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**Conjunctival hyperemia with the use of latanoprost versus
other prostaglandin analogues in patients with ocular
hypertension or glaucoma: a meta-analysis of randomized
clinical trials**

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key word: latanoprost; bimatoprost; travoprost; conjunctival hyperemia

Abstract

Aim

To conduct a meta-analysis of randomized clinical trials (RCTs) in order to evaluate the development of conjunctival hyperemia after the use of latanoprost versus travoprost and bimatoprost, in patients with ocular hypertension or glaucoma.

Methods

In order to identify the potentially relevant RCTs, a systematic literature retrieval was conducted in Medline, Embase and Cochrane Controlled Trials Register (1995-April 2007) databases. The outcome measure was the appearance of conjunctival hyperemia during the study. Statistical analyses included the calculation of odds ratio (OR) and its respective confidence interval, along with inter-trial statistical heterogeneity. Publication bias was evaluated through a funnel plot and a sensitivity analysis was also performed.

Results

In total, 13 RCTs involving 2,222 patients with ocular hypertension or glaucoma were included, 5 comparing latanoprost versus travoprost, 7 comparing latanoprost versus bimatoprost and 1 comparing latanoprost versus travoprost and bimatoprost.

The combined results showed that latanoprost produced lower occurrence of conjunctival hyperemia than both travoprost (OR = 0.51; 95 % CI: 0.39-0.67, $p < 0.0001$) and bimatoprost (OR = 0.32; 95 % CI: 0.24-0.42, $p < 0.0001$). No significant heterogeneity was found between the included RCTs. There was no evidence of publication bias. In the sensitivity analysis performed, none of clinical trials included in this meta-analysis has an important impact in the global estimation of OR.

Conclusions

According to available data, the use of latanoprost is associated with a lower incidence of conjunctival hyperemia when compared to travoprost and bimatoprost in the treatment of patients with ocular hypertension or glaucoma.

The estimated prevalence of glaucoma is 2 % in the general population, 3 % in people over 50, 5.7 % in subjects 73 and 74 years old and 23.2 % in those aged 75 years and older. This number is expected to increase in the future, given the progressive aging of the population (1-3).

For patients with ocular hypertension or open-angle glaucoma, drug therapy focuses on reducing intraocular pressure (IOP) levels in order to delay or prevent the progression of ocular hypertension to glaucoma, and to slow disease progression in glaucoma patients (4,5). In both cases, patients require life long treatment and follow-up care to preserve vision, so it is essential long-term patient compliance and medication persistency, because those who do not continue therapy risk developing elevated IOP levels and, over time, progressing to blindness (6).

Compliance and persistency depends on many factors, including patient satisfaction with medication, medication costs, ease of medication administration and patient understanding of the importance of taking their medication over the long term, although one of the most important factors is local and systemic side effects (7).

Currently, first-line treatment usually consists of monotherapy with a topical hypotensive drug. Although ophthalmologists traditionally have prescribed beta-blockers as first-line ocular hypotensive therapy, due to the possibility of producing systemic side effects, other therapeutic options are currently preferred, being prostaglandin analogues one of the most widely used(8).

Topical prostaglandins such as latanoprost, bimatoprost and travoprost are similar in that they require once-daily instillation, produce few systemic side effects and reduce IOP levels similarly (9-11). However, some prostaglandin-treated patients experience conjunctival hyperemia (12), and this condition is of concern because this side effect may negatively affect whether the patient takes the drug as directed (compliance) and/or continues to use the drug over time (persistency).

Although a lower rate of conjunctival hyperemia has been reported with latanoprost in contrast to bimatoprost and travoprost (13), no systematic review and meta-analysis has examined this issue. Therefore, the aim of this work was to conduct a meta-analysis of RCTs comparing latanoprost against bimatoprost and travoprost, either together or in separated studies, in patients with ocular hypertension and/or glaucoma.

Methods

Search strategy

Reports of RCTs comparing latanoprost, bimatoprost and travoprost were identified through a systematic search. A computerized literature search was conducted in Medline, Embase and Cochrane Controlled Trials Register databases from 1995 to April 2007 for relevant articles in English.

