·Meta-Analysis·

Intraocular pressure elevation after intravitreal triamcinolone acetonide injection: a Meta-analysis

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Abstract

• AIM: To report on intraocular pressure (IOP) after intravitreal injections of triamcinolone acetonide.

• METHODS: Systematic literature review of studies that investigated the effects of an injection of triamcinolone Intravitreal triamcinolone acetonide on IOP was conducted according to the Cochrane Collaboration methodology and the reported effects have been analyzed with Meta-analysis.

• RESULTS: We found that the IOP follows an inverted-U shape pattern over time starting with an average value of 14.81 ±1.22 mm Hg before the injection, rising to a maximum of 19.48 ±2.15 mm Hg after one month of injection and falling down to 16.16 ±1.92 mm Hg after 6mo. Moreover, country of study, age, previous history of glaucoma and gender compositions matter for cross-study were different in reported IOP changes.

• CONCLUSION: Our findings may be helpful in determining pressure elevation risk of intravitreal triamcinolone acetonide therapy as well as comparing it with those of more recent therapies such as the anti-vascular endothelial growth factor agents.

• KEYWORDS: intravitreal injections; intraocular pressure; Meta-analysis
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INTRODUCTION

Intravitreal triamcinolone acetonide (IVTA) injection has been widely used to treat several intraocular neovascular, inflammatory, and edematous diseases[1-6]. However, steroid-induced increase in the intraocular pressure (IOP) is one of the most-widely cited side effects of IVTA injection [7-8]. A significant amount of corticosteroid passes to intravitreal issues after the injection, leading to a significant elevation in the IOP.

More recently, especially considering its side effects such as glaucoma and cataract, use of anti-vascular endothelial growth factor (VEGF) agents took place of intravitreal steroids. However, the need for multiple injections and their significantly higher costs are among the disadvantages of anti-VEGF agents. Moreover, as suggested by some research [9-10] triamcinolone shows similar performance with several anti-VEGF agents in establishing vision quality.

The main purpose of this study is to conduct a global Meta-analysis for a post IVTA-injection elevation of IOP and to find the main factors behind such an elevation. Such an analysis will shed light on the evolution of IOP after an IVTA injection and allow comparing possible advantages and disadvantages of the procedure. To the best of our knowledge, this is the most comprehensive and the only global Meta-analytic research for a post IVTA-injection elevation of IOP after an IVTA injection. Moreover, our paper is also unique in presenting the Meta-analytic results along with a Meta-regression analysis in this area of research.

MATERIALS AND METHODS

We conducted a systematic literature search from 2000 to 2014 using the National Library of Medicine PubMed interface (www.pubmed.gov) as well as Google Scholar (www.scholar.google.com). Both authors independently scanned the titles, abstracts, and keywords of every study obtained in the search process. For any study included in the analysis, full articles were retrieved. Throughout the search, in the initial step we have looked for all articles including the keywords "intravitreal triamcinolone acetonide injection", and "intraocular pressure". Out of 260 identified articles, we ended up with 195 studies after eliminating the duplicates and then with 127 eligible papers examining the relationship between IVTA injection and IOP. For these 127 eligible papers, inclusion criteria were reporting preoperative IOP and at least two IOP measures in two different times after the injection as well as providing summary statistics about gender and age compositions of the samples. Moreover, we also excluded unpublished papers, reports and theses as well

