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The Role of Topical Nasal Steroid in Treatment of Otitis Media with Effusion in Children: Systematic Review

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ABSTRACT

Background: otitis media with effusion is common in children and the treatment is still controversial issue. **Objective**: this study aimed to evaluate the role of topical nasal steroid in treatment of otitis media with effusion in children.

Patients and Method: this was a systematic review of the literature to collect data through searching the Medoline data base (www.pubmed .com) until March 2017 concerning the effectiveness of topical nasal steroids in treatment of otitis media with effusion in children using the different keywords in different combination.

Results: meta analysis by relative risk for persistence of OME of 0.551 with 95% CI of 0.314 to 0.966 , meta analysis by risk difference for persistence of OME of -0.229 with a 95% CI of -0.569 to -0.030 and meta analysis by odds ratio for persistence of OME of 0.214 with a 95% CI of 0.049 to 0.936, which was statistically significant favoring topical steroid over control .

Conclusion : topical nasal steroid is an effective treatment for otitis media with effusion without the complications of oral steroid , nasal steroid spray can be used for longer period, with much greater safety. It can also be helpful in controlling nasal allergy and the adenoid size, which are contributing factors in developing and recurring otitis media with effusion.

Kay words: otitis media with effusion, nasal steroid, tympanometry, otitis media with effusion treatment.

INTRODUCTION

Otitis media with effusion (OME) is defined as the presence of fluid in the middle ear without signs or symptoms of acute ear infection[1]. OME may occur during an upper respiratory infection, spontaneously because of poor Eustachian tube function, or as an inflammatory response following AOM. It happens most often between the ages of 6 months and 4 years .

In the first year of life, >50% of children have OME, increases to >60% by age 2 years[2].When children aged 5 to 6 years in primary school they are screened for OME, about 1 in 8 are found to have fluid in one or both ears. The prevalence of OME in children with Down syndrome or cleft palate, however, is much higher, ranging from 60% to 85%[3]. One potential etiologic factor for otitis media with effusion is inflammation, which may be reduced with steroids.

Other potential mechanisms of action included: directly shrinking tissue around the Eustachian tube, improving Eustachian tube surfactant secretion, and reducing middle ear effusion viscosity[4].

Treatment of OME is still a controversial issue[5]as conventional treatment approaches fail to provide satisfactory and permanent relief of otologic symptoms[6].

Standard treatments for OME, such as hearing aids and ventilation tube insertion are not trouble-free. Ventilation tube insertion involves a general anesthesia. It is associated with an improvement in the mean hearing levels of 4 to 10 dB in children with bilateral tubes during the first six months of follow up, but this diminishes with time[7]. Oral and topical nasal steroids have been used to treat otitis media with effusion. Use of oral steroids is associated with behavioral changes, increased appetite, weight gain, adrenal suppression, and a vascular necrosis of the femoral head. Topical steroids have fewer adverse effects because of minimal systemic absorption[8].Topical intranasal steroids may be safer than systemic preparations because the glucocorticoid is rapidly degraded in the nasal mucosa to less active metabolites and any unchanged drug that is absorbed is metabolized in the first pass through the liver. Systemic adverse effects are therefore less likely, while the desired anti-inflammatory effects may be similar[9].

AIM OF THE WORK

This study was systematic review of the literature to collect data through Medline search to evaluate the role of topical nasal steroid in treatment of otitis media with effusion.

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PATIENTS AND METHODS

Target question

What is the role of topical nasal steroid in treatment of otitis media with effusion in children?

Identification and location of articles

This study included published medical articles concerning effectiveness of topical nasal steroid in treatment of OME in children through searching the Medline data base (www.pubmed.com) until March 2017 using the following keywords in the different combinations: otitis media with effusion , topical steroid , tympanometry and otitis media with effusion treatment.

Over 3892 articles were found, after customizing the date, age and language they narrowed to about 690 articles, after exclusion of non-relevant articles about 12 relevant articles were found by application of inclusion criteria 4 articles were found meeting the inclusion criteria and can undergo meta-analysis.

Screening and evaluation of the articles

The screening form of articles was used by the investigators to screen the articles which were yielded by searching the author name and journal of publication. Only articles fulfilling all inclusion criteria were included for further steps of data collection, data analysis and reporting these articles were screened regarding 5 inclusive criteria. (Screen form of the articles).

Irrelevant article: articles that may have one of the keywords, but different purpose from our study (678).