We used the Medical Subject Heading and the following key words: glaucoma, ocular hypertension, randomization, trial, latanoprost, bimatoprost, travoprost and conjunctival /ocular hyperemia. References from the reviewed articles were also searched for relevant titles.

Study selection

Two reviewers independently conducted the literature search and extraction of relevant articles. The title and abstract of potentially relevant studies and review articles were screened for appropriateness before retrieval of the full articles.

The following selection criteria were used to identify published studies for inclusion in this meta-analysis: a) study design – RCTs in adults (age > 18 years); b) population – patients with ocular hypertension and/or glaucoma; c) intervention – latanoprost versus other prostaglandins analogues (bimatoprost or travoprost) as monotherapy; d) outcome variable – conjunctival hyperemia. These articles were written in English. Abstracts from conferences without raw data available for retrieval and duplicate publications were excluded.

Data extraction

Two reviewers performed separately the data extraction and methodological quality assessment of trials that were included. The reviewers were blinded for the names of the authors and their institution, the names of the journals, sources of funding and acknowledgments. Any disagreements between the reviewers were resolved by discussion to reach consensus. A third reviewer was involved when required.

A customized form was created to record the information of selected articles: year of publication, information of study design (double-blind, parallel or cross-over), length of study, number of subjects, age, sex, type of glaucoma and proportion of conjunctival hyperemia.

The primary outcomes measure was the incidence of conjunctival hyperemia over treatment visits. The reason for exclusion was recorded on a standard form. Excluded publications were reassessed to ensure that all eligible publications were included.

Assessment of study quality

Two reviewers independently rated study quality using the Jadad instrument for the assessment of the quality of trials reports (14). This instrument is a point scale ranging from 0 to 8, with points derived from the description of randomization, blinding, inclusion and exclusion criteria, withdrawals, and method of assessing adverse events.

Statistical methods and assessment of heterogeneity

The statistical analysis was carried out by Comprehensive Meta-Analysis software version 2.2 (Biostat, Inc., Englewood, New Jersey) (www.meta-analysis.com).

For dichotomous outcomes we calculated a pooled odds ratio (OR) and 95 % confidence intervals. Odds ratio was defined as the odds of an outcome in those who received latanoprost therapy compared to the odds in those who received bimatoprost or travoprost. The odds ratio of different RCTs were combined by using the fixed effects model of Mantel-Haenszel (15) and the random effects model of Der Simonian and Laird (16).

Inter-trial statistical heterogeneity was explored using the Cochran Q test with calculated I^2 , indicating the percentage of the total variability in effect estimates among trials that is due to heterogeneity rather than to chance (17). I^2 values of 50 % or more indicate a substantial level of heterogeneity. Publication bias was assessed by visually inspecting a funnel plot.

All P values were 2 sided with statistical significance set at an α level of 0.05. We followed the QUORUM (the Quality of Reporting Meta-analysis) guidelines for reporting and discussing these meta-analytic results (18).

To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by systematically excluding each study at a time and then re-running the analysis to assess the change in ORs.

Results

Literature search

There were 31 articles relevant to the search term. A total of 18 potential RCTs of latanoprost versus other prostaglandin analogues were identified through the literature search (19-36), 5 comparing latanoprost vs travoprost, 7 comparing latanoprost vs bimatoprost and 1 comparing latanoprost vs bimatoprost and travoprost.

Finally, 13 articles involving 2,222 patients with ocular hypertension or glaucoma were included in this meta-analysis (24-36). The algorithm flowchart for the selection of RCTs to be included in our analysis is shown in Figure 1.

Characteristics of trials

Table I shows the characteristics of the RTCs that were included in this meta-analysis. Over all, 2,222 patients were evaluated for an average period of follow-up of 4.1 months (min = 2 weeks; max = 9 months). Nine hundred and thirty-one patients were treated with latanoprost, 624 with bimatoprost and 667 with travoprost.

