REVIEW ARTICLE

Meta-analysis of studies comparing adjuvant dexamethasone to glycerol to improve clinical outcome of bacterial meningitis

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Background: Neurological complications are a problematic factor in acute bacterial meningitis; hence, its prevention is the key to ensure the success of meningitis treatment. Glycerol and dexamethasone are both applied in this regard. Oral glycerol is an appropriate alternative instead of intravenous dexamethasone because it does not have problems related to intravenous injection, the high cost, and drug complications. The main objective of this study was to compare the efficacy of adjuvant dexamethasone versus glycerol in order to improve the clinical outcome of bacterial meningitis. **Materials and Methods:** We conducted a search on the available resources including PubMed, Ovid, Elsevier, Cochrane, and another search engines such as Google till 2014. All clinical trials that were performed in the field of comparing the effectiveness of the two drugs and met the inclusion criteria were gathered and after extraction the relative risk (RR) values, the pooled RR was calculated. The main outcome was neurological complications. Meta-analysis of the data was performed in Stata version 11.2 using both fixed and random effect models, weighting each study by inverse of variance. **Results:** In 5 comparative studies (1,340 patients), the rate of neurological complications of glycerol compared to that of dexamethasone was 1.02 [95% confidence interval (CI), 0.98 compared to 1.12]. The rate of neurological complications of dexamethasone compared to dexamethasone + glycerol was 1 (95% CI, 0.97 compared to 1.03), dexamethasone compared to placebo was 0.99 (95% CI, 0.97 compared to 1.03), glycerol compared to glycerol + dexamethasone was 0.98 (95% CI, 0.94 compared to 1.02), and glycerol compared to placebo was 0.97 (95% CI, 0.94 compared to 1.01). In these studies, no difference was reported between dexamethasone and glycerol in terms of reducing neurological complications. **Conclusion:** Although there were some weak evidences for the nonstatistical significant effect of glycerol in the prevention of neurologic complication after meningitis, there was no difference between glycerol and dexamethasone.

Key words: Dexamethasone, glycerol, meningitis, neurological complications

How to cite this article: Vaziri S, Mansouri F, Sayad B, Ghadiri K, Torkashvand E, Rezaei M, Najafi F, Azizi M. Meta-analysis of studies comparing adjuvant dexamethasone to glycerol to improve clinical outcome of bacterial meningitis. J Res Med Sci 2016;21:22.

INTRODUCTION

Bacterial meningitis is a serious infection of the nervous system[1] and hearing impairment is the most common complication of this disease[2-4] although other neurological complications such as quadriplegia, spasticity, and mental retardation are also observed after meningitis.[5-8]

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/1735-1995.179890

Hearing defects in children have become a growing problem in developing countries, especially in those countries where there are not enough resources for providing rehabilitation facilities and hearing aids. The best solution to prevent bacterial meningitis and its complications is the use of vaccine.[9,10] The conjugate vaccine against three common causes of meningitis, i.e., *Haemophilus influenzae, Streptococcus pneumoniae,* and *Neisseria meningitidis* has a significant effect in

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Received: 10-09-2015; **Revised:** 08-12-2015; **Accepted:** 09-02-2016

reducing the incidence of meningitis. However, due to the extremely high demand for the vaccine and the relatively less access to it across the world, its application has not been possible.[11,12] Furthermore, new antimicrobial factors such as the third-generation cephalosporins have failed in the effective prevention of neurological complications of meningitis.[13] Hence, doctors believe that these patients may benefit from complementary medicine with antimicrobial treatments.[14-18] The fact is that the pathophysiologic mechanisms that cause neurological complications of meningitis and hearing defects have not yet been fully recognized[19-22] but intracerebral edemas with decreased cerebral perfusion, ischemia, and nerve injury have been proposed as the most important factors. In fact, the risk of cerebral edema intensifies when antimicrobial therapy is initiated due to the release of cellular components and toxic agents.[23] Because the severe inflammatory response in the subarachnoid space can have an important role in the damages caused by meningitis,[24-26] someone may conclude that steroidal and nonsteroidal anti-inflammatory drugs are effective in inhibiting this inflammation.[27-29] Hence, dexamethasone has been suggested as an anti-inflammatory drug in preventing neurological complications although the results of various studies have been different in this area.[28-31] In fact, in different studies the desirable effect of dexamethasone as a complementary therapy, especially in Haemophilus influenza meningitis in children has been proved.[14-18] Furthermore, because of the increase in intracranial pressure during meningitis, the use of hyperosmolar agents such as glycerol is also strongly recommended.[31,32] Glycerol has been widely used as an osmotic dehydrating agent and has been applied as a safe drug for children and adults in the treatment of cerebral edema, increased intracranial pressure due to cerebral infarction or intracranial hemorrhage, brain tumors, encephalopathy, Reye's syndrome, and encephalitis. This drug is cheap and readily available and is administered orally. The osmotic property of glycerol decreases the increased intracranial pressure during meningitis.[32] Considering that various studies have reported different effectiveness for dexamethasone and glycerol in patients with meningitis, we conducted this study to compare the efficacy of adjuvant dexamethasone and/or glycerol in improving the clinical outcome of bacterial meningitis.

