

# Effectiveness of Paromomycin on Cutaneous Leishmaniasis in Iran: A Systematic Review and Meta-Analysis

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## What's Known

- Failure to implement the findings of studies on cutaneous leishmaniasis has rendered its proper treatment challenging.

## What's New

- We observed no significant difference between paromomycin and other treatments regarding effectiveness on cutaneous leishmaniasis.

## Abstract

**Background:** Some treatment reported for cutaneous leishmaniasis. The studies examined the impact of the paromomycin has different characteristics and results. The aim of the present study was to conduct a systematic review and meta-analysis of all randomized clinical trials evaluating the effectiveness of paromomycin in the treatment of cutaneous leishmaniasis in Iran.

**Methods:** Literature search was conducted using MEDLINE, Web of Science, Scopus, Scientific Information Database, IranMedex, Magiran, Iranian Registry of Clinical Trials (from February 2000 to May 2016), and references cited in the text of selected studies. Search terms used were “paromomycin”, “cutaneous leishmaniasis”, “randomized”, “aminosidine”, “controlled trial”, and “clinical trial”. Random effects models were used to calculate the measure of association, with 95% confidence intervals, to analyze the efficacy of paromomycin in the treatment of cutaneous leishmaniasis.

**Results:** Initial search yielded 76 citations. Of these original results, 9 met our specific selection criteria. Four of the randomized controlled trials compared the efficacy of paromomycin in the treatment of cutaneous leishmaniasis with that of a placebo; they were included in the meta-analysis. The success rate of treatment with paromomycin was higher than that with the placebo (pooled RR=4.50, 95% CI: 2.54 to 8.02; P=0.001 and I<sup>2</sup>=26.7%), whereas the difference with the non-placebo treatments was nonsignificant (pooled RR=0.79, 95% CI: 0.58 to 1.073; P=0.131 and I<sup>2</sup>=83.3%).

**Conclusion:** No significant difference was observed between paromomycin and the other treatments in their effectiveness in the treatment of cutaneous leishmaniasis. Because no single drug is effective against all the forms of leishmaniasis, we suggest multidrug therapy.

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**Keywords** • Paromomycin • Cutaneous leishmaniasis • Meta-analysis

## Introduction

Leishmaniasis, a vector-borne disease,<sup>1</sup> is endemic in over 98 countries worldwide,<sup>2, 3</sup> with an annual incidence of about 1.3 million cases. Of these, one million cases are cutaneous

and found mainly in Afghanistan, Algeria, Brazil, Colombia, the Islamic Republic of Iran, Pakistan, Peru, Saudi Arabia, the Syrian Arab Republic, and Tunisia.<sup>3</sup> There are two types of cutaneous leishmaniasis in Iran: rural (wet) and urban (dry). Rural cutaneous leishmaniasis is zoonotic, while the urban type is anthrophophilic. Although statistics show that approximately 20 000 individuals are infected every year in Iran, researchers believe that the actual number of the individuals affected is four to five times higher.<sup>4</sup> Cutaneous leishmaniasis is the most prevalent form of leishmaniasis; it causes ulcers that heal spontaneously. The treatment of cutaneous leishmaniasis is estimated to cost US\$ 13 million (US\$ 11–14 million) per year during the period between 2015 and 2030, from US\$ 17 million in 2015 to US\$ 9 million by 2030. Medicines account for about 17% of the total cost.<sup>3</sup> Risk factors facilitating the spread of this disease include poor socioeconomic status, malnutrition, climatic change, population movement, conflicts, immune-suppressive status such as HIV infection and, in some places, rapid urbanization or establishment of new settlements.<sup>3, 5, 6</sup>

Some treatments have been reported for cutaneous leishmaniasis. Intralesional meglumine antimoniate (MA) is one of these treatments; nonetheless, high cost, low compliance, and systemic toxicity have restricted the use of all these treatments. To remove some of these restrictions, investigators developed paromomycin.<sup>7</sup> On the other hand, studies examined the impact of the paromomycin has different characteristics and results.

One of the priorities set by the World Health Organization is to address the major gap in the available therapies for leishmaniasis.<sup>3</sup> There is also currently a dearth of reviews and meta-analyses of relevant articles in Iran. Indeed, previous work in this domain failed to include articles in Persian published in Iran.<sup>7</sup> It is, therefore, vitally important that the efficacy of paromomycin in the treatment of cutaneous leishmaniasis be fully elucidated. Of course the effectiveness of paromomycin in the treatment of cutaneous leishmaniasis varies depending on the parasite species. Paromomycin is effective against zoonotic cutaneous leishmaniasis caused by *leishmania major*, while it lacks efficacy against anthroponotic cutaneous leishmaniasis caused by *leishmania tropica*.<sup>7-10</sup>

The aim of the present study was to conduct a systematic review and meta-analysis of all randomized clinical trials that have evaluated the effectiveness of paromomycin in the treatment of cutaneous leishmaniasis in Iran.