Patients' age ranged from 58 to 73 years with a mean of 65.4. 4 % were men, 1,364 patients (61.4 %) suffered from open-angle glaucoma, 678 (30.5 %) from ocular hypertension and 180 (8.1 %) from another type of glaucoma (chronic angle-closure glaucoma, exfoliative glaucoma and pigmentary glaucoma).

The proportion of patients treated with latanoprost who developed conjunctival hyperemia was 16.5% (min = 3.3%; max = 47.1%), in the bimatoprost group 40.2% (min = 14.3%; max = 68.6%) and in the travoprost group 33% (min = 6.2%; max = 58%).

Hyperemia outcome

The combined results of different clinical trials suggested that the use of latanoprost 0.005% caused a lower percentage of appearance of conjunctival hyperemia compared to travoprost 0.004% (OR = 0.51; 95 % CI: 0.39 – 0.67, $p < 0.00001$). No significant heterogeneity found between included clinical trials ($Q = 3.98$; $p = 0.56$) (Figure II).

Moreover, the results of this meta-analysis also showed that the utilization of latanoprost 0.005 % is associated with a lower development of conjunctival hyperemia when compared to bimatoprost 0.003 % (OR = 0.32; 95 % CI: 0.24 – 0.42, $p > 0.00001$). Heterogeneity between included clinical trials did not show significance ($Q = 4.18$; $p = 0.75$) (Figure III).

Sensitivity analysis

In order to analyze the consistency and robustness of the results, a sensitivity analysis was performed (Table II). First, the results obtained were compared using the fixed and random models. Changing the model from fixed to random effects did not change the results of our meta-analysis.

Secondly, in order to assess the influence of each individual clinical trial included in the meta-analysis, each study was excluded at a time and the analysis performed again to appraise the change in the OR. The punctual estimators for OR change between 0.46 and 0.54 in the latanoprost-travoprost analysis, and between 0.29 and 0.34 in the latanoprost-bimatoprost analysis after excluding one by one each original clinical trial. None of clinical trials included in

this meta-analysis had an important impact in the global estimation of the OR.

Publication bias

An analysis of publication bias was conducted. For each separated analysis (latanoprost-travoprost and latanoprost-bimatoprost), Based on a visual analysis of the funnel plots, no evidence of publication bias was found, (Figures IV and V).

Discussion

The hypotensive prostaglandin analogues are a novel class of intraocular-lowering medications used primarily for the treatment of glaucoma. In recent years, prostaglandins have emerged as the mainstay of treatment for ocular hypertension and/or glaucoma. These include latanoprost, travoprost and bimatoprost, which are ester or amide pro-drug analogues of the prostaglandin F₂-alpha.

The efficacy in lowering IOP of the three compounds is very similar and in a recent meta-analysis it was found that the difference in decreasing IOP between the three products was very small (37). However, according to the literature, it has been described that conjunctival hyperemia occurs more frequently with either bimatoprost and travoprost than with latanoprost (12,13,38), although neither systematic review nor meta-analysis have been performed to date to assess properly this issue. The reason for the reduction of hyperemia caused by latanoprost in the eye compared to bimatoprost and travoprost is likely lays in the latanoprost molecule and its pharmacologic receptor profile (39).

This meta-analysis was aimed at comparing the development of conjunctival hyperemia of three prostaglandin analogues on the information reported in the international literature, as conjunctival hyperemia is a condition of concern, since local side effects may negatively affect whether the patient takes the drug as directed (compliance), and/or continues to use the drug over time (persistency). Other local side effects such as the change in iris color and the development of darker and longer eye lashes, may also cause a decrease of treatment compliance and persistency, so it will be necessary to explore this issue in the future by conducting new studies.

The results of this meta-analysis show that the use of latanoprost is associated with a lower incidence of conjunctival hyperemia. Arcieri et al (40) found in a study that there was a significant increase in hyperemia scores in the latanoprost, bimatoprost, and travoprost groups 1 week after baseline. Hyperemia scores reached their peak 15 days after baseline and started to decrease 1 month after therapy was initiated. So it is

important to point out that the conjunctival hyperemia could decrease during the use of prostaglandin analogues in daily medical practice.