MATERIALS AND METHODS

Identification of studies and study selection

In the available published resources PubMed, Ovid, Elsevier, Cochrane, and search engines such as Google, a search was begun with the keywords meningitis, neurological sequelae, dexamethasone, glycerol, and then other keywords such as deafness and hearing loss were added. Meanwhile, journals related to the topic were also studied. After reviewing the titles and abstracts, 268 articles were obtained. Of these articles, 46 papers that compared the neurological complications of bacterial meningitis prevention by glycerol or dexamethasone were selected. Furthermore, in order to review all studies, references of the mentioned articles were also reviewed. These articles were reviewed by two groups, including the main researcher and colleagues. Finally, clinical trials that compared the effectiveness of oral glycerol to intravenous dexamethasone in preventing neurological complications of bacterial meningitis were included in this study.

Data extraction

The data were extracted based on neurological complications. Neurological complications that were evaluated in our study included the degree of hearing loss, the level of reduction in intracranial pressure, or neurological damage such as paralysis of the limbs and increased plasma osmolality. The studies that only examined the results of the administered dexamethasone and did not compare the two drugs were excluded.[1,14,16-19,29,33-47] Meanwhile, the studies with objectives other than those of our study were also excluded, for example, if the studies showed the stroke rate reduction,[48] studies on animals,[49-52] or the studies that only focused on glycerol and were not comparative.[31,53-64] In the end, the articles were evaluated by Jadad criteria that are used in assessing the quality of clinical trials and five papers[11,30,32,65,66] that were based on JADAD criteria and had scores higher than 3 were selected and included in the study [Figure 1]. If there was a serious disagreement between the two groups about some articles in terms of inclusion in the study, an agreement was made in a joint session.

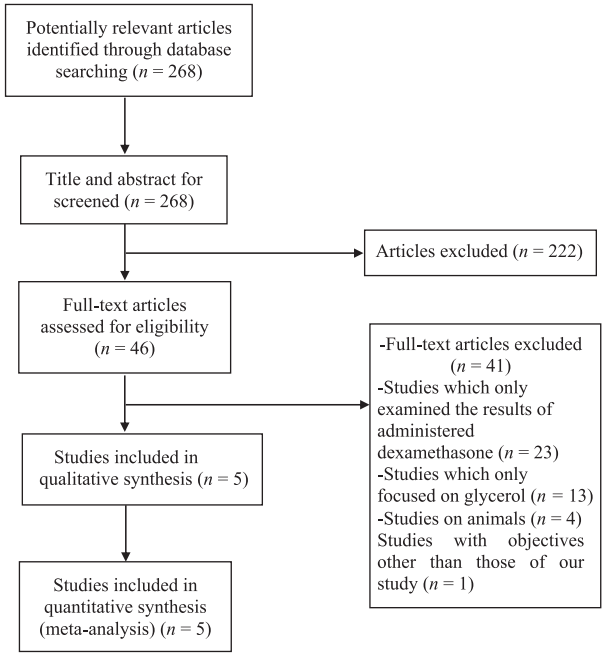

Figure 1: Flow diagram for study selection

Eventually, the two groups separately extracted the required information and the accuracy of the information extraction was also discussed step by step in the joint session and an agreement was made and the final data were collected for the purpose of analysis.

