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Meta analysis about the efficacy and safety of anti-ocular hypertension eye drops without benzalkonium chloride

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ABSTRACT

Objective: To explore the safety and efficacy of eye drops without benzalkonium chloride (BAK) in treating glaucoma and ocular hypertension. **Methods:** The clinical case-control literatures about eye drops without BAK treating glaucoma and ocular hypertension were retrieved in PubMed, EMBASE, Cochrane and Chinese Biological and Medical database. Meta 5.0 software was used to analyze the literatures. **Results:** Five clinical control studies were included. The results indicated both eye drops could lower the intraocular pressure, and the intraocular pressure-lowering difference between two eye drops was 0.07 mmHg (95% *CI*: 0.04, 0.19) ($P>0.05$). Two adverse reactions occurred more were conjunctival injection (10.78%) and allergic conjunctivitis (4.78%). The odd ratio of two eye drops occurring conjunctival injection and allergic conjunctivitis was 0.67 (95% *CI*, 0.25, 1.10) and 0.82 (95% *CI*, 0.09, 1.54), respectively ($P<0.05$) in fixed effect model. **Conclusions:** There is no difference between the eye drops with or without BAK in lowering intraocular pressure, but the latter is of higher safety. In consideration of the relatively small sample size of this research, more high-quality clinical research contrasts are needed as evidence.

1. Introduction

Glaucoma is a severe optic neuropathy. Lack of treatment can lead to blindness of the patients with it. There are about 70 million people influenced by this disease all around the world[1]. This kind of cryptogenic disease, the main reason of irreversible blindness, is with increased intraocular pressure due to a resistance in the trabecular meshwork outflow pathway of aqueous humor[2]. Eye drops treating glaucoma usually contain a preservative, benzalknium chloride (BAK), a quaternary ammonium salt composed of a mixture of benzododecinium $C_{21}H_{38}N^{+}$(BAK C_{12}) and myristalkonium $C_{23}H_{42}N^{+}$(BAK C_{14}) chlorides.

Studies have showed that BAK-free eye drops have favorable IOP-lowering effect[3], but this clinical result lacks theoretical evaluation and data research. This paper explores the safety and effectiveness of BAK-free eye drops in treating glaucoma and ocular hypertension with Meta analysis and also emphasize on the exploration of the toxic effects of BAK on endothelial cells, cornea and other cells constituting the intraocular microenvironment.

2. Materials and methods

2.1. Research objectives

The clinical case-control literatures about eye drops (with/without BAK) treating glaucoma and ocular hypertension were retrieved in PubMed, EMBASE, Cochrane and CBM database. The data were sourced from the published literatures in the database. The main search items included BAK, glaucoma, high intraocular pressure, adverse effect, *etc*. The publication time is from 2003 to 2010.

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2.2. Classification standard of glaucoma

At present, in clinic, the classification of glaucoma in China was according to "Preliminary advice for early diagnosis of primary glaucoma" established in 1987, while in scientific research, ISGEO classification is adopted. Glaucoma is mainly divided into primary closed-angle glaucoma, open-angle glaucoma, acute angle-closure glaucoma, *etc*.

2.3. Inclusive criteria

The inclusive criteria of this research are as following: (i) Only the publicly published papers in the journals can be collected and selected; (ii) The research hypothesis and methods were similar; (iii) The research objects should be normal people; (iv) The detection result was expressed by mean and standard deviation; (v) All the clinical case control researches on the comparison between using eye drops containing BAK and using BAK-free eye drops were used in the therapeutic scheme. Factors like the age of the patient and intraocular pressure before operation were considered at grouping. Bias caused by human factor was excluded.

2.4. Exclusive criteria

(i) Literatures containing duplicated data, study of own-control before and after the treatment, and cohort study; (ii) Literatures can't be used for poor quality, low information or incomplete data, like case reports; (iii) Original literatures without efficacy evaluation for the treatment; (iv) Unreasonable research design (unreasonable design of the control group, fuzzy description about the sample data, and none-standardized diagnosis or curative judgment); (v) Duplicate published literatures.

2.5. Statistical analysis

All the literature data (including authors, publication time, cases of the objects, *etc*.) were input in the Review Manager 5.0 software for the heterogeneity and Meta analysis. If no heterogeneity existed in each study ($P \geqslant 0.1$, $I^2=0$), fixed effect model was adopted; on the contrary, random effect model was adopted for the data analysis. Mantel-Haenszel (fixed effect model) and DerSimonian and Laird method (random effect model) were used for the calculation of combined effect value. For all the statistical data, the statistical value of utility analysis was expressed by *OR* value, and the corresponding 95% *CI* was calculated. There was no statistical difference of the two therapeutic scheme when $P<0.05$.