Table 1 Summary of selected papers

Authors (Year)	Country	Patients	Eyes	Age (a)	Female (%)
Ansari and Naser[11] (2008)	Bahrain	41	52	64.10±13.44	53.70
Kahook *et al*[18] (2005)	USA	26	33	64.10±12.01	42.30
Ghoneim and Abd El Ghany[20] (2013)	Egypt	19	38	56.15±11.10	89.50
Kreissig *et al*[21] (2005)	Germany	69	81	66.60±9.40	55.10
Mingaine[17] (2009)	Kenya	61	72	59.61±9.30	47.50
Jonas *et al*[7] (2005)	Germany	272	305	73.00±11.00	60.30
Jonas *et al*[22] (2003)	Germany	71	75	76.83±7.15	71.30
Wang and Song[12] (2007)	China	87	93	59.80±10.80	43.70
Rhee *et al*[23] (2006)	USA	528	528	70.26±11.77	45.80
Lau *et al*[19] (2008)	China	147	147	66.80±12.80	29.30
Smithen *et al*[8] (2004)	USA	89	89	76.40±9.90	58.40
Inatani *et al*[13] (2008)	Japan	427	427	64.78±11.80	39.60
Ozkiris and Erkilic[25] (2005)	Turkey	180	212	54.70±10.80	62.80
Simsek *et al*[26] (2006)	Turkey	51	51	53.20±14.50	49.00
Koc *et al*[27] (2009)	Turkey	179	217	62.70±12.70	40.80
Can *et al*[28] (2013)	Turkey	98	145	59.60±12.60	54.10
Torun Acar and Acar[29] (2010)	Turkey	50	50	59.60±11.62	58.00
Mahar and Memon[14] (2012)	Pakistan	150	198	50.61±10.59	45.30
Park *et al*[16] (2005)	S. Korea	60	60	57.30±11.10	50.00
Ansari and Ali[24] (2008)	UK	41	52	64.10±13.44	46.30
Bashshur *et al*[15] (2008)	Lebanon	185	226	64.20±11.90	43.80

as articles that were not written in English, German and Turkish (*i.e.* languages fluently spoken by both authors). At the end we were left with 21 articles[7-8,11-29]. Figure 1 presents the flow-chart diagram associated with this process.

From all the 21 studies included in the Meta-analysis we have collected the number of patients, number of eyes, the age and gender compositions and the IOP measure in mm Hg before the injection as well as whenever available after 1wk, 1, 2, 3, 4, 5 and 6mo of the injection. When some of these measures were not available, we e-mailed the corresponding authors of the articles to ask for the relevant data. Using these follow up measures of the IOP, percentage changes of the IOP in a different time period from its initial pre-injection level are calculated and included in the Meta-analysis. When conducting the Meta-analysis, the presence of heterogeneity was checked using the calculated I-squared value and a random-effects model was chosen when heterogeneity is present, and the fixed-effects when otherwise. Moreover, we have also conducted a Meta-regression analysis where we have regressed the percentage change of the IOP in different time periods on the initial pre-injection level of IOP, percentage of female eyes in the study, mean age of subjects included in the study, publication year of the study, the number of eyes in the study sample and a dummy variable taking the value of 1 for the developed economies and 0 otherwise using the World Bank Classification. In the Meta-regression analysis we have used the "Empirical Bayes" method to estimate tau-square, which is the additive (between study) component of the variance[30]. All the statistical analyses were performed using the Stata software version 12.1.

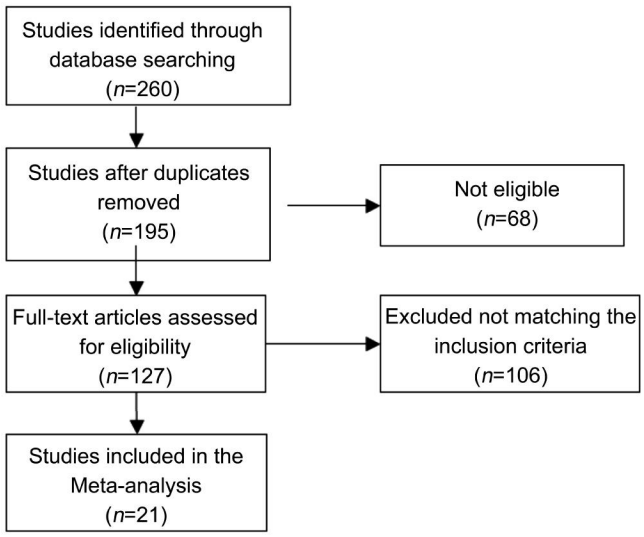

Figure 1 Flow diagram of the Meta-analysis.