Relevant articles: after exclusion of repeated and non-relevant articles. Articles which contain one or more from the above keywords (12).

Included articles: these were **4** articles which fulfilled the following inclusion criteria:

1) Patients with otitis media with effusion, which was diagnosed clinically or by tympanometry
2) Patient, who used topical nasal steroid in treatment of otitis media with effusion
3) Restricted to English language articles
4) Patients with full response compared with placebo or non-intervention control
5) Articles in the last 30 years.
6)

Table 1: included articles

No	Reference name	Year of publication	Title
1	**Cenngel and Akyol**	**2006**	The role topical nasal steroids in the treatment of children with otitis media with effusion and/or adenoid hypertrophy
2	**Bhargava and Chakravarti**	**2014**	A double blind randomized placebo controlled trial of topical intranasal mometasone furoate nasal spray in children of adenoidal hypertrophy with otitis media with effusion
3	**EL-Anwar *et al.***	**2015**	The efficacy of nasal steroids in treatment of otitis media with effusion :A Comparative study
4	**Williamson *et al.***	**2009**	A double blind randomized placebo controlled trial of topical intranasal corticosteroids in 4 to 11 year old children with persistent bilateral otitis media with effusion in primary care

Excluded articles: articles which miss one or more of the above mentioned inclusion criteria (8).

Table 2: excluded article

No	Reference name	Year of publication	Title	Cause of exclusion
1	**Barkman *et al.***	**2013**	Otitis Media with Effusion: Comparative Effectiveness of Treatments	Type of study: review article
2	**Butler and van d voot**	**2002**	Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children	Type of study: systematic review
3	**Lildholdt and Kortholm**	**1982**	Beclomethasone nasal spray in the treatment of middle-ear effusion - a double-blind study	More than 30 year
4	**Liewellyn *et al.***	**2014**	Interventions for adult Eustachian tube dysfunction: a systematic review	Type of study: systematic review & adult Pt
5	**Shapiro *et al.***	**1982**	Treatment of persistent eustachian tube dysfunction in children with aerosolized nasal dexamethasone phosphate versus placebo	More than 3 years
6	**Simpson *et al.***	**2011**	Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children	Type of study: systematic review
7	**Thomas *et al.***	**2006**	Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children	Systematic review
8	**Tracy *et al.***	**1998**	Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion	Use topical steroid + antibiotic

Data collection

Information was gathered for each individual study on the ability of topical nasal steroids in treatment of otitis media with effusion in children.

Data analysis

Statistical analysis was done by using MedCalc© version 15.8 (MedCalc© Software bvba, Ostend, Belgium).

Testing for heterogeneity:

Studies included in meta-analysis were tested for heterogeneity of the estimates using the following tests:

1. **Cochran Q chi square test**: a statistically significant test (p-value <0.1) denoted heterogeneity among the studies.
2. **Squared (I^2) index** was calculated as follows:

$$\boldsymbol{I = \left(\frac{Q-df}{Q}\right) * 100\%}$$

The I-squared was interpreted as follows:

0% to 40%: might not be important

30% to 60%: may represent moderate heterogeneity

50% to 90%: may represent substantial heterogeneity

75% to 100%: considerable heterogeneity

Effect size estimation:

Effect size for binary outcome measures was expressed as risk ratio (RR), risk difference (RD) and odds ratio (OR) with their 95% confidence limits (95% CI).

Pooling of estimates:

Estimates from included studies were pooled using both the Mantel-Haenszel fixed-effects method (FEM) and the Der Simonian Laird random-effects method (REM). In view of the presence of significant heterogeneity, the REM was considered.

Examination of publication bias

Publication bias was assessed by examination of funnel plots. A funnel plot is a plot of the estimated effect size (OR) on the horizontal axis versus the standard error (SE) for the effect size as a measure of study size on the vertical axis.

Large studies appear toward the top of the graph and tend to cluster near the mean effect size.

Smaller studies appear toward the bottom of the graph and (since there was more sampling variation in effect size estimates in the smaller studies) was dispersed across a range of values.
In the absence of publication bias the studies were expected to be distributed symmetrically about the combined effect size. By contrast, in the presence of bias, it is expected that the bottom of the plot would show a higher concentration of studies on one side of the mean than the other. This would reflect the fact that fewer studies (which appear toward the bottom) were more likely to be published if they have larger than average effects, which makes them more likely to meet the criterion for statistical significance. The Duval and Tweedie's trim and fill method was used toimpute the number and effect size of missing studies and to recalculate the estimated effect size with the imputed studied included in the meta analysis.