3. Results

3.1. Information about the included literatures

Seventy-eight related literatures were preliminarily retrieved according to the data collection methods and retrieval strategy. Five clinical control literatures published between 2003 and 2010 were finally included strictly according to the inclusive and exclusive criteria. Based on different research objectives, the patients with glaucoma, ocular hypertension, *etc*., who have to control IOP through long term use of medicine, were grouped according to equilibrium principle. The sample size of each research was between 80-780 eyes, and the follow-up time ranged from 3 weeks to 1 year. The basic information and quality evaluation of the included research are showed in Table 1. The included eyes of the five research were 1 549, 774 of which used eye drops containing BAK and 775 used BAK-free eye drops. There was no statistical significance between the two groups in terms of age, sex, IOP before treatment, *etc*.

3.2. IOP-lowering efficacy of eye drops with BAK and BAK-free eye drops

3.2.1. Effectiveness evaluation of lowering IOP

All the five literatures reported the IOP of the research objects before treatment and in the follow-up period. The statistical value of the heterogeneity test was $I^2=0$, $P>0.1$. Random effect model was adopted. The IOP-lowering

Table 1

The basic information and quality evaluation of the included research.

Authors	Publication time	Eyes (B/B-free)	Eye drops with BAK	BAK-free eye drops	Follow-up time (month)	Quality evaluation
Mundorf *et al*[4]	2003	407(204/203)	0.2% Brimonidine	0.15% Brimonidine -Purite	3.0	3
Lewis *et al*[5]	2007	690(346/344)	0.004% Travoprost	0.004%Travoprost-BAKfree	3.0	3
Hamacher *et al*[6]	2008	85(42/43)	0.001 5 Tafluprost	0.001 5Tafluprost-BAKfree	1.0	3
Gross *et al*[7]	2008	106(52/54)	0.004%Travoprost	0.004%Travoprost-BAKfree	0.5	3
Shedden *et al*[8]	2010	261(130/131)	Fixed formula 2% Dorzolamide/0.5% Timolol	Fixed formula 2% Dorzolamide/0.5% Timolol-BAK free	3.0	3

In all studies, follow-up investigation was performed and the conditions were balanced.

difference between the patients using two kinds of eye drops was 0.07 mmHg (95% *CI* −0.04, 0.19) (*P*=0.07). IOP lowering was taken as the index to evaluate the efficacy of eye drops with and without BAK in treating glaucoma and ocular hypertension, and the result indicated that there was no significant difference between the efficacies of the two kinds of eye drops (Figure 1).

3.2.2. Potential publication bias

Using IOP-lowering as the analysis index, the funnel plot was drawn. Due to the few included researches, the distribution tendency was unobvious, but the funnel plot was symmetric which meant the publication bias was small (Figure 2).

Study of subgroup	BAK			BAK-free			Weight (%)	Mean difference IV, Fixed, 95% *CI*
	Mean	SD	Total	Mean	SD	Total		
Gross *et al* (2008)	0.47	0.86	204	0.44	0.88	203	47.2	0.03 [−0.14, 0.20]
Hamacher *et al* (2008)	0.73	1.84	346	0.62	1.57	344	20.7	0.11 [−0.15, 0.37]
Lewis *et al* (2007)	0.37	0.83	42	0.34	0.86	43	10.5	0.03 [−0.33, 0.39]
Mundorf *et al* (2003)	0.51	1.14	52	0.43	0.71	54	10.2	0.08 [−0.28, 0.44]
Shedden *et al* (2010)	0.66	1.48	130	0.45	1.36	131	11.3	0.21 [−0.13, 0.55]
Total (95% *CI*)			774			775	100.0	0.07 [−0.04, 0.19]
Heterogeneity Chi^2=4.28, *df*=4 (*P*=0.37); I^2=7%								
Test for overall ellect: *Z*=3.10 (*P*=0.002)								

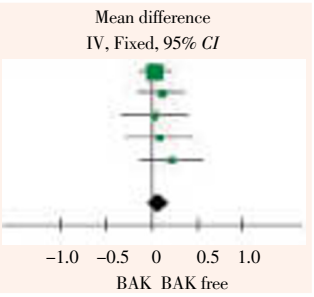

Figure 1. Meta analysis of the IOP-lowering effect of patients using eye drops with BAK and BAK-free eye drops.

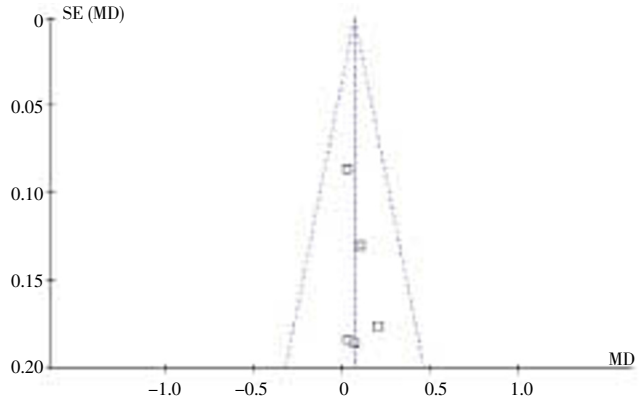

Figure 2. Funnel plot of the publication bias.