## Methods

### Search Strategy and Data Sources

The following databases were searched to identify clinical studies in which patients with cutaneous leishmaniasis were treated with paromomycin compounds: MEDLINE; Web of Science; Scopus; and Iranian Journal Databases such as Scientific Information Database, IranMedex, Magiran, and Iranian Registry of Clinical Trials (from February 2000 to May 2016). Also to diminish publication bias, references cited in the text of selected studies were further searched. The Medical Subject Headings (MeSH) and keywords for the population and the intervention were “paromomycin”, “cutaneous leishmaniasis”, “randomized”, “controlled trial”, and “clinical trial”. Boolean operators were also used. The search terms comprised [(cutaneous leishmaniasis)] AND [paromomycin OR aminosidine OR topical paromomycin].

Studies were included if they met the following criteria:

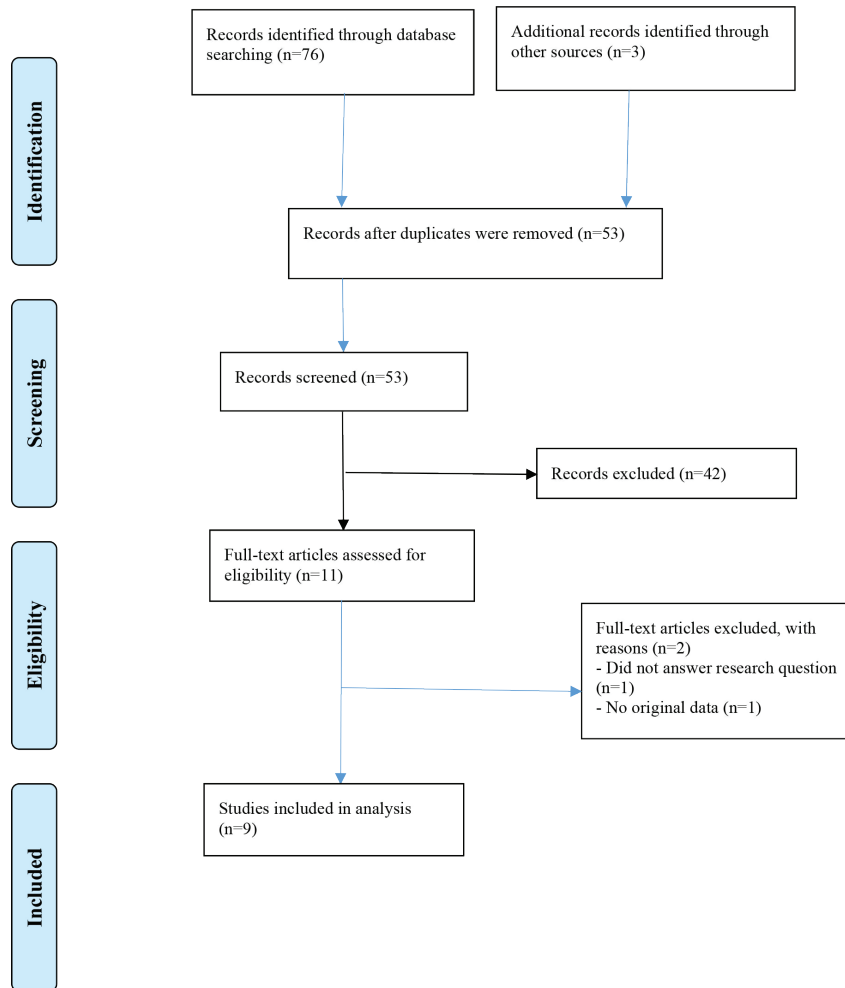
1. Types of participants: patients with cutaneous leishmaniasis
2. Types of interventions: paromomycin compounds, without restrictions regarding the dose, route of administration, or dosage interval (The comparison group can be any comparison group, except for materials with a combination of paromomycin.)
3. Types of outcome measures: any reported improvement with the drug
4. Type of studies: randomized controlled trials or controlled studies

Although no language barriers were imposed, all the studies included in the current review were written in Persian or English. Studies on the following subjects were excluded from the review: animal experiments, chemistry, cell-line studies and commentaries, case reports, editorial pieces, and review articles.

Two reviewers (RM and PG) independently screened the studies. In the first screening, the related studies were identified by their titles and abstracts. The full text of the relevant articles was reviewed for validation before final inclusion in the systematic review. A diagram of the study selection process is depicted in figure 1.

### Methodological Quality Assessment

The studies included were critically appraised using risk of bias and a risk of bias assessment tool. According to the recommendations outlined in the Cochrane book, the following criteria were applied:<sup>11</sup> “random sequence generation”, “allocation concealment”, “blinding of participants and personnel”, and “incomplete outcome data”.