This meta-analysis may have some limitations. Firstly, we cannot fully exclude publication bias, because there were no sufficient studies to detect asymmetry in a funnel plot and we did not perform a statistical test for the detection of publication bias: these tests have very low power in meta-analysis of a small number of trials. In addition, we did not attempt to gain access to unpublished results and only publications written in English were accepted. Secondly, clinical trials included in this meta-analysis were undertaken in many different countries, so we cannot eliminate location bias. Lastly, the studies included were heterogeneous in terms of study population, length of each study, number of patients of different studies, basal condition, associated co-morbidities and the way of evaluating conjunctival hyperemia. Access to individual level data could have certainly improved the quality of adjustment as well as the precision of estimates.

Conclusion

The results of this meta-analysis suggest that latanoprost is associated with a lower incidence of conjunctival hyperemia versus the use of bimatoprost and travoprost in the treatment of ocular hypertension and/or glaucoma. This information may be useful for determining the optimal treatment strategy for individual patients.

More research is needed to know the incidence of conjunctival hyperemia after the use of prostaglandin analogues in mid and long term, as well as in real world daily medical practice.

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Competing Interest

SJ is an employee of Pfizer Spain

H F, G-S J, P V and M JM have participated in advisory boards for several pharmaceutical companies (Pfizer, Alcon, Allergan and MSD).

Figure legends

Figure 1.- Selection algorithm for the randomized controlled trials (RCTs) included in this meta-analysis

Figure II.- Global and partial statistical data of clinical trials comparing latanoprost and travoprost

Figure III.- Global and partial statistical data of clinical trials comparing latanoprost and bimatoprost

Figure IV.- Funnel plot of clinical trials included in the meta-analysis comparing latanoprost vs travoprost

Figure V.- Funnel plot of clinical trials included in the meta-analysis comparing latanoprots vs bimatoprost

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Table 1.- Characteristics of 13 trials meeting criteria for inclusion in the meta-analysis

Source	Design	Intervention	Duration Study	Nº of patients	% patients with hyperemia			Jadad Score
					LAT	BIMAT	TRAVO	
Gandolfi et al ²⁴	Parallel	LAT vs BIMAT	3 months	LAT = 113; BIMAT = 119	14.2	36.1		7
Dubiner et al ²⁵	Parallel	LAT vs BIMAT	1 month	LAT = 22; BIMAT = 21	13.6	14.3		5
Noecker et al ²⁶	Parallel	LAT vs BIMAT	6 months	LAT = 136; BIMAT = 133	20.6	44.4		7
Walters et al ²⁷	Parallel	LAT vs BIMAT	1 month	LAT = 38; BIMAT = 38	15.8	39.5		6
Konstas et al ²⁸	Crossover	LAT vs BIMAT	7 weeks each treatment	LAT = 21; BIMAT = 21	28.6	71.4		5
Dirks et al ²⁹	Parallel	LAT vs BIMAT	3 months	LAT = 27; BIMAT = 33	7.4	21.2		6
Konstas et al ³⁰	Crossover	LAT vs BIMAT	3 months each treatment	LAT = 123; BIMAT = 123	7.3	26		7
Netland et al ³¹	Parallel	LAT vs TRAVO	12 months	LAT = 193; TRAVO = 402	27.6		44	6
Parrish et al ³²	Parallel	LAT vs TRAVO vs BIMAT	3 months	LAT = 136 ; BIMAT = 136 ; TRAVO = 138	47.1	68.6	58	7
Parmaksiz et al ³³	Parallel	LAT vs TRAVO	9 months	LAT = 16 ; TRAVO = 18	6.2		38.8	5
Chen et al ³⁴	Parallel	LAT vs TRAVO	3 months	LAT = 36 ; TRAVO = 37	8.3		13.5	6
Garcia-Feijoo et al ³⁵	Parallel	LAT vs TRAVO	2 weeks	LAT = 30 ; TRAVO = 32	3.3		6.2	5
Konstas et al ³⁶	Crossover	LAT vs TRAVO	8 weeks each treatment	LAT = 40 ; TRAVO = 40	15		37.5	6