Level of significance

A two-sided p-value <0.05 denote statistical significance.

The study was approved by the Ethics Board of Ain Shams University.

RESULTS

The four studies included in this study was level 1 of evidence and two of these studies were double blind prospective randomized study.

Table 3: meta-analysis by relative risk for persistence of OME

Study	***Topical steroid***	***Control***	***Relative risk***	***95% CI***	***z***	***P***
Cengel and Akyol (2006)	37/64	47/55	0.677	0.534 to 0.857		
Bhargava and Chakravarti (2014)	2/30	16/32	0.133	0.033 to 0.532		
El-Anwar *et al.* (2015)	12/40	32/40	0.353	0.216 to 0.577		
Williamson *et al.* (2009)	57/96	54/98	1.078	0.845 to 1.375		
Total (fixed effects)	108/230	149/225	0.690	0.585 to 0.813	-4.433	<0.001
Total (random effects)	***108/230***	***149/225***	***0.551***	***0.314 to 0.966***	***-2.082***	***0.037***
Test for heterogeneity						
Q	25.496					
DF	3					
Significance level	P < 0.0001					
I^2 (inconsistency)	88.2%					
95% CI for I^2	72.3% to 95.0%					

Table 3 showed the results of meta-analysis for persistence of OME by relative risk. There was a significant heterogeneity of the estimates across included studies (Cochran Q = 25.496, DF = 3, p-value <.0001; I^2, 88.2%). Pooling of estimates using a random effects model showed a relative risk of 0.551 with a 95% CI of 0.314 to 0.966, which was statistically significant (p-value = .037) favoring topical steroid over control (**Figure 1**).

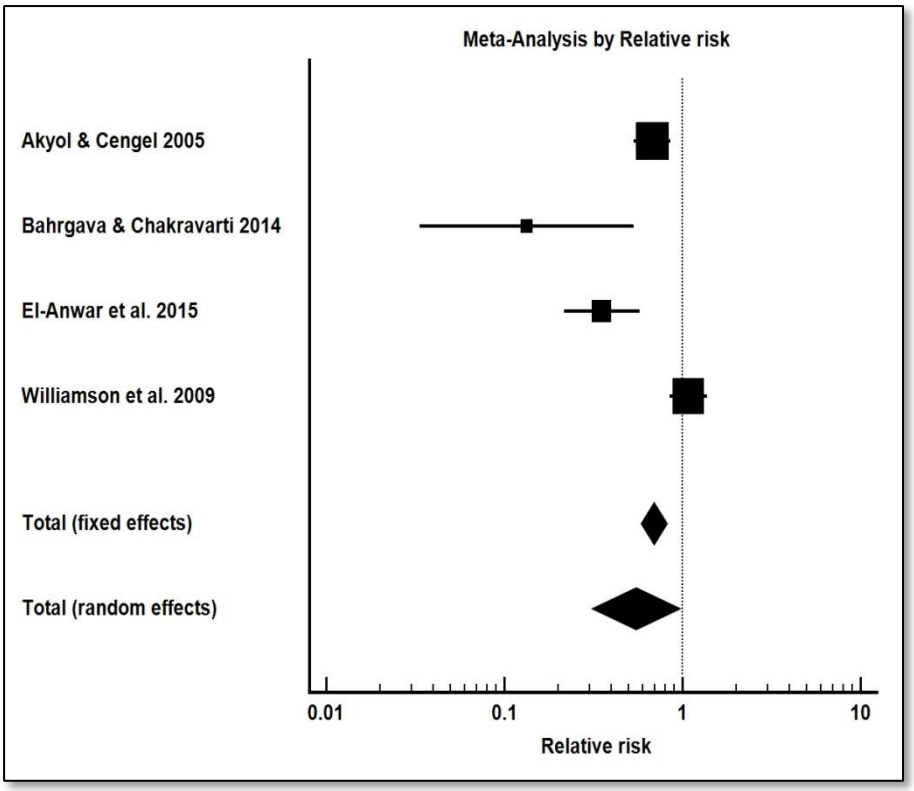

Figure 1: forest plot showing the results of meta-analysis for persistence of OME by relative risk. There was a significant heterogeneity of the estimates across included studies (Cochran Q = 25.496, DF = 3, p-value <.0001; I^2, 88.2%). Pooling of estimates using a random effects model showed a relative risk of 0.551 with a 95% CI of 0.314 to 0.966, which was statistically significant (p-value = .037) favoring topical steroid over control.