**Figure 1:** PRISMA flow diagram of the process of participant selection for analysis.

We assigned a judgment relating to the risk of bias by answering a pre-specified question about the adequacy of the clinical trial study in relation to the entry, such that a judgment of “-” illustrates low risk of bias, “+” illustrates high risk of bias, and “?” illustrates unclear risk of bias. Two of the authors independently determined bias; any disagreements were resolved by consensus.

Data extraction was conducted using a pilot form. The following information was extracted from the published reports: the authors’ names and the year of publication, inclusion and exclusion criteria, age and sex of the subjects, location of the study area, description of the interventions, sample size of the intervention and comparison groups, number randomized and analyzed, number of missing data, outcomes, items included in the quality assessment forms, and treatments used in the comparison groups.

#### Statistical Analysis

We combined similar study designs only for the meta-analysis. The data were measured

on dichotomous outcomes (clinically or laboratory-confirmed).

Risk ratios (RRs) and confidence intervals (CIs) were calculated for each study. The RR was obtained through dividing the success rate of treatment with paromomycin by the success rate of treatment in the comparison group. An RR greater than 1 indicated that paromomycin could be effective and, otherwise, it could not.

A random-effects analysis model was employed for meta-analysis. We assessed evidence of heterogeneity using the  $\chi^2$  test and  $I^2$  statistic; a  $\chi^2$  value less than 0.10 or an  $I^2$  value greater than 50% indicated significant heterogeneity.<sup>12</sup> Subgroup analysis was planned when significant heterogeneity was present. According to the heterogeneity of the studies included, fixed- or random-effects models were selected to find the pooled measures of association. A meta-regression analysis was conducted to assess whether the heterogeneity among the trials was explained by the sample size and the type of regimen in the comparison group.

To assess potential publication bias, we also examined funnel plots for each outcome. All the statistical analyses were performed with STATA software, version 12.0.

## Results

Our initial literature search yielded 79 citations, 26 of which were duplicate studies; they were, therefore, excluded. Following the screening process, a total of 44 studies were excluded based on the selection criteria. Forty-two of these citations were excluded following an examination of their abstracts, and the other two citations were excluded because they failed to answer the research question and offered no access to original data. Ultimately, nine studies were identified as relevant to our review. Therefore, we analyzed nine studies<sup>13-21</sup> containing the data of 1005 patients (table 1). A detailed flow chart of the literature search and the study selection is illustrated in figure 1. In the current review, a placebo comparison group was used in four trials<sup>13, 18-20</sup> and other treatment comparison groups were used in five controlled trials.<sup>14-17, 21</sup> The sample sizes ranged from 56 to 280. The years of publication for the studies ranged from 2002 to 2012. Seven studies were conducted in Isfahan (a region in central Iran) and two studies in Khuzestan and Ilam provinces (regions in the west of Iran).

Four types of paromomycin regimen were evaluated: topical paromomycin alone,<sup>14, 16, 20</sup> topical paromomycin with methylbenzethonium chloride,<sup>13, 18, 21</sup> an ointment containing 15% paromomycin sulfate and 10% urea Paromo-U,<sup>15, 17</sup> and paromomycin 15% and gentamicin 0.5%.<sup>19</sup>

Four types of comparison groups were used in different studies. One study drew upon photodynamic therapy,<sup>21</sup> and four studies used placebos.<sup>13, 18-20</sup> Four trials applied intralesional MA.<sup>14-17</sup> After a follow-up period of 20 to 30 days (the range of period of treatment in the

selected studies), the effectiveness was assessed clinically<sup>15-17</sup> or in combination with parasitological examinations.<sup>13, 14, 18-21</sup> Reported outcomes with full (confirmed parasitology) and relative recovery (reduction in the size, color, or induration) were entered into the meta-analysis.

### Methodological Quality in the Studies Included

The quality assessment for the included studies is presented in table 2. In terms of random sequence generation (risk of selection bias), 8 studies<sup>13, 14, 16-21</sup> had adequate methodology, while methodology was inadequate in 1 study.<sup>15</sup> Of the 9 randomized controlled trials, 1 study<sup>16</sup> offered clear explanations about allocation concealment but the other 8 studies were vague in this regard. Patient and practitioner blinding or performance bias possibilities were low in 4 studies<sup>13, 18-20</sup> and unreported in 5 studies.<sup>14-17, 21</sup> Most studies reported the number of their patients with missing data; only 1 study<sup>17</sup> had a high number of missing data (25.2%), while this was unclear in 1 study.<sup>20</sup> Generally, most of the controlled trials included in our meta-analysis were categorized as low risk of bias, indicating high quality.