3.2.3. Adverse effect in the follow-up period

All the five literatures included in Meta analysis mentioned adverse effects in the follow-up period which included conjunctival injection, allergic conjunctivitis, dry eye, taste dysfunction, *etc*. The two most common adverse effects were conjunctival injection (10.78%) and allergic conjunctivitis (4.78%). The heterogeneity test of the adverse effect was *P*>0.1, I^2<50%. Random effect model was adopted for the Meta analysis (Table 2). The results indicated that the percentage of patients developing conjunctival injection and allergic conjunctivitis using eye drops containing BAK were 0.67 and 0.82 times of those using BAK-free eye drops respectively (P_{both}<0.05), which revealed the notable difference between the two kinds of eye drops in safety. The safety of eye drops containing BAK was better than those without BAK. The forest graph and funnel plot are shown in Figures 3-6 which indicated that the publication bias was small.

Table 2

Adverse effect comparison in the follow-up period between eye drops with BAK and BAK-free eye drops (*n*=1 549).

Adverse effect	*OR* (95% *CI*)	*P* value
Conjunctival injection	0.67(0.25, 1.10)	0.002
Allergic conjunctivitis	0.82(0.09, 1.54)	0.030

Study of subgroup	BAK			BAK-free			Weight (%)	Mean difference IV, Fixed, 95% *CI*
	Mean	SD	Total	Mean	SD	Total		
Gross *et al* (2008)	1.93	1.37	26	0.37	2.28	14	10.7	1.56 [0.25, 2.87]
Hamacher *et al* (2008)	1.21	2.28	22	0.28	1.09	20	16.0	0.93 [−0.14, 2.00]
Lewis *et al* (2007)	2.36	2.61	36	1.48	1.01	32	21.4	0.88 [−0.04, 1.80]
Mundorf *et al* (2003)	1.74	1.67	38	1.23	1.41	34	35.8	0.51 [−0.20, 1.22]
Shedden *et al* (2010)	0.74	1.67	24	0.81	1.78	18	16.2	−0.07 [−1.13, 0.99]
Total (95% *CI*)			146			118	100.0	0.67 [0.25, 1.10]
Heterogeneity Chi^2=4.28, *df*=4 (*P*=0.37); I^2=7%								
Test for overall ellect: *Z*=3.10 (*P*=0.002)								

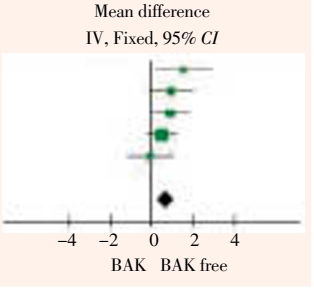

Figure 3. Meta analysis of conjunctival injection in patients using eye drops with BAK and BAK-free eye drops to lower IOP.

Study of subgroup	BAK			BAK-free			Weight (%)	Mean difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% *CI*
Grosset *et al* (2008)	1.93	1.67	10	0.37	2.28	6	12.0	1.56 [-0.54, 3.66]
Hamacher *et al* (2008)	1.41	2.28	14	0.28	1.09	6	24.1	1.13 [-0.35, 2.61]
Lewls *et al* (2007)	2.36	2.61	20	1.18	1.01	8	29.4	1.18 [-0.16, 2.52]
Muncorf *et al* (2003)	0.74	1.67	12	0.63	1.41	4	18.8	0.11 [-1.56, 1.78]
Shedden *et al* (2010)	0.74	1.67	8	0.81	1.78	6	16.7	-0.07 [-1.91, 1.77]
Total (95% *CI*)			64			30	100.0	0.82 [0.09, 1.54]
Heterogeneity Chi^2=4.28, *df*=4 (*P*=0.37); I^2=7%								
Test for overall ellect: *Z*=3.10 (*P*=0.002)								

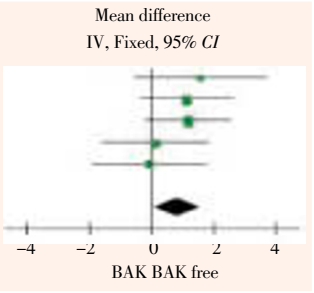

Figure 4. Meta analysis of allergic conjunctivitis in patients using eye drops with BAK and BAK-free eye drops to lower IOP.