LAT = Latanoprost ; BIMAT = Bimatoprost ; TRAVO = Travoprost

Table II.- Sensitivity analysis of the association of conjunctival hyperemia and the use of latanoprost, travoprost and bimatoprost

<u>Latanoprost vs Bimatoprost</u>			
<u>Statistical model</u>	<u>N° of Studies</u>	<u>N° of Patients</u>	<u>OR (95 % CI)</u>
Fixed effects	8	1,240	0.32 (0.24-0.42)
Random effects	8	1,240	0.32 (0.24-0.42)
<u>Analyses excluding</u>			
Dubiner et al ²⁵	7	1,197	0.31 (0.24-0.41)
Gandolfi et al ²⁴	7	1,008	0.33 (0.24-0.44)
Noecker et al ²⁶	7	971	0.32 (0.23-0.44)
Parrish et al ³²	7	968	0.29 (0.21-0.40)
Walters et al ²⁷	7	1,164	0.32 (0.24-0.43)
Konstas et al ²⁸	7	1,198	0.33 (0.25-0.43)
Dirks et al ²⁹	7	1,180	0.32 (0.24-0.42)
Konstas et al ³⁰	7	994	0.34 (0.25-0.45)
<u>Latanoprost vs Travoprost</u>			
<u>Statistical model</u>	<u>N° of Studies</u>	<u>N° of Patients</u>	<u>OR (95 % CI)</u>
Fixed effects	6	1,118	0.51 (0.39-0.67)
Random effects	6	1, 118	0.51 (0.39-0.67)
<u>Analyses excluding</u>			
Netland et al ³¹	5	523	0.54 (0.36-0.80)
Parrish et al ³²	5	844	0.46 (0.33-0.64)
Parmaksiz et al ³³	5	1,084	0.53 (0.40-0.69)
Chen et al ³⁴	5	1,045	0.51 (0.39-0.67)
Garcia-Feijoo et al ³⁵	5	1,056	0.51 (0.39-0.68)
Konstas et al ³⁶	5	1,038	0.53 (0.40-0.71)