In the studies selected, the success rate of treatment with paromomycin in all the formulations was 0.17 to 0.94. The success rate of treatment among individuals receiving paromomycin only was 20/29,<sup>14</sup> 8/48,<sup>16</sup> and 5/30,<sup>20</sup> while the success rate of treatment among individuals receiving paromomycin with methylbenzethonium chloride was 14/34,<sup>13</sup> 14/34,<sup>21</sup> and 29/34.<sup>18</sup> The success rate of treatment was 120/140 in the paromomycin group<sup>15</sup> and 52/76 in the 10% urea Paromo-U group.<sup>17</sup> Where paromomycin was administered with gentamicin, the success rate of treatment was reported to be 94/100.<sup>19</sup>

The range of RRs in the different studies included in the current meta-analysis was 0.4

**Table 1:** Main characteristics and outcomes of the studies included in the present meta-analysis

Author (y)	Province	Male (%)	Age(y)	Control Group	Paromomycin Group* (n*)	Control Group* (n*)
Asilian <sup>13</sup> (2006)	Isfahan	46	23	Placebo	14 (34)	4 (30)
Moosavi <sup>15</sup> (2005)	Khuzestan	68	23.3	MA*	120 (140)	140 (140)
Faghihi <sup>16</sup> (2003)	Isfahan	42	16	MA*	8 (48)	20 (48)
Shazad <sup>14</sup> (2005)	Ilam	100	21	MA*	20 (29)	18 (27)
Nilforoshzadeh <sup>17</sup> (2004)	Isfahan	U*	1-20	G*	52 (76)	45 (81)
Asilian <sup>21</sup> (2006)	Isfahan	46	23	PDT*	14 (34)	29 (31)
Asilian <sup>18</sup> (2012)	Isfahan	58	23	Placebo	14 (34)	4 (30)
Mostaghim <sup>19</sup> (2002)	Isfahan	79	21	Placebo	94 (100)	8 (58)
Iraji <sup>20</sup> (2005)	Isfahan	51	21	Placebo	5 (40)	7 (40)

\*Paromomycin group, Number of individuals improved in the paromomycin group; Control group, Number of individuals improved in the control group; n: Total; RR: Risk ratio; U: Unknown; MA: Meglumine antimoniate; G: Glucantime; PDT: Photodynamic therapy

**Table 2:** Assessment of risk of bias in the included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data
Asilian <sup>13</sup> (2006)	—	?	—	—
Moosavi <sup>15</sup> (2005)	?	?	?	—
Faghihi <sup>16</sup> (2003)	—	—	?	—
Shazad <sup>14</sup> (2005)	—	?	?	—
Nilforoshzadeh <sup>17</sup> (2004)	—	?	?	+
Asilian <sup>21</sup> (2006)	—	?	?	—
Asilian <sup>18</sup> (2012)	—	?	—	—
Mostaghim <sup>19</sup> (2002)	—	?	—	—
Iraji <sup>20</sup> (2005)	—	?	—	?

to 6.82.<sup>16, 19</sup> When paromomycin was compared with a placebo,<sup>13, 18-20</sup> PDT,<sup>21</sup> and intralesional MA,<sup>14-17</sup> the RRs were 0.97<sup>20</sup> to 6.82,<sup>19</sup> 0.44,<sup>21</sup> and 0.40<sup>16</sup> to 1.23,<sup>17</sup> respectively.

In the studies included in this meta-analysis, the mean age of the participants was 16<sup>16</sup> to 24<sup>18</sup> years and the male ratio was 42<sup>16</sup> to 100%.<sup>14</sup>

The results of our meta-analysis are presented in 3 categories: (1) the results of all the studies, (2) the results of any combination of paromomycin and placebos, and (3) the results of any combination of paromomycin and intralesional MA. The study that used a PDT comparison group<sup>21</sup> was not analyzed separately because it was the only investigation with this comparison group.

When all the studies (n=9) were entered in the meta-analysis, the pooled RR was calculated to be 1.22 (95% CI: 0.74 to 1.99), which was not statistically significant (P=0.44). These results were also heterogeneous (heterogeneity  $\chi^2=127.46$ , df=8; P=0.001;  $I^2=93.7\%$ ; and  $\tau^2=0.46$ ) (figure 2).