Data synthesis and meta-analysis

To compare neurological complications in both drugs, the relative risk (RR) index was used. After entering the data related to the risk of neurological complications of dexamethasone compared to glycerol and calculation of the standard error of each RR, the studies were combined with both fixed and random effect models so that ultimately the final RR could be calculated. For the meta-analysis, inverse variance method was used by the fixed method and in the random effect model Der Simonian and Laird method was used. For all comparisons, a forest plot diagram was mapped and the results were presented in the form of RR and 95% confidence intervals (CIs). Heterogeneity on RR estimation was tested among different studies by the Q statistic (significant level less than 0.01). Moreover, statistic value I^2 indicating little heterogeneity between the studies was also calculated. In order to investigate possible publication bias, we uses Egger's and Begg's tests at the 5% significance level. All analyses were done using Stata version 11.2.

RESULTS

Study characteristics

Finally, five studies with a total number of 1,340 patients were included in our study. Because in one article (Peltola, 2007) two ultimate goals of our study were examined separately, i.e., decrease in neurological complications and hearing loss, the results of both the studies were entered separately into our study and in total we meta-analyzed six studies. The results of extracted data from the entered articles are summarized in Table 1.

The oldest study with a sample size of 122 was performed in 1995 and the latest study with a sample size of 383 was conducted in 2009.

In the smallest study, the sample size was 36 and in the Peltola study the sample size was 654, which was the largest study [Table 1].

Main results and findings from meta-analyses

In the comparison of dexamethasone to glycerol in reducing neurological complications of bacterial meningitis among the six studies and based on the fixed effect model, it was shown that no statistically significant difference existed between the two drugs in terms of the incidence rate of

Table 1: Characteristics of the five studies included in the analysis and pooled RR (CI: 95%)

Year	Author	Dexamethasone (*N*)	GLY orally (*N*)	DXM plus GLY (*N*)	Placebo (*n*)	Dose DXM	Dose GLY	The aim	RR (CI: 95%)
1995	Kilpi	32	30	34	26	1.5 mg/kg/day	4.5 mg/kg/day	Preventing hearing impairment	4.69 (0.30-72.94)
2006	Snakar	12	12	19	12	0.15 mg/kg/qid	1.5 mg/kg/qid	Preventing hearing impairment	2.29 (0.43-12.14)
2007	Peltola (1)	166	166	159	163	0.15 mg/kg/qid	1.5 mg/kg/qid	Neurologic abnormalities	1.48 (0.82-2.67)
2007	Peltola (2)	135	136	132	131	0.15 mg/kg/qid	1.5 Mg/kg/qid	Prevented deafness	1.29 (0.77-2.17)
2008	Singhi	8	9	11	8	0.6 mg/kg/day	6 g/kg/day	Serum osmolality	1.02 (0.97-1.08)
2009	Peltola	191	92	95	95	0.15 mg/kg/qid	1.5 mg/kg/qid	Preventing hearing impairment	1.02 (0.97-1.07)

neurological complications. Hence, the incidence rate of neurological complications of dexamethasone was only 2.1% higher than glycerol, which was certainly not statistically and clinically significant.

(RR: 1.021, 95% CI: 0.98-1.12%) [Figure 2].

It should be noted that *Q* test results showed there was no significant heterogeneity among the different studies ($P = 0.36$). The results of test I^2 also confirmed the previous results in that it indicated the variance between the studies to be 0.005.

The results of Egger's test and Begg's test showed that in the current study, there was no publication bias (*P* values were 0.188 and 0.672, respectively) [Figure 3].

In the comparison of dexamethasone to dexamethasone + glycerol in reducing neurological complications of bacterial meningitis in the six studies and based on the random effect model, it was indicated that no statistically significant difference existed between the two drugs in terms of the incidence rate of the neurological complications.

(RR: 1, 95% CI: 0.97-1.03%) [Figure 4].

It should be noted that *Q* test results showed that there was no significant heterogeneity among the different studies ($P = 0.648$). The results of test I^2 also confirmed the previous results in that it indicated the variance among studies to be 0.00.