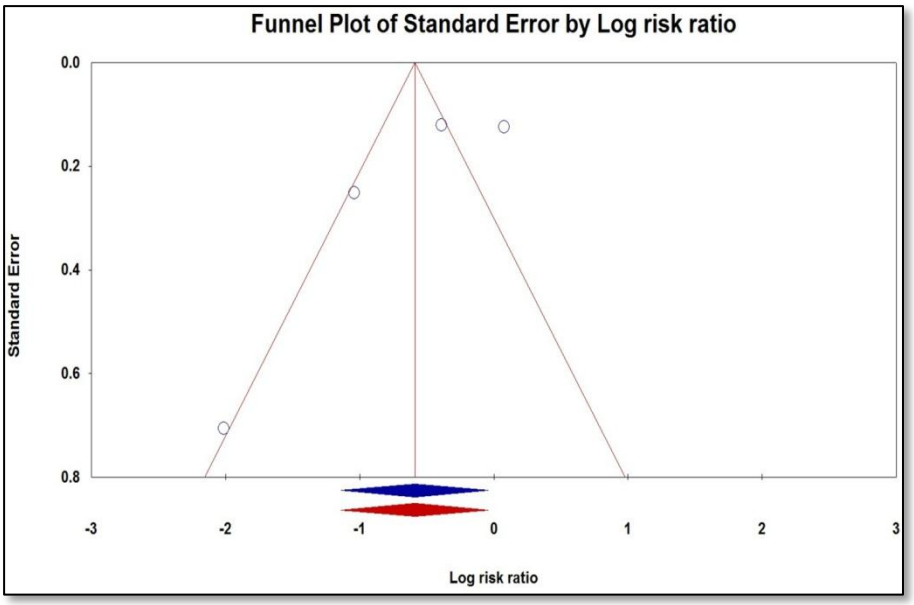

Figure 2: funnel plot showed the results of meta-analysis for persistence of OME by relative risk. Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.551 (0.314, 0.966). Using trim and fill these values were unchanged denoting no possibility of publication bias.

Table 4: meta-analysis by risk difference for persistence of OME

Study	*Topical steroid*	*Control*	*Risk Difference*	*95% CI*	*z*	*P*
Cengel and Akyol (2006)	37/64	47/55	-0.276	-0.429 to -0.124		
Bhargava and Chakravarti (2014)	2/30	16/32	-0.433	-0.628 to -0.238		
El-Anwar *et al*. (2015)	12/40	32/40	-0.550	-0.730 to -0.370		
Williamson *et al.* (2009)	57/96	54/98	0.0427	-0.096 to 0.182		
Total (fixed effects)	108/230	149/225	-0.210	-0.292 to -0.127	-4.976	<0.001
Total (random effects)	***108/230***	***149/225***	***-0.299***	***-0.569 to -0.030***	***-2.178***	***0.029***
Test for heterogeneity						
Q	32.167					
DF	3					
Significance level	P < 0.0001					
I^2 (inconsistency)	90.7%					
95% CI for I^2	79.2 to 95.8%					

Table 4 showed the results of meta-analysis for persistence of OME by risk difference. There was a significant heterogeneity of the estimates across included studies (Cochran Q = 32.167, DF = 3, p-value <.0001; I2, 90.7%). Pooling of estimates using a random effects model showed a risk difference of -0.299 with a 95% CI of -0.569 to -0.030, which was statistically significant (p-value = .029) favoring topical steroid over control (**Figure 3).**