RESULTS

Table 1 presents all the papers used in the final stage of the Meta-analysis as well some descriptive statistics of their samples. In total, we included 21 studies with 3132 eyes (1514 females and 1618 males) of 2831 patients (1367 females and 1464 males) in the analysis. The 21 studies originate from 12 different countries and 4 of the 12 countries (Germany, Japan, UK and USA) are categorized as a "developed economy" by the World Bank, whereas the rest

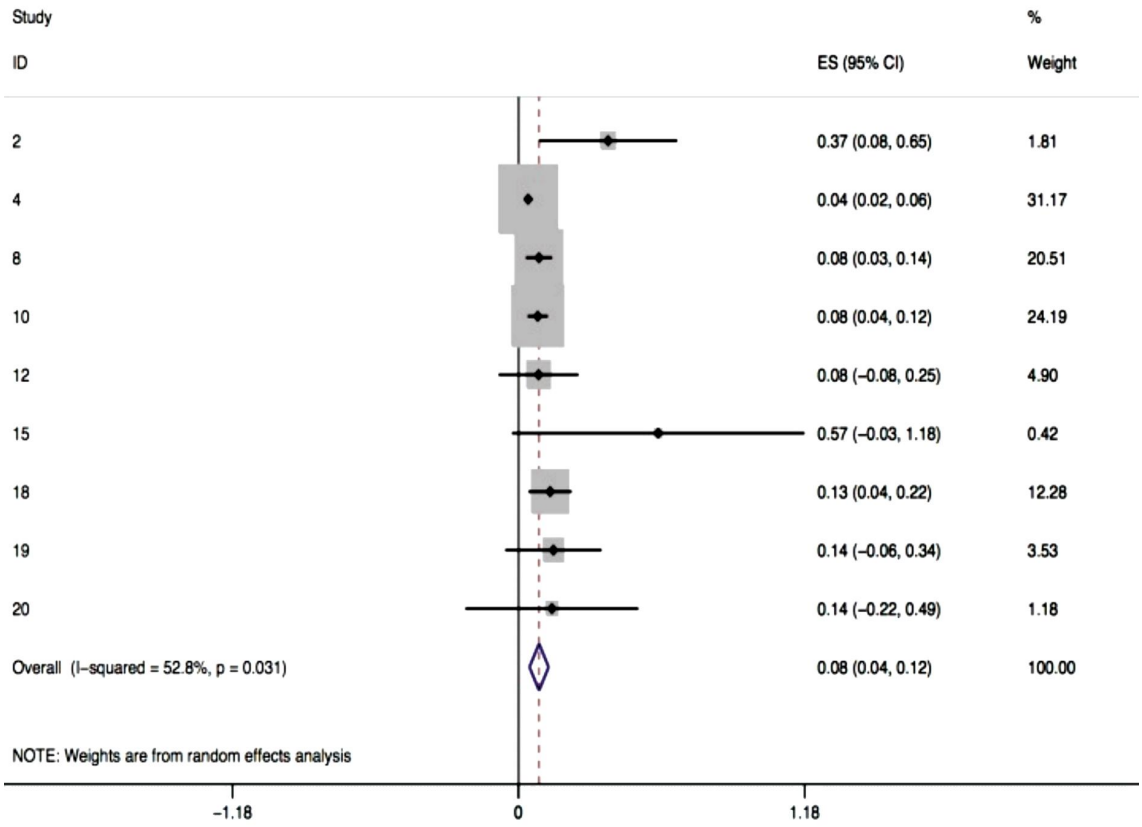

Figure 2 IOP after one week.