In the comparison of dexamethasone to placebo in reducing neurological complications of bacterial meningitis in the six studies and based on the random effect model, it was indicated that there was no statistically significant difference between the two drugs in terms of the incidence rate of the neurological complications.

(RR: 0.99, 95% CI: 0.97-1.03%) [Figure 5].

It should be noted that *Q* test results showed that there was no significant heterogeneity between different studies ($P = 0.477$).

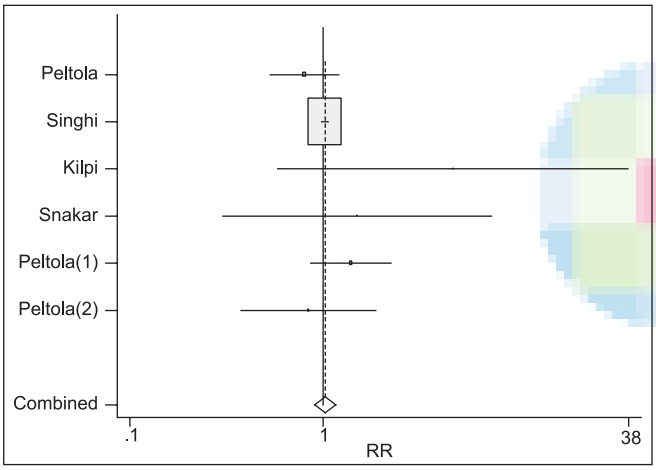

Figure 2: The comparison of dexamethasone with glycerol based on the random effect model

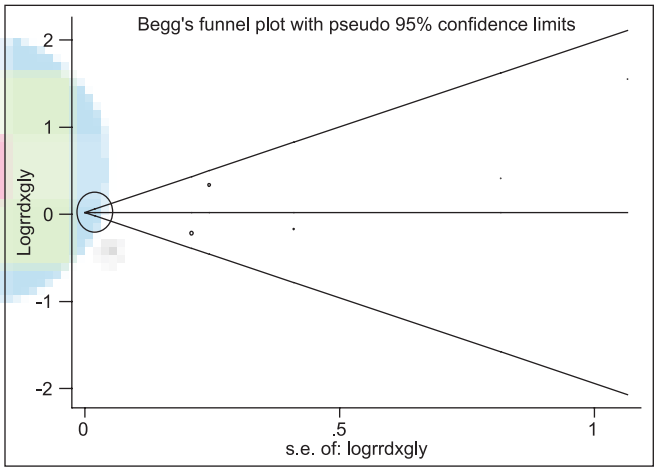

Figure 3: Funnel plot with pseudo 95% confidence limits by event rate

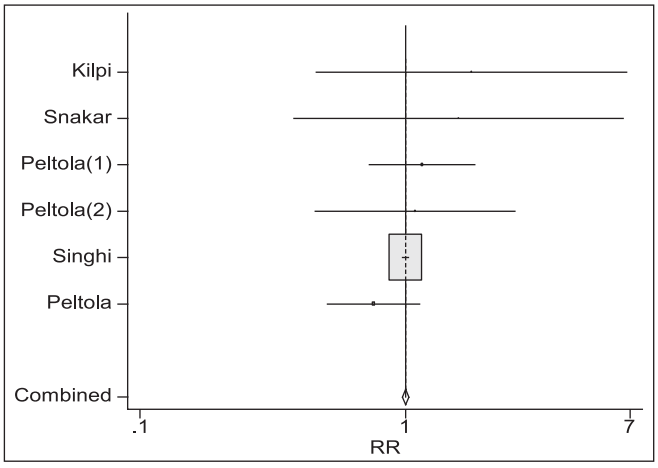

Figure 4: The comparison of dexamethasone with dexamethasone + glycerol based on the random effect model