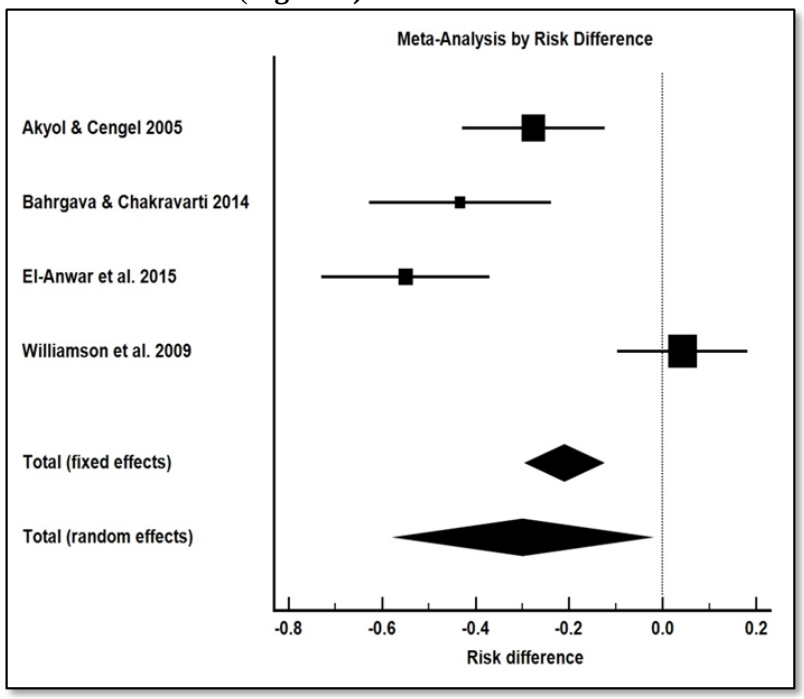

Figure 3: forest plot showing the results of meta-analysis for persistence of OME by risk difference. There is significant heterogeneity of the estimates across included studies (Cochran Q = 32.167, DF = 3, p-value <.0001; I^2, 90.7%). Pooling of estimates using a random effects model showed a risk difference of -0.299 with a 95% CI of -0.569 to -0.030, which was statistically significant (p-value = .029) favoring topical steroid over control.

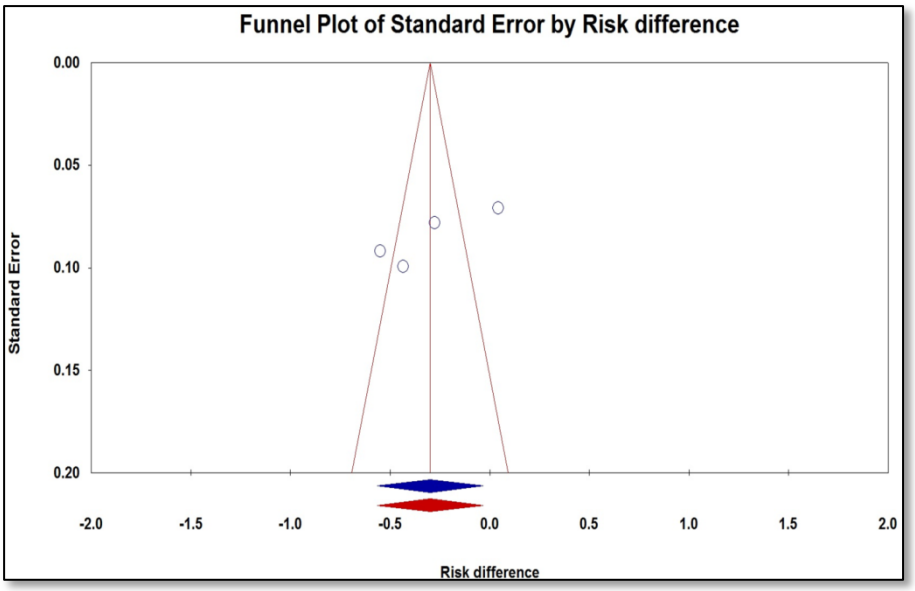

Figure 4: funnel plot showing the results of meta-analysis for persistence of OME by risk difference. Under the random effects model the point estimate and 95% confidence interval for the combined studies was -0.299 (-0.569, -0.030). Using Trim and Fill these values were unchanged denoting no possibility of publication bias.

Table 5: meta-analysis by odds ratio for persistence of OME

Study	***Intervention***	***Controls***	***Odds ratio***	***95% CI***	***z***	***P***
Cengel and Akyol (2006)	37/64	47/55	0.233	0.095 to 0.573		
Bhargava and Chakravarti (2014)	2/30	16/32	0.0714	0.015 to 0.351		
El-Anwar *et al.* (2015)	12/40	32/40	0.0756	0.025 to 0.227		
Williamson *et al.*(2009)	57/96	54/98	1.191	0.674 to 2.105		
Total (fixed effects)	108/230	149/225	0.414	0.281 to 0.610	-4.459	<0.001
Total (random effects)	***108/230***	***149/225***	***0.214***	***0.049 to 0.936***	***-2.048***	***0.041***
Test for heterogeneity						
Q	28.6306					
DF	3					
Significance level	P < 0.0001					
I^2 (inconsistency)	89.52%					
95% CI for I^2	75.98 to 95.43					