In this situation, publication bias was considerable (figure 3a), although the number

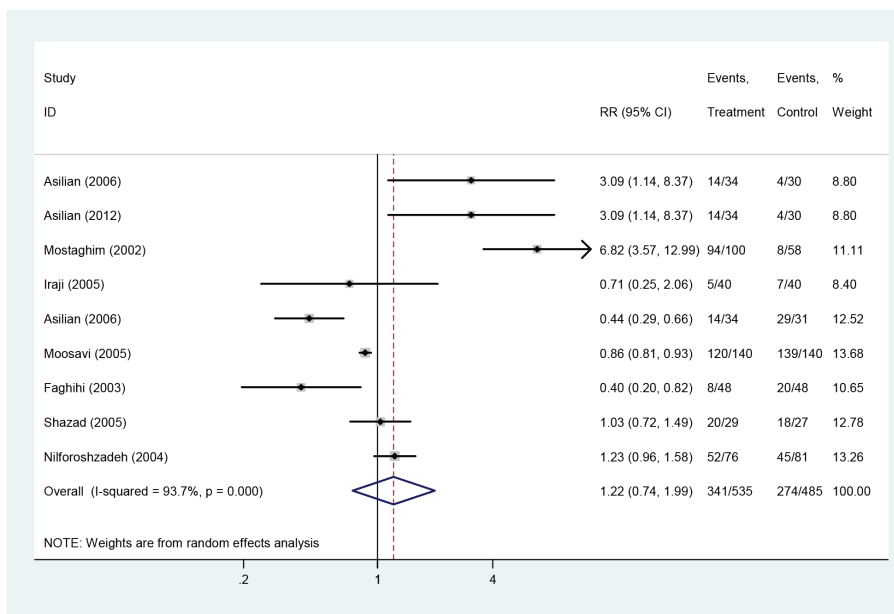
of studies included in the meta-analysis for determining the presence or absence of publication bias based on the funnel plot should not be fewer than 10.

To find the source of heterogeneity by meta-regression, we included sample size and study comparison group (placebo and non-placebo) in the model: sample size had no impact on heterogeneity (P=0.315), but comparison group exerted a significant effect on heterogeneity (P=0.013, regression coefficient=1.42).

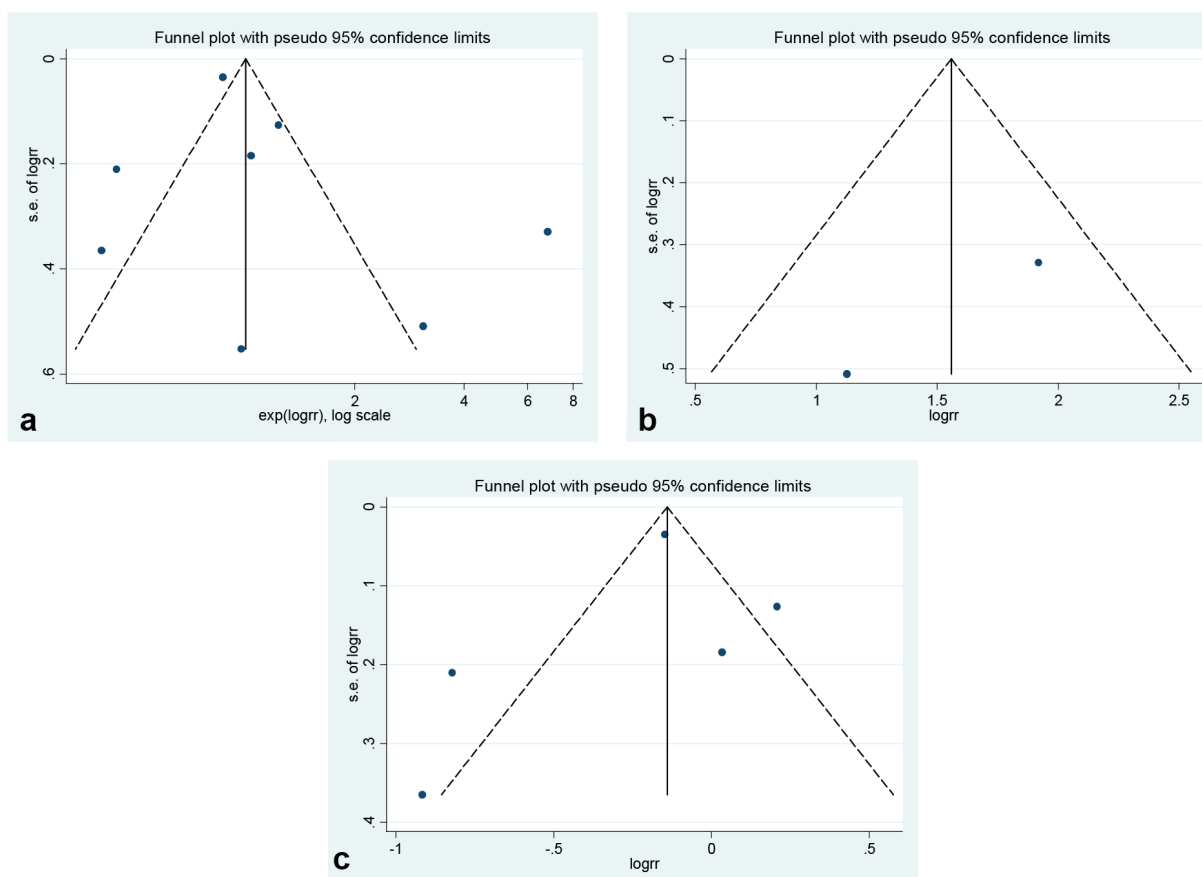
Thereafter, according to the results of the meta-regression, a meta-analysis was conducted in 2 subgroups: studies with placebo comparison groups and those with non-placebo comparison groups.