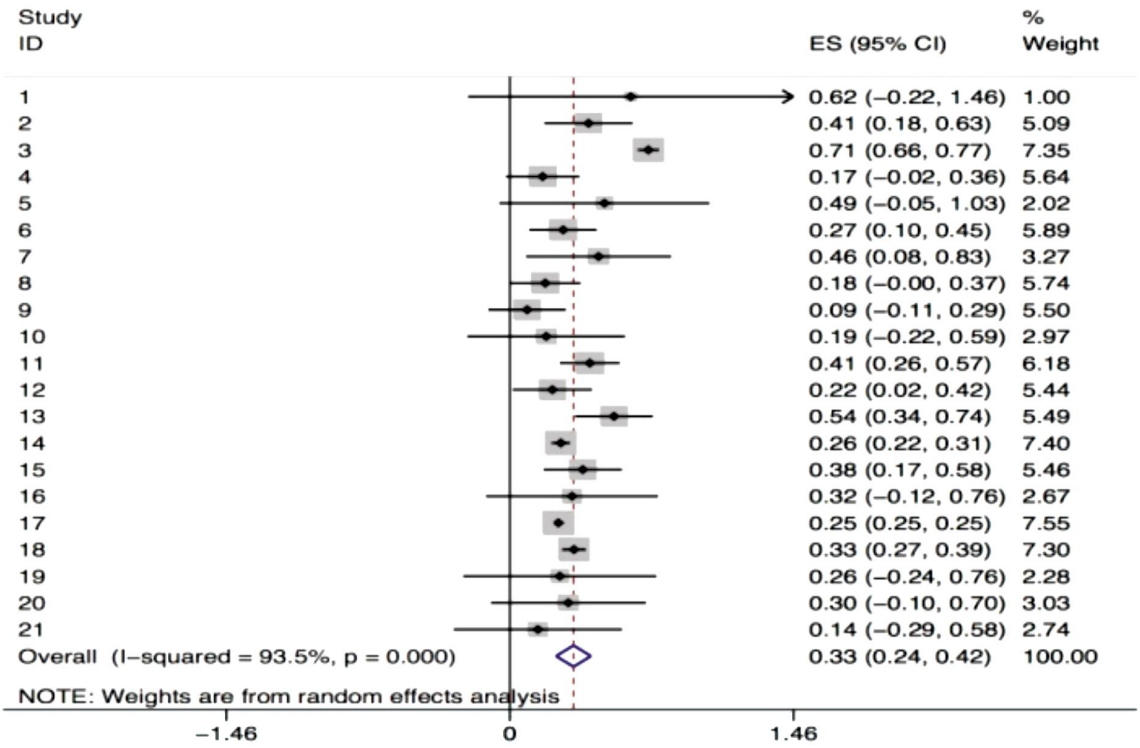

Figure 3 IOP after one month.

of them are not. The average age of subjects in all the studies is 62.89±7.31y.

According to the Meta-analysis of IOP percentage increases from the baseline levels, the percentage increases in IOP from its pre-injection baseline level are as follows: 8% (95% CI, 0.04-0.12) after one week (Figure 2), 33% (95% CI, 0.24-0.42) after one month (Figure 3), 28% (95% CI, 0.14-0.38) after two months, 26% (95%CI, 0.19-0.32) after three months (Figure 4), 12% (95%CI, 0.08-0.16) after four months, 17% (95% CI, 0.03-0.30) after five months and finally 8% (95%CI, 0.08-0.09) after six months (Figure 5) of injection. We present the Meta-analysis results for the changes in the first week, first, third and six months in Figures 2 to 5.

Table 2 Results of the Meta-regressions

Regressor	Dependent variable			
	1wk	1mo	3mo	6mo
Initial IOP	-0.20 (1.19)	-0.03 (0.44)	-0.10 (1.52)	-0.07 (1.32)
Glaucoma	[1]0.14 (4.56)	[1]0.15 (3.95)	[2]0.16 (2.61)	[3]0.19 (1.90)
Female	-0.05 (0.76)	[2]0.63 (2.38)	[1]0.81 (4.09)	0.27 (1.27)
Age	-0.003 (0.97)	-0.004 (0.54)	[2]0.02 (2.44)	[2]0.02 (2.49)
Developed	0.03 (0.19)	0.09 (0.72)	[2]-0.29 (2.40)	[2]-0.06 (2.70)
Publication year	0.02 (1.07)	0.01 (0.50)	[1]-0.03 (3.54)	-0.002 (0.20)
No. of eyes	-0.002 (1.09)	0.002 (0.08)	-0.005 (0.15)	-0.002 (1.30)
Adjusted R^2(%)	-12.57	26.45	78.89	52.67
P	0.31	0.05	0.02	0.04
I^2 (%)	0.00	63.95	12.61	16.10

Absolute values of t-statistics are reported in parentheses. [1]1%, [2]5% and [3]10% significance levels.