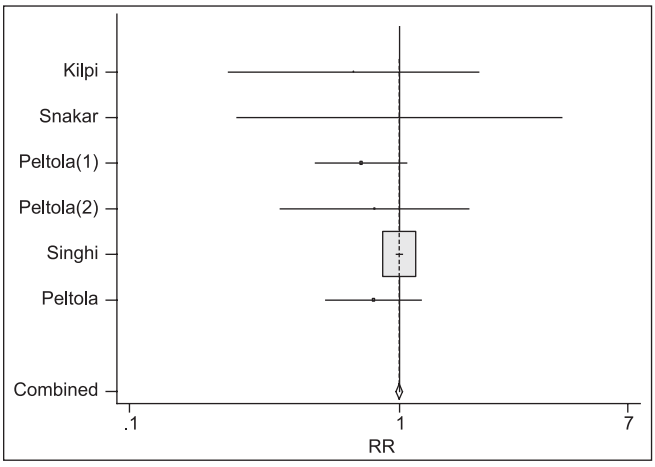

Figure 5: The comparison of dexamethasone with placebo based on the random effect model

The results of test I^2 also confirmed the previous results in that it indicated that the variance among studies was 0.000.

In the comparison of glycerol to glycerol + dexamethasone in reducing neurological complications of bacterial meningitis in the six studies and based on the random effect model, it was indicated that no statistically significant difference existed between the two drugs in terms of incidence rate of the neurological complications.

(RR: 0.98, 95% CI: 0.94-1.02%) [Figure 6].

It should be noted that *Q* test results showed that there was no significant heterogeneity between different studies ($P = 0.901$). The results of test I^2 also confirmed the previous results in that it indicated that the variance among studies was 0.000.

In the comparison of glycerol to placebo in reducing neurological complications of bacterial meningitis in the six studies and based on the random effect model, it was indicated that there was no statistically significant difference between the two drugs in terms of incidence rate of the neurological complications.

(RR: 0.97, 95% CI: 0.94-1.01%) [Figure 7].

Despite this result, as it can be seen in Figure 6 it seems that glycerol is more effective than placebo in reducing neurological complications. It should be noted that *Q* test results showed there was no significant heterogeneity among the different studies ($P = 0.044$). The result of test I^2 also confirmed the previous results in that it indicated that the variance between studies was 0.060.

DISCUSSION

In this study, a comparison between the effectiveness rate of dexamethasone and glycerol in reducing neurological complications of bacterial meningitis was made, and according to the results there was no statistically significant difference between the two drugs. Although this study did not prove the superiority of glycerol over dexamethasone, given that the figures do not imply its less effectiveness than dexamethasone in the above area, it can be concluded that oral glycerol compared to intravenous dexamethasone can be as successful as dexamethasone in reducing neurological complications of acute bacterial meningitis such as deafness in children. The advantages of glycerol compared to dexamethasone are ease of its administration, more cooperation from and acceptance by the patient, lower complications, and lower cost.

In many clinical trials and meta-analyses, dexamethasone has been compared to placebo and different results have been obtained.[33-47] In the meta-analysis conducted in 1998, Peter Mclntyre *et al*. examined 11 clinical trials and showed that dexamethasone is more effective than placebo in pneumococcal meningitis and is effective in Haemophilus influenza only if it is administered very early (less than 2 h from the onset of disease).[34]

In another meta-analysis in 2010 by Vandebeek, five clinical trials involving a total of 2,029 patients were examined. The results showed that dexamethasone compared to placebo could not reduce neurological complications and mortality.[47] In another study conducted in 2012 by Kameshwar Prasad, the effect of dexamethasone in reducing neurological complications compared to placebo was only indicated in special circumstances such as pneumococcal meningitis or only in rich countries.[67] According to the results of the previous studies and the results obtained in our study, the role of dexamethasone in reducing neurological complications of bacterial meningitis is generally unknown but it seems that it can be effective in certain circumstances such as pneumococcal meningitis. In this

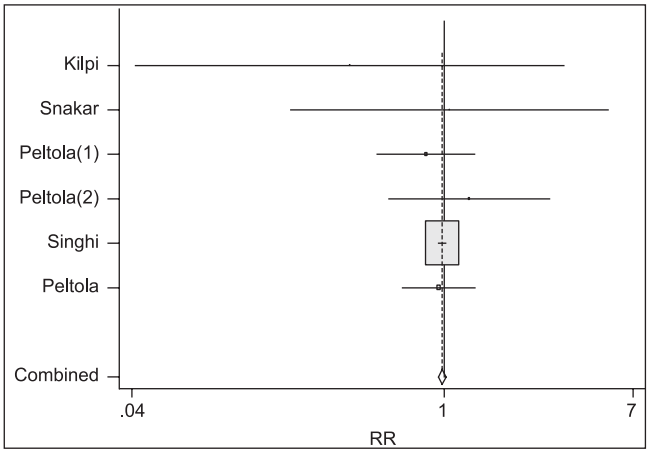

Figure 6: The comparison of glycerol with glycerol + dexamethasone based on the random effect model