Our meta-analysis in the placebo comparison groups showed that paromomycin was 2.75 times (95% CI: 1.06 to 7.12) more effective than the placebo, which was statistically significant (P=0.037). Nevertheless, in this case, heterogeneity was observed (heterogeneity  $\chi^2=13.15$ , df=3; P=0.004;  $I^2=77.2\%$ ; and  $\tau^2=0.72$ ) (figure 4).

Subsequently, 1 study<sup>20</sup> was excluded



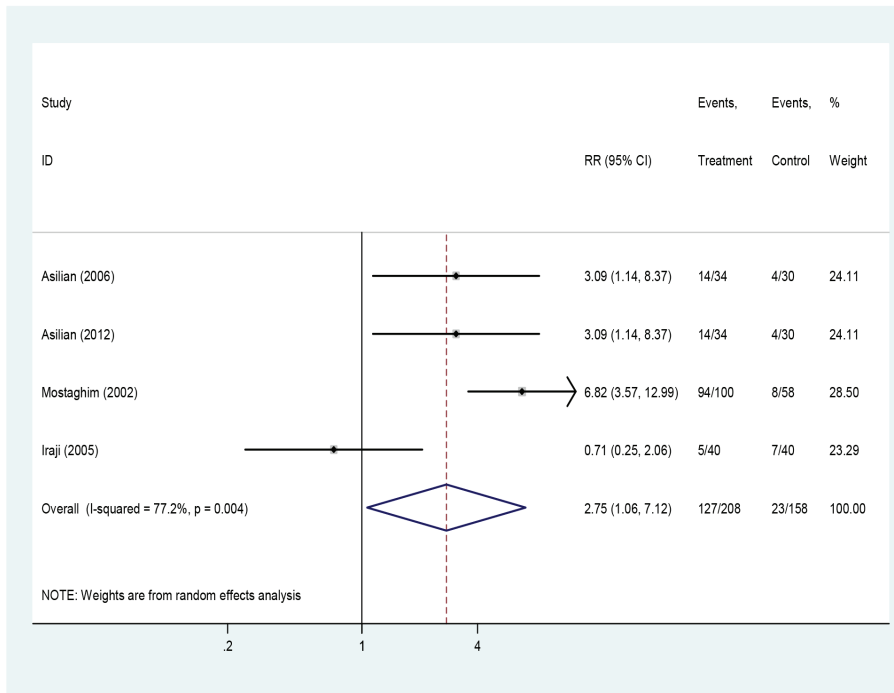
**Figure 2:** Forest plot of the meta-analysis for all the studies included. Each study is identified by the first author and year. The individual effect sizes are identified as “risk ratios” with lower and upper limits (95% CI) for each study. The overall summary effect size of the meta-analysis is noted as a diamond on the bottom line.



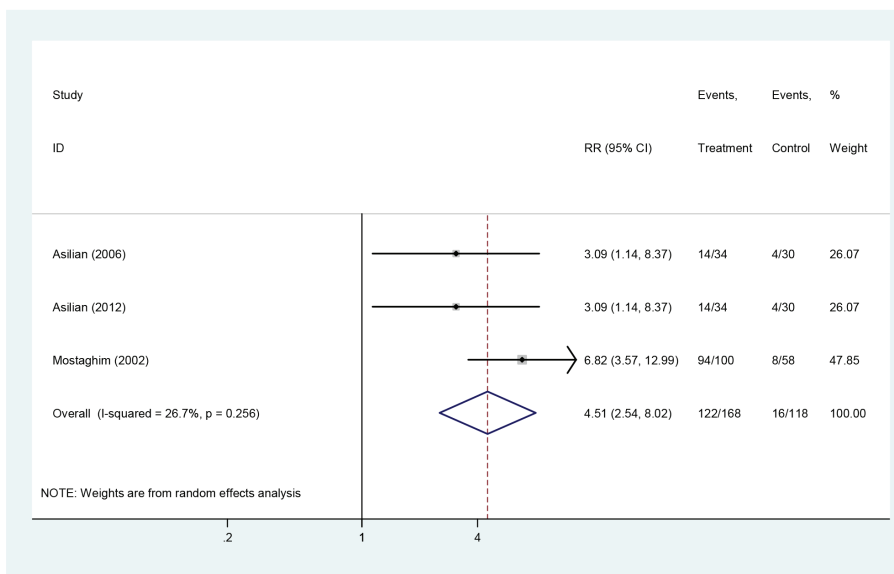
**Figure 3:** These figures indicate the funnel plots of the meta-analysis for a) all the included studies b) the studies with placebo comparison groups. c) the studies with non-placebo comparison groups. The y-axis represents the standard error of the study, with the x-axis showing effect size in each study. The hollow circles represent the studies in the meta-analysis.