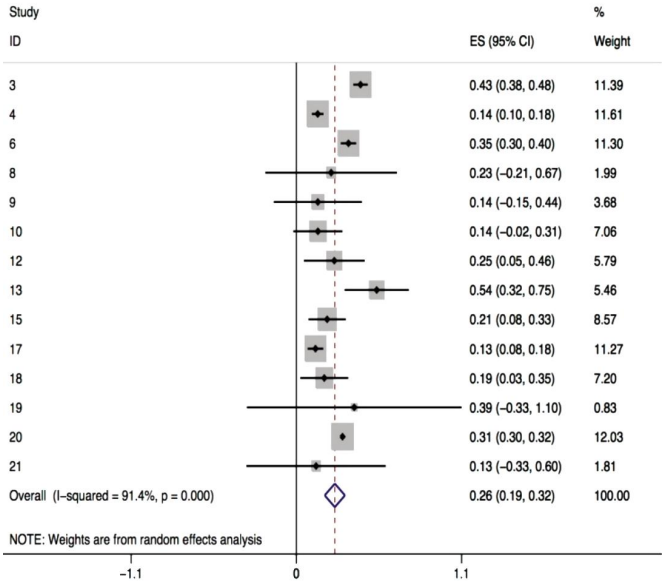

Figure 4 IOP after three months.

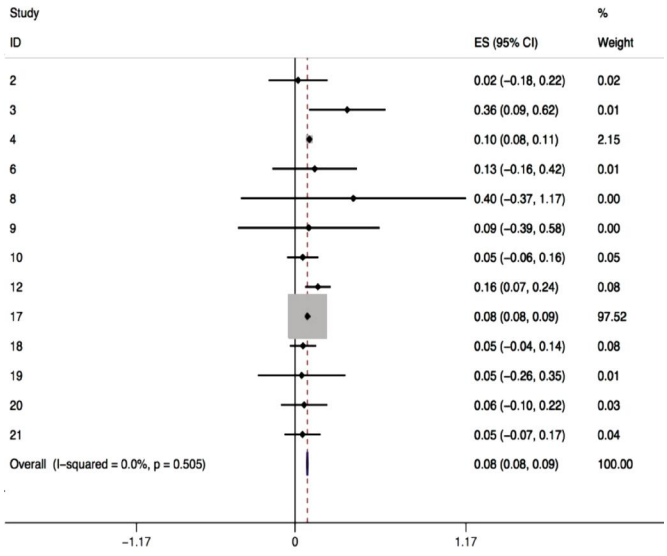

Figure 5 IOP after six months.

In Figure 6 we report a weighted average of the IOP obtained from a Meta-analysis across different studies over time with a 95% lower and upper confidence interval. We

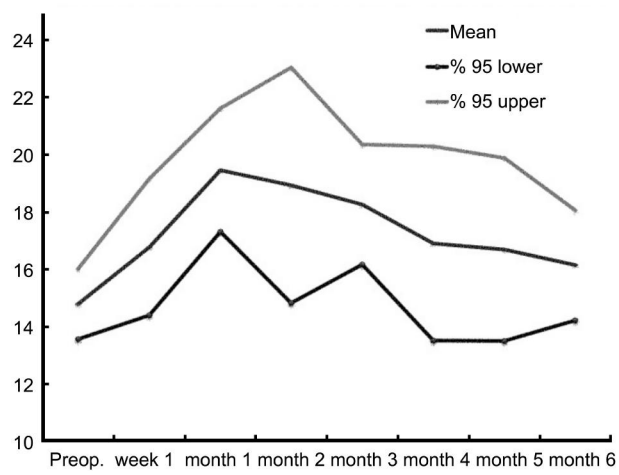

Figure 6 Evolution of the IOP over time.

observe that the IOP follows an inverted-U shape pattern over time starting with an average value of 14.81±1.22 mm Hg before the injection, rising to a maximum of 19.48±2.15 mm Hg after one month of injection and falling down to about 16.16±1.92 mm Hg after 6mo.