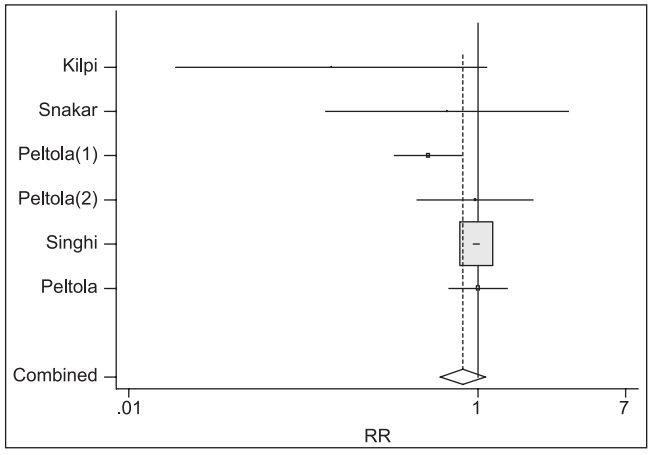

Figure 7: The comparison of glycerol with placebo based on the random effect model

study, we did not deal with the causes of meningitis separately and only examined all the factors that cause meningitis; so we cannot comment on the effective role of dexamethasone in particular types of meningitis, for example, pneumococcal meningitis.

In the current study, glycerol was compared to placebo and no statistically significant difference was observed between these in reducing neurological complications. Not many studies have compared these two drugs but in two clinical trials on animals, it was indicated that there was no difference between glycerol and placebo in reducing neurological complications. Though in our study there was no significant difference between the two drugs according to RR: 0.97, 95% CI: 0.94-1.01%, it seems that glycerol is more effective than placebo in reducing neurological complications.

In this study, the comparison of glycerol to glycerol + dexamethasone as well as dexamethasone with glycerol + dexamethasone was performed and no significant difference was observed between the two groups. Till date, no clinical trial has been conducted in this field that could be compared to our results.

One of the features of our study was to compare the therapeutic use of dexamethasone and glycerol that has not yet been addressed in meta-analysis studies. We could not examine the causes of meningitis separately because this separation was not addressed in most studies. Another limitation of our study was the lack of access to non-English articles although it did not seem that there was a study in this field in another language.

CONCLUSIONS

Due to the fact that the effect of glycerol is not less effective than dexamethasone in preventing neurological complications of bacterial meningitis, the ease of prescription, lower cost, and lower complications, it is suggested that oral glycerol be used instead of intravenous dexamethasone in reducing neurological complications. However, further studies should be done by focusing on the complications of these two drugs and their effectiveness in reducing neurological complications so that their safe administration is ensured in addition to their effectiveness.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

SV contributed to the original idea and protocol, conception of the work, conduct of the study, revision of the draft, approval of the final version of the manuscript, and agreed with regard to all aspects of the work. FM contributed to the conception of the work, conduct of the study, revision of the draft, approval of the final version of the manuscript, and agreed with regard to all aspects of the work. BS contributed to the conception of the work, conduct of the study, revision of the draft, approval of the final version of the manuscript, and agreed with regard to all aspects of the work. KGh contributed to the conception of the work, conduct of the study, revision of the draft, approval of the final version of the manuscript, and agreed with regard to all aspects of the work. ET and MA contributed to the conception of the work, conduct of the study, revision of the draft, approval of the final version of the manuscript, and agreed with regard to all aspects of the work. MR contributed in the design of the work, performance of the analysis, revision of the draft, approval of the final version of the manuscript, and agreed with regard to all aspects of the work. FN contributed to the the design of the work, performance of the analysis, writing and editing of this manuscript, revision of the draft, approval of the final version of the manuscript, and agreed with regard to all aspects of the work.

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