from the meta-analysis and the results were obtained based on 3 studies.<sup>13, 18, 19</sup> The pooled RR was 4.50 (95% CI: 2.54 to 8.02), which was statistically significant (P=0.001); in addition,

homogeneity was observed ( $\chi^2=2.73$ ,  $df=2$ ;  $P=0.26$ ;  $I^2=26.7\%$ ; and  $\tau^2=0.07$ ) (figure 5). For these findings, the possibility of publication bias also existed (figure 3b).



**Figure 4:** Forest plot of the meta-analysis for 4 of the studies included with placebo comparison groups. Each study is identified by the first author and year. The individual effect sizes are identified as “risk ratios” with lower and upper limits (95% CI) for each study. The overall summary effect size of the meta-analysis is noted as a diamond on the bottom line.



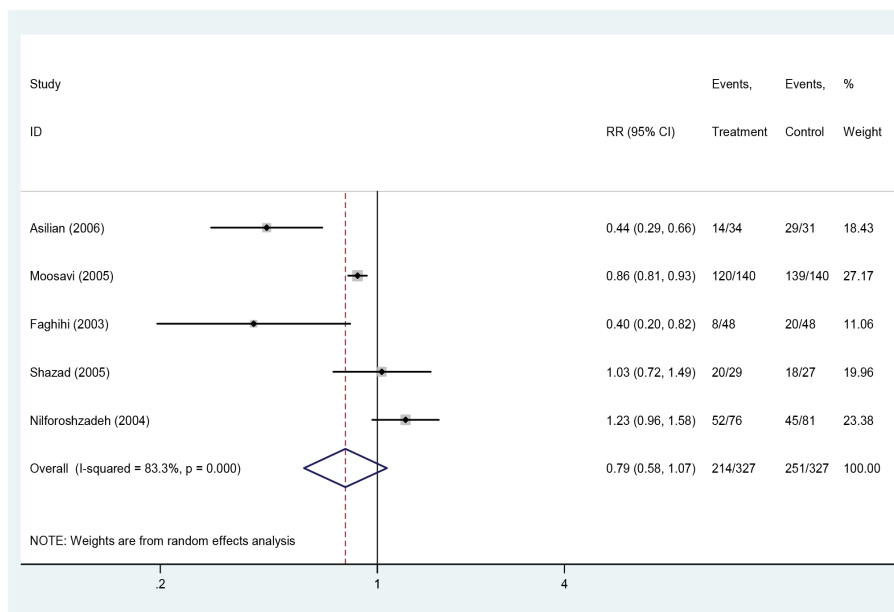
**Figure 5:** Forest plot of the meta-analysis for 3 of the studies included with placebo comparison groups. Each study is identified by the first author and year. The individual effect sizes are identified as “risk ratios” with lower and upper limits (95% CI) for each study. The overall summary effect size of the meta-analysis is noted as a diamond on the bottom line.

The pooled finding of the meta-analysis from the studies with non-placebo comparison groups<sup>14-17,21</sup> showed a low rate of improvement with the paromomycin compounds compared with the other drugs (RR=0.79, 95% CI: 0.58 to 1.073), but it was statistically insignificant (P=0.131).

The result was heterogeneous ( $\chi^2=23.91$ ,  $df=4$ ;  $P=0.001$ ;  $I^2=83.3\%$ ; and  $\tau^2=0.09$ ) (figure 6) and there was publication bias (figure 3c).

## Discussion

In the present study, we found that paromomycin, compared to any other intervention (i.e., placebo, PDT, and intralesional MA), had a high success rate of treatment. However, when we compared the success rate of treatment between paromomycin and the placebos, the rate was substantially higher than the abovementioned overall condition. This finding is inconsistent



**Figure 6:** Forest plot of the meta-analysis for 5 studies included with non-placebo comparison groups. Each study is identified by the first author and year. The individual effect sizes are identified as “risk ratios” with lower and upper limits (95% CI) for each study. The overall summary effect size of the meta-analysis is noted as a diamond on the bottom line.

with the results of the studies included in the meta-analysis in that they reported that the success rate of treatment with paromomycin was substantially lower than that in the non-placebo comparison groups.