Finally in Table 2 we report results of the Meta-regression analysis. From the four different regressions done with the percentage changes in the IOP after 1wk, 1, 3 and 6mo (all compared to the baseline IOP before the IVTA injection) we only have few significant explanatory variables. The number of eyes included in the study and the initial IOP level are not significant determinants of IOP changes. On the other hand, studies conducted with samples with a larger female percentage report a larger percentage increase in IOP after 1 and 3mo of the injection but this effect disappears after 6mo. Moreover, in line with the previous research, studies with an older sample tend to experience a smaller percentage increase in the IOP after 3 and 6mo of injection. On the other hand, presence of a history of glaucoma is associated with a significantly larger increase in the IOP 1wk, 1 and 3mo after the injection. However, 6mo after the injection, the significance is reduced to 10%, indicating a reduction in

the effect of the presence of a glaucoma history on the IOP increase. Furthermore, studies conducted in the four developed economies tend to report a lower percentage increase in the third and sixth months but not earlier. Finally, more recent studies report a significantly lower percentage increase of the IOP in the third month but not at other times.

DISCUSSION

Intravitreal steroids and especially IVTA have been widely used to treat several intraocular neovascular, inflammatory, and edematous diseases [31-32] but generally lead to significant elevation of IOP and generate some other complications[33]. Even though several anti-VEGF agents as well as more expensive steroids, such as Ozurdex [34-35] are increasingly taking place of IVTA, Meta-analytic research on the IOP effects of IVTA is still very much needed.

Our Meta-analysis results shed light on the IOP effects of IVTA as well as how these effects correlate with several characteristics of study groups. Our Meta-analysis results indicate that there exists a 33% (95%CI, 0.24-0.42) increase in the IOP measure at its peak one month after the injection similar to some other studies[36-38]. However, six months after the injection, the increase in IOP compared to its pre-operative level reduces to about 8% (95%CI, 0.08-0.09). Moreover, in several existing studies no significant relationship was found between age and IOP after IVTA [8,13,22,39-41], however some others indicate that younger patients tend to experience a larger increase in the IOP [22-29,42-44]. Our Meta-regression results suggest that age is an important determinant of IOP elevation when measured 3 and 6mo after the IVTA injection. Accordingly, studies with older samples report a smaller elevation in the IOP. Somewhat similarly, contrary to some earlier findings[8,13,22,24] we also have found that gender plays an important role. Specifically, when measured 1 and 3mo after the injection, studies with a larger percentage of female patients report a larger elevation in the IOP, which is contrary to some earlier studies [45]. Moreover, we also observe that the presence of a history of glaucoma is also an important determinant of the increase in the IOP after an IVTA injection. Finally, we also have found that studies conducted in the four advanced (developed) economies in our dataset tend to report lower IOP increases 3 and 6mo after the injection, indicating that the place of the injection is also an important determinant of the IOP change.

In summary, our study shows that the IOP elevation is a significant side effect of IVTA injection; however the level of the elevation can easily be taken under control with medical treatment. Moreover, the factors that we outline in our Meta-regression analysis should also be taken into account when designing the treatment.

One limitation of our study stems is from the fact that the range of disease etiology necessitating an IVTA injection is quite wide. As it reduces our sample size significantly, our study does not take the etiology into account. Moreover, ideally we could have included more variables regarding the study samples, such as cup to disc ratio, pachymetry, visual field analysis, optical coherence tomography findings, glaucomatous eye drops, previous intravitreal injections, laser trabeculoplasty history, trabeculectomy history, or other previous surgery history. Unfortunately, the more data we look for in the papers in the literature, the less is the number of papers that we end up with; as the existing papers in the literature do not report most of these variables. We agree that this is a limitation of our study; however the main purpose of this paper was to conduct the most comprehensive Meta-analytic research on the IOP elevation effects of IVTA.

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Conflicts of Interest: Yuksel-Elgin C, None; **Elgin C,** None.

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