Figure I

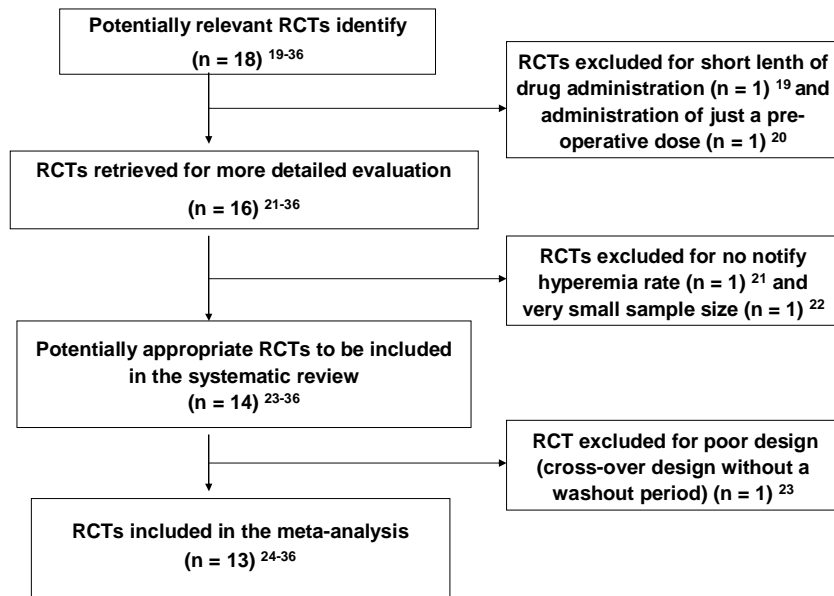
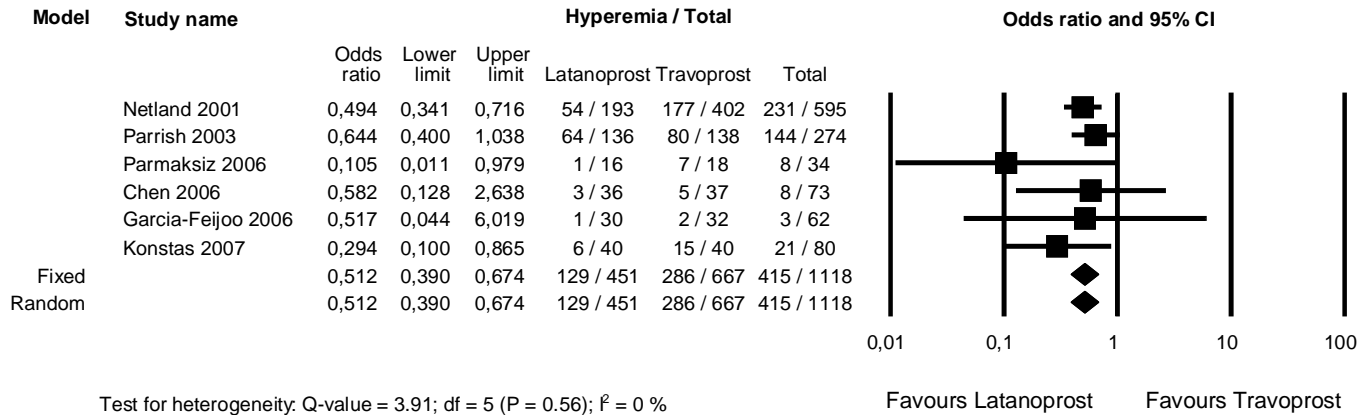


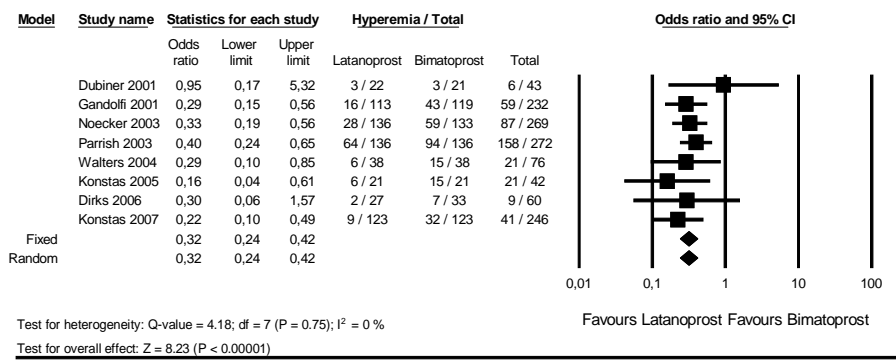
Figure II.- Global and partial statistical data of clinical trials comparing latanoprost and travoprost



Test for heterogeneity: Q-value = 3.91; df = 5 (P = 0.56); I² = 0 %

Test for overall effect: Z = 4.78 (P < 0.00001)

Figure III.- Global and partial statistical data of clinical trials comparing latanoprost and bimatoprost