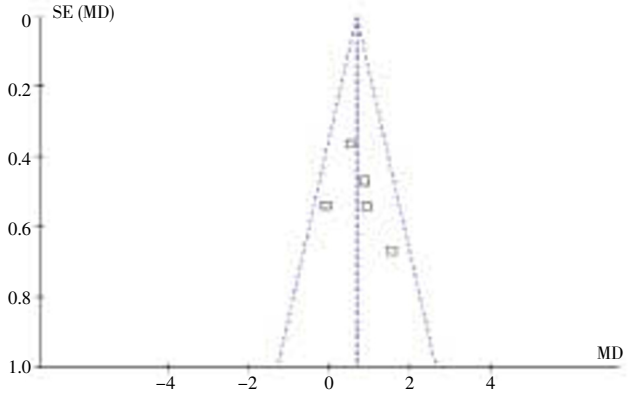

Figure 5. Funnel plot of the publication bias about conjunctival injection in patients using eye drops with BAK and BAK-free eye drops to lower IOP.

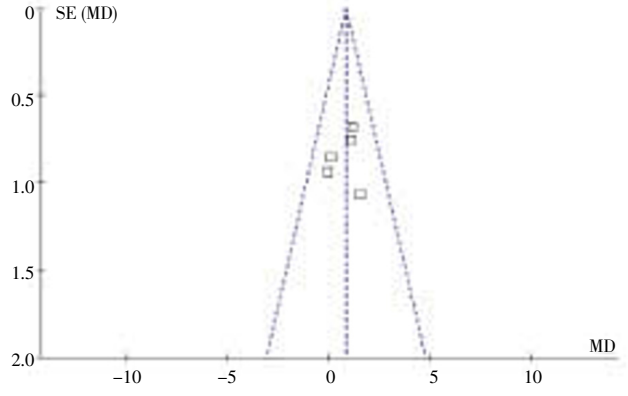

Figure 6. Funnel plot of the publication bias about allergic conjunctivitis in patients using eye drops with BAK and BAK-free eye drops to lower IOP.

4. Discussion

In recent two decades, anti-glaucoma drug research has witnessed significant progress, which results in the increase of the options of drugs treating glaucoma. In this study, we analyzed five controlled clinical studies on eye drops with BAK and BAK-free eye drops treating glaucoma and ocular hypertension. We found that the main reason for the impact factor of glaucoma transferred from the previous IOP increase to current optic nerve damage was the two clinical conditions associated with glaucoma, that is, glaucoma with ocular hypertension and normal tension glaucoma. The compliance of the primary open angle glaucoma and eye hypertension patients in the treatment period would directly influence the prognosis[9,10]. At present, lowering the increased IOP is the only way proved feasible in clinic to prevent the visual impairment and the development of glaucoma[11,12].

BAK has bacteriostasis and bactericidal effect, which had been widely used as the preservative of ophthalmic drugs since the end of the 1940s[13]. Studies of recent years have shown that the adverse reactions of IOP-lowering medication including conjunctival congestion and dryness are connected with the preservative, mainly BAK, in the medication[14,15]. A number of in vitro and in vivo experiments have confirmed that BAK can lead to patients' adverse reactions through ways like increasing the inflammatory level in the tear, inducing the apoptosis of trabecular meshwork cells and generating toxic effect on corneal endothelial and epithelial cells[16-18]. Currently, over 70% eye drops on the market (including those against intraocular hypertension) contain BAK[19]. In addition, there is another preservative slfZia. It is an ionic buffer system containing borate, sorbitol, propylene glycol and zinc which could be used as the substitute of BAK. In this research, this ionic buffer system was used to replace the traditional preservative BAK in many BAK-free eye drops. The results showed that the lack of BAK did not affect the IOP-lowering effect of these eye drops, however, their safety was worse than those containing BAK. Ryan *et al* designed an experiment to compare the antimicrobial activity of eye drops against intraocular hypertension containing these two preservatives[20]. Their research results indicated that although both the two eye drops accorded with the pharmacopoeia criterion of the United States and Japan, the bacteriostasis and bactericidal activity of eye drops containing BAK were notably better than those without BAK, which is close to the results of our research. The five literatures in this research reported the adverse reactions like conjunctival injection and allergic conjunctivitis. The analysis results indicated that the safety of eye drops containing BAK was better than those without BAK ($P<0.05$). The reason may lie in the superiority of the bactericidal activity of eye drops containing BAK over those without BAK. When patients were faced with contamination

and subsequent exposure to microorganisms during use, the former could provide a more protective environment.

In short, the present results of the controlled clinical research indicated that there was no statistical significance between the IOP-lowering effect of BAK-free eye drops and eye drops containing BAK in treating glaucoma and eye hypertension, and the safety of eye drops containing BAK was higher. However, the literature sample size of this research was small, and more high-quality, prospective randomized controlled trials are still in need as the corroboration for this conclusion.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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