There are some problems in the quality of the implementation of the studies incorporated in our meta-analysis; these shortcomings can be reduced through the inclusion of further studies or studies with better quality. With regard to the small sample size in the different studies included in the current study, we suggest that original studies with larger sample sizes be designed in future studies. Furthermore, the accuracy of the results can be augmented by reporting them based on different leishmaniasis-related parasite species. One factor of great significance is, nonetheless, the role of bias in the analysis of randomized clinical trials.<sup>22, 23</sup>

A 15% paromomycin combination was used in most of the implemented research, the result of which could have been improved if other formulations and also paromomycin with other therapies had been used.

EL-On et al.<sup>24</sup> reported that the success rate of treatment with paromomycin was 2.79 times higher than that with the placebo, which is consistent with the results of our research; however, we did not include their study in our meta-analysis because it was done in a country other than Iran. In the study by Asilian et al.,<sup>18</sup> allocation concealment to prevent selection bias could not be concluded from the article but the rest of the quality evaluation criteria were

properly implemented. The success rate of treatment with paromomycin in their study was reported to be 3 times more than that with the placebo. The results of the study by Mostaghim et al.<sup>19</sup> also showed that the success rate of treatment with paromomycin was sixfold that with the placebo. From the point of view of components, their article had a good quality despite the uncertainty regarding allocation concealment. In contrast, in the study by Iraj et al.,<sup>20</sup> there were no results indicating the success rate of treatment with paromomycin by comparison with the placebo. Additionally, the authors failed to mention allocation concealment in their quality assessment and their data were incomplete.

In the study by Shazad et al.,<sup>14</sup> the success rate of treatment with paromomycin was almost similar to that with intralesional MA. In their study, however, there was no clear reference to allocation concealment as well as blinding of participants and personnel (performance bias) and the outcome data were incomplete.

The study by Moosavi et al.,<sup>15</sup> implemented in Khuzestan Province in the southeast of Iran, reported that the success rate of treatment with paromomycin was substantially less than that with intralesional MA. Although the authors incorporated a large sample size in their investigation, they were unclear with respect to the 3 quality indices of allocation concealment, blinding of participants and personnel, and random sequence generation. In the study by Faghihi et al.,<sup>16</sup> the success rate



of treatment with paromomycin was lower than that with intralesional MA; what, nevertheless, was unclear in their investigation was blinding of participants and personnel. In the study by Nilfroushzadeh et al.,<sup>17</sup> the data on 53 individuals, who initially participated in the study but later quit, were deleted (incomplete outcome data). The authors reported a considerably lower success rate of treatment with paromomycin than that with glucantime injections. What should be considered in the interpretation of their results, however, is the fact that their article was vague concerning such criteria as allocation concealment and blinding of participants and personnel.

There is some discordance between the results of the present study and another meta-analysis conducted by Kim et al.<sup>7</sup> on a different group of studies. We found that the success rate of treatment with paromomycin, in comparison to that with the placebo, was considerably higher than what Kim and coworkers reported. Moreover, the difference in the success rate of treatment between paromomycin and the placebo was statistically significant in our study, while that was not the case in the study by Kim and colleagues. When considering the non-placebo comparison group, no differences were spotted between the results of the 2 meta-analyses insofar as the success rate of treatment with paromomycin was 0.79 in the present study and 0.70 in the study by Kim et al. In terms of the placebo comparison group, the current investigation and that by Kim and coworkers had only 2 studies in common; the other studies incorporated in the meta-analysis by Kim and colleagues were related to research outside Iran.

Among the 9 studies selected for the current meta-analysis, 7 papers were reported from the Iranian city of Isfahan. Isfahan is widely deemed an endemic region for cutaneous leishmaniasis, but there are other endemic regions for the disease in Iran such as Mashhad and Yazd. Therefore, the figure of 7 out of 9 studies may not be proportional to the distribution of the disease in Iran. On the other hand, the studies that we entered into our meta-analysis were published in the time period between 2002 and 2012. Considering that the time of search comprised the studies having been published by 2016, the results of our study may have been affected by publication bias. In other words, the final conclusion may have overstated the significance of the results due the fact that some relevant articles with nonsignificant results may not have been published.

## Conclusion

According to the results of the present systematic review and meta-analysis, no significant difference was observed between paromomycin and other treatments in terms of effectiveness in the treatment of cutaneous leishmaniasis. As the current study had a sufficient statistical power, it may be claimed that paromomycin and other treatments have similar efficacy in the treatment of the disease. In other words, paromomycin and other treatments may be alternatively applied to treat cutaneous leishmaniasis. Eventually, no single drug is effective against all the forms of leishmaniasis. Monotherapy being no longer effective, we suggest multidrug therapy while granting priority to pentavalent antimonials (glucantime or pentostam) as first-line drugs in combination with second-choice compounds including paromomycin.

**Conflict of Interest:** None declared.

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