4	14.4	12	0.3%	-4.30 [-14.22 , 5.62]
Pece 2016	26.9	8.41207	100	29.3	12	50	2.3%	-2.40 [-6.11 , 1.31]
Pokrosvkaya 2018	21.75	8.42	38	24.95	8.06	42	2.4%	-3.20 [-6.82 , 0.42]
Shoeibi 2021	17.937213	10.01628	61	17.76	6.73	13	1.6%	0.18 [-4.26 , 4.62]
Theoulakis 2010	19.9	1.1	44	24.9	1.8	44	82.0%	-5.00 [-5.62 , -4.38]
Total (95% CI)			**344**			**244**	**100.0%**	**-4.69 [-5.25 , -4.13]**

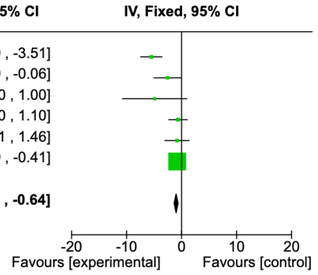
Heterogeneity: Chi² = 9.24, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 16.29 (P < 0.00001)
Test for subgroup differences: Not applicable



C. 15-29 minutes after anti-VEGF injection

Study or Subgroup	Anti-Glaucoma Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
Dettoraki 2021	12.4	3.5	31	17.9	4	25	3.3%	-5.50 [-7.49 , -3.51]
ElChehab 2013	13.225	5.847215	200	15.8	8.6	50	2.0%	-2.58 [-5.09 , -0.06]
Murray 2014	15.7	4.3	12	20.6	9.5	12	0.4%	-4.90 [-10.80 , 1.00]
Pece 2016	18.05	4.579301	100	18.7	5.4	50	4.3%	-0.65 [-2.40 , 1.10]
Shoeibi 2021	10.727705	4.056438	61	11.55	3.76	13	2.5%	-0.82 [-3.11 , 1.46]
Theoulakis 2010	17.2	1.1	44	18	0.7	44	87.6%	-0.80 [-1.19 , -0.41]
Total (95% CI)			**448**			**194**	**100.0%**	**-1.00 [-1.36 , -0.64]**

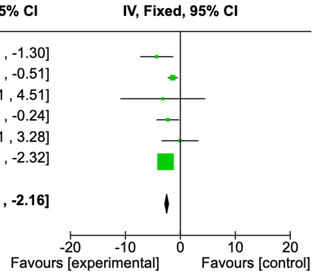
Heterogeneity: Chi² = 23.96, df = 5 (P = 0.0002); I² = 79%
Test for overall effect: Z = 5.43 (P < 0.00001)
Test for subgroup differences: Not applicable



D. >30 minutes after anti-VEGF injection

Study or Subgroup	Anti-Glaucoma Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
ElChehab 2013	17.4	7.279665	200	21.7	10.2	50	1.3%	-4.30 [-7.30 , -1.30]
Felfeli 2019	15.9	0.7	58	17.3	3.4	58	14.4%	-1.40 [-2.29 , -0.51]
Murray 2014	21.3	7	12	24.5	11.7	12	0.2%	-3.20 [-10.91 , 4.51]
Pokrosvkaya 2018	13.92	3.35	38	16.2	5.76	42	2.8%	-2.28 [-4.32 , -0.24]
Shoeibi 2021	13.585738	7.167924	61	13.65	5.19	13	1.0%	-0.06 [-3.41 , 3.28]
Theoulakis 2010	17.2	1	44	19.9	0.8	44	80.3%	-2.70 [-3.08 , -2.32]
Total (95% CI)			**413**			**219**	**100.0%**	**-2.50 [-2.83 , -2.16]**

Heterogeneity: Chi² = 10.39, df = 5 (P = 0.06); I² = 52%
Test for overall effect: Z = 14.42 (P < 0.00001)
Test for subgroup differences: Not applicable



Summary

Twelve studies were identified by three reviewers (A. M., J. L., L. I.) independently screening articles for inclusion criteria, while blinded to each other's selections.

Preliminary statistical analysis of the selected studies demonstrate that mean IOP prior to IVI of anti-VEGF inhibitors was slightly lower in the anti-glaucoma medication group compared to control groups (Table 1), yet no statistical significance was found (P = 0.30).

Mean IOP difference had a statistically significant (P < 0.00001 at all 4 time points) decrease in the anti-glaucoma medication prophylaxis group at four different time points compared to control groups:

- **0-4 min: mean = -5.92 mmHg, 95% CI [-6.70, -5.13]**
- **5-14 min: mean = -4.69 mmHg, 95% CI [-5.25, -4.13]**
- **15-29 min: mean = -2.50 mmHg, 95% CI [-2.83, -2.16]**
- **>30 min: mean = -1.00 mmHg, 95% CI [-1.36, -0.64]**

Conclusion

Key findings from our analysis thus far is that although there is a statistically significant change in IOP with the use of anti-glaucoma prophylaxis prior to IVI of anti-VEGF inhibitors, the clinical impact is minimal as these agents only reduce post-injection IOPs by a few mmHg over time compared to when they are not used. However, an argument can be made that patients with end stage glaucoma, who are more vulnerable to IOP fluctuations and often receive multiple IVI treatments per year, may still benefit from any available intervention that reduces IOP spikes following these injections.

References

1.Lam LA, Mehta S, Lad EM, Emerson GG, Jumper JM, Awh CC; Task Force on Intravitreal Injection Supplemental Services. Intravitreal Injection Therapy: Current Techniques and Supplemental Services. J Vitreoretin Dis. 2021 Jul 22;5(5):4 .

2.Kim GN, Han YS, Chung IY, Seo SW, Park JM, Yoo JM. Effect of Dorzolamide/Timolol or Brinzolamide/Timolol prophylaxis on intravitreal anti-VEGF injection-induced intraocular hypertension. Semin Ophthalmol. 2013 Mar;28(2):61-7.

3.Segal O, Ferencz JR, Cohen P, Nemet AY, Nesher R. Persistent elevation of intraocular pressure following intravitreal injection of bevacizumab. Isr Med Assoc J. 2013 Jul;15(7):352-5.