Table 5 showed the results of meta-analysis for persistence of OME by odds ratio. There is significant heterogeneity of the estimates across included studies (Cochran Q = 28.631, DF = 3, p-value <.0001; I2, 89.5%). Pooling of estimates using a random effects model showed an odds ratio of 0.214 with a 95% CI of 0.049 to 0.936, which was statistically significant (p-value = .041) favoring topical steroid over control (**Figure 5).**

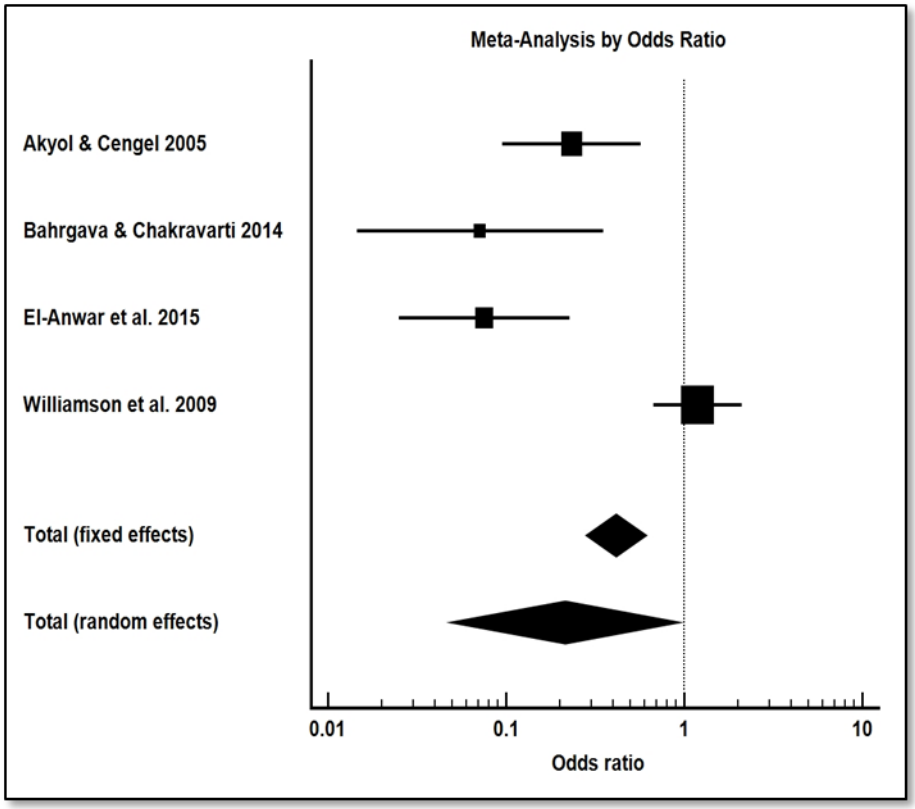

Figure 5: forest plot showing the results of meta-analysis for persistence of OME by odds ratio. There is significant heterogeneity of the estimates across included studies (Cochran Q = 28.631, DF = 3, p-value <.0001; I2, 89.5%). Pooling of estimates using a random effects model showed an odds ratio of 0.214 with a 95% CI of 0.049 to 0.936, which was statistically significant (p-value = .041) favoring topical steroid over the control.