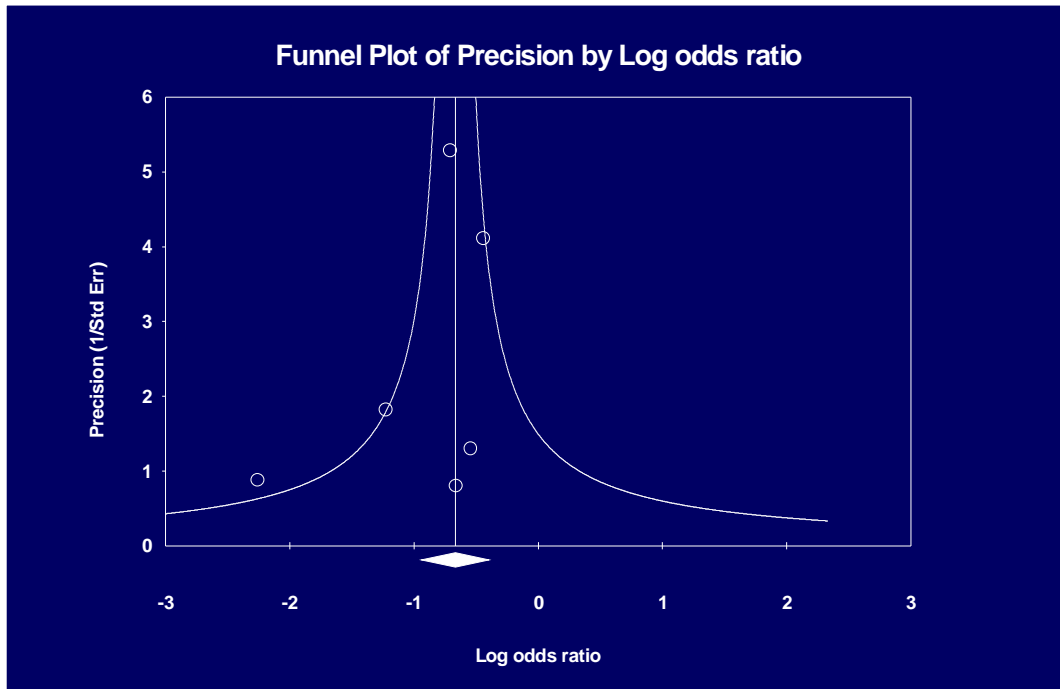


Figure IV

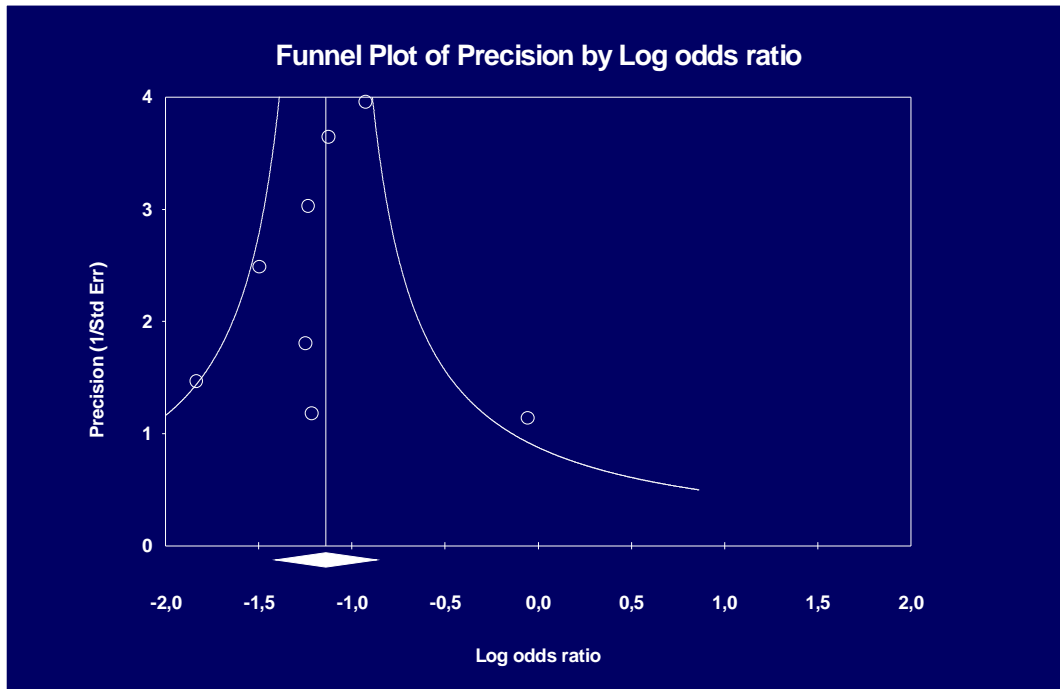


Figure V