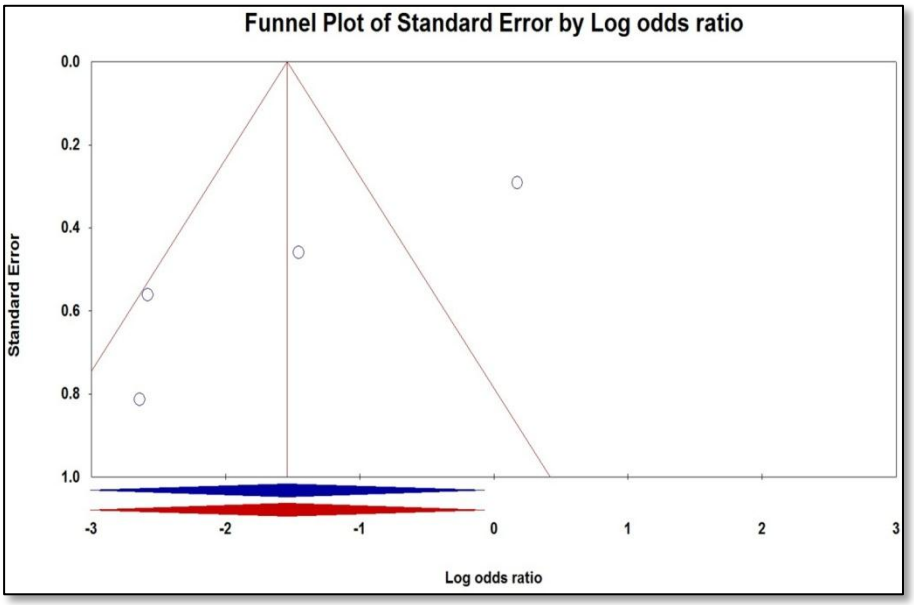

Figure 6: funnel plot showing the results of meta-analysis for persistence of OME by odds ratio. Under the random effects model the point estimate and 95% confidence interval for the combined studies was 0.214 (0.049, 0.936). Using Trim and Fill these values are unchanged denoting no possibility of publication bias.

DISCUSSION

Otitis media with effusion (OME) is defined as effusion in the middle ear without signs and symptoms of an acute infection. It is a leading cause of hearing impairment in children, and its early and proper management can avoid hearing and speech impairment, which can cause developmental delay in children[5]. Treatment of OME is still a controversial issue, as conventional treatment approaches fail to provide satisfactory and permanent relief of otologic symptoms. There is lack of proven effectiveness of the commonly given treatments, such as antibiotics, decongestants, and antihistamines, which are potentially harmful and have disadvantages[6].

In the current study, there was a significant heterogeneity of the estimates across the included studies. Pooling of estimates using a random effects model showed a relative risk of 0.551 with a 95% CI of 0.314 to 0.966 which was statistically significant favoring topical steroid over control. Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.551. Using Trim and Fill, these values are unchanged denoting no possibility of publication bias.

This result agrees with **results of Cengel and Akyol[10].** Who conducted a prospective, controlled, randomized clinical study and level 1 of evidence on total of 122 children (3 – 15 years old) who were on the waiting list for adenoidectomy and / or ventilation tube placement were enrolled into the study and control groups. The study group (67 patients with adenoid hypertrophy, 34 of them with OME) received intranasal mometasone furoate monohydrate 100 mcg / day, one spray in each nostril once a day for 6 weeks. The control group (55 patient with AH, 29 of them with OME) was followed up without any treatment. All patients were evaluated at 0 and 6 weeks. The assessment of each patient included history, a symptoms questionnaire, a skin prick test, a tympanogram, if possible a pure tone audiogram, otoscopic examination and endoscopic examination. Adenoidal hypertrophy and the upper air way were evaluated by flexible endoscopy. Resolution of OME in the study group (42%) was significantly higher than that in the control group (14.5%) according to the tympanogram. Forty five patients (67.2%) with adenoid hypertrophy in the study group showed significant decreases in adenoid size according to the endoscopic evaluation compared with the control group. A significant improvement in obstructive symptoms was seen in treatment group. These results indicate that nasal mometasone furoate monohydrate treatment can significantly reduce adenoid hypertrophy and obstructive symptoms and it is a useful alternative to surgery, at least in short term for OME, also this result agreeswith another two studies **Bhargava and Chakravart.[11] and EL-Anwar *et al.* [12],** but disagrees with results of **Williamson *et al.*[13]** who concluded that topical nasal steroids are unlikely to be an effective treatment for otitis media with effusion in the primary care setting.

In the current study, there is significant heterogeneity of the estimates across included studies. Pooling of estimates using a random effects model showed a risk difference of -0.299 with a 95% CI of -0.569 to -0.030 which was statistically significant favoring topical steroid over control. Under the random effects model the point estimate and 95% confidence interval for the combined studies was -0.299. Using Trim and Fill these values were unchanged denoting no possibility of publication bias.

This result agrees with results of **Bhargava and chakravarti[11]** who conducted prospective randomized double blind placebo controlled study and level 1 of evidence on total of 100 children (2-12 years old) having grade 3 and 4 adenoidal hypertrophy with duration of symptoms for at least 3 months and not responsive previous medical treatment were enrolled. 62 children of adenoidal hypertrophy were diagnosed with bilateral otitis media with effusion on otoscopy and tympnogram (type B or C2) were divided randomly into study and control groups. The study group included 30 patients with bilateral otitis media with effusion received initial treatment of 2 puffs of mometasone furoate nasal spray (50mcg /puff) in each nostril once a day for the first 8 weeks. This was followed by a maintenance dose of 2 puffs of mometasone furoate nasal spray in each nostril on alternate days for 16 weeks. The control group 32 patients with bilateral otitis media with effusion received initial treatment of 2 puffs of saline nasal spray in each nostril once a day for 8 weeks, followed by 2 puffs of saline nasal spray on alternate days for 16 weeks. Follow up was done at every 2 weeks for the first 8 weeks and then monthly for the next 16 weeks. After completion of therapy, patients were evaluated with symptoms score. Otoscopic picture, change in adenoid size, PTA and tympanogram. Resolution of OME in study group (93%) was statistiscally significant higher than in the control group (50%).A significant improvement in hearing and symptoms was seen in the studied group($p<0.04$). Statistically significant change in

quality of life was seen with mometasone nasal spray (37.11) as compared saline nasal spray (11.02)(p value 0.0001). On the basis of thiese results they advocated the use of mometasone furoate nasal spray in the management of otitis media with effusion with adenoidal hypertrophy. Also this result agrees with another two studies **Cengel and Akyol[10] and El-Anwar *et al.* [12],** but disagrees with those of **Williamson *et al*.[13].**

In our study, there was a significant heterogeneity of the estimates across the included studies. Pooling of estimates using a random effects model showed an odds ratio of 0.214 with a 95% CI of 0.049 to 0.936 which was statistically significant favoring topical steroid over control. Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.214. Using Trim and Fill these values are unchanged denoting no possibility of publication bias.

This result agrees with results of **El-Anwar *et al*.[12]** conducting randomized placebo controlled study and level 1 of evidence on 60 children (6-14 years old) having bilateral otitis media with effusion with type B tympanogram and conductive hearing loss. The patients were divided into three equal groups. In group 1, 20 patients received mometasone furoate spray, one puff in each nostril daily for 3 months. In group 2, 20 patients received oral prednisolone, 5 mg three times per day for 3 weeks then gradual withdrawal over 2 weeks. In group 3, 20 patients received nasal saline spray, one puff in each nostril daily for 3 months. Otoscopic examination, basic audiological evaluation including pure tone audiometry, and tympanogram were performed before treatment and repeated at 3 and 6 months after treatment. Resolution of OME in group 1 was 70%, in group 2 it was 65% and in group 3 it was 20%. They concluded that nasal steroid spray can be used as an effective treatment for OME, giving a significant result similar to systemic steroid but without the hazard of corticosteroid side effects. It could be used for longer periods to maintain its effect for persistent relief of OME. Also this result agrees with another two studies **Cengel and Akyol[10] and Bhargava and Chakravarti [11],** but disagreeswith **Williamson *et al.* [13].**

Williamson *et al*.[13] reported prospective randomized double blind placebo controlled trial and level 1 of evidence on 217 children (4-11years old) presenting with one or more episode of otitis media or ear related problems in the previous 12 months and with bilateral otitis media with effusion confirmed by a research nurse using otoscopy plus tympanomtry (B/B or B/C2) were enrolled into two groups. In the studied group, 105 patients received mometasone nasal spray one puff in each nostril daily for three months. In the control group, 112 patients received placebo nasal spray one puff in each nostril daily for three months. Resolution or cure of bilateral glue ear (B/B or B/C2 tympnograms) was defined by children with residual unilateral OME only (B/A or C1 or C2/A or C1) or complete bilateral clearance (A /C1 or A or C1/A or C1). An overall 40.6% of the topical steroid group and 44.9% of the placebo group were cured in one or both ears at 1 month. At three months, 58.1% of the topical steroid group and 52.3% of the placebo group were cured. At nine months 55.6% of the topical steroid group and 65.3% of the placebo group were cured. They concluded that topical nasal steroids were unlikely to be an effective treatment for otitis media with effusion in the primary care setting. This result disagrees with results of **Cengel and Akyol[10] , Bhargava and Chakravarti [11] and El-Anwar *et al*.[12]**this result may be due to is that the primary care sample was not severe to show any benefit of treatment, also if adherence had been poor in the study, this might have explained this negative findings**.**

CONCLUSION

Topical nasal steroid is an effective treatment for otitis media with effusion without the complications of oral steroid. Nasal steroid spray can be used for longer period, with much greater safety. It could also be helpful in controlling nasal allergy and the adenoid size, which are contributing factors in developing and recurring otitis media with effusion.

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