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Meta-analysis

Is cotoneaster manna improving the treatment of neonatal jaundice?

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Abstract

The aim of this systematic review is to evaluate the effects of cotoneaster manna on neonatal jaundice. The studies were selected from 1980 to 2017 using the main databases. Eight clinical trials with a total of 862 infants were selected from the 116 primary studies. All these trials had at least two groups for which the studied outcomes were measured before the intervention and at 12, 24, 36 and 48 hours after intervention. Generally, the meta-regression analysis showed a direct insignificant relationship between the baseline bilirubin level in the infants before the intervention and the estimated results. Although the findings confirm the effectiveness of cotoneaster manna products in the treatment of neonatal jaundice compared to the standard interventions or treatments (phototherapy), further clinical trials are strongly recommended, especially with larger sample sizes, more extensive geographical areas, and a variety of subjects in different parts of the world.

Introduction

Neonatal jaundice is one of the most common disorders in the neonatal period that occurs in 60-80% of the healthy babies around the world (Burke et al., 2009). Several studies have shown that 8-11% of infants experience hyperbilirubinemia (Ullah et al., 2016). The serious complication associated with neonatal jaundice is chronic encephalopathy (Muchowski, 2014).

Phototherapy and exchange transfusion have been recommended but have their adverse effects that show the necessity to improve a marginal herbal management plans (Kliegman et al., 2007; Kassem, 2013). Fok conducted a brief review of the Chinese medicine products used in treating neonatal jaundice, and in his overview of the products listed by Dennery, emphasized their long-term use over the centuries. However, he noted that their effectiveness has not yet been approved in standard clinical trials (Fok, 2001).

Traditional and herbal medicine products have been used to treat neonatal jaundice in Iran for a long time. Despite the development and the spread of modern medicine in Iran, these herbal products are still commonly used (Fakhri et al., 2016; Fakhri et al., 2017).

The manna of the cotoneaster species namely Shir-e-Khesht as laxative especially good for neonates and the elderly and bile purgative (Fakhri et al., 2016), has had greater applications over other traditional medicine products in the oral treatment of neonatal jaundice. Manna is a sugary compound produced by some species of plants such as the cotoneaster, consists of

Figure 1: *Alhagi camelorum* (A), and *Cotoneaster discolor* (B) as the sources of manna

different types of carbohydrates such as mannitol and glucose (Figure 1). It is supposed that using Shir-e-Khesh in treatment of neonatal jaundice with phototherapy can reduce the adverse effects of phototherapy and also reduce the duration of neonatal hospitalization (Azadbakht et al., 2005; Shah Farhat et al., 2005; Ghotbi et al., 2006; Mansouri et al., 2012; Fallah et al., 2014; Rafieian-Kopaei et al., 2016; Ameli et al., 2017).

Khodashenas et al. (2016) conducted a systematic review study in which they searched for foreign and local primary studies on global databases including PubMed/MEDLINE and Google Scholar and found nine studies in the effectiveness of cotoneaster manna and *Alhagi camelorum* products (khodashenas et al., 2016). Nonetheless, due to the lack of transparency this systematic review regarding the inclusion criteria for the primary studies, the failure to incorporate the crucial step of assessing the methodological quality of the primary studies, and above all, the absence of a meta-analysis in the study and the failure to explain the reasons for this lack, drawing evidence-based conclusions from that study was impossible. Its findings, therefore, cannot be a basis for decision-making about neonatal jaundice.

Given the gap in information for deciding on this matter and the need for collecting data from clinical trials conducted at the international and national levels, the present systematic review was designed and conducted to summarize the evidence from the earlier studies in order to compare the effectiveness of cotoneaster manna and phototherapy in newborns with jaundice. The aim was that, if possible, the evidence can be combined together through a meta-analysis and so that a new and higher level of evidence can be gathered.

Materials and Methods

The present article was designed and prepared based on the PRISMA (Moher et al., 2009), which has been designed for writing articles derived from systematic review and meta-analysis studies.

Inclusion criteria

The primary studies included in this systematic review were randomized or non-randomized clinical trials with or without blinding, in which the subjects were newborns with neonatal jaundice and whose interventions consisted of any product of the manna of cotoneaster plant. The intervention group in the trials included in this study had used this product exclusively or in combination with phototherapy and the control group had been given either no intervention at all (i.e. one-group before-after trials), or placebos or the routine intervention for neonatal jaundice (i.e. phototherapy, exchange transfusion or a combination of both). The eligible trials had evaluated at least one (primary or secondary) outcome of the total serum bilirubin level, but may have also evaluated additional outcomes, such as the number of hospitalization days or the frequency of discharged newborns.

Statistically, the minimal data required for the outcome included the sample size and the mean and standard deviation of the outcome in the intervention and control groups or in terms of the before- and after-intervention (in one-group before-after trials). The primary studies with an observational design (such as single or multi-group cohort studies with prospective follow-up) and trials without the minimum required indexes for the outcome variable for meta-analysis were excluded.

Search strategy

This systematic review searched electronic databases including PubMed/MEDLINE, SCOPUS, Web of Science, EMBASE, ProQuest and Google Scholar for the relevant articles published from January 1, 1980, to February 31, 2017. Given that most of the eligible studies had been conducted in Iran, an electronical search was carried out in the local Iranian bibliographic databases including the Scientific Information Database (SID), the former IranMedex and Magiran. To search for grey literature, the information system Irandoc was searched for theses, research reports and conference or seminar articles. The registry of clinical trials available at the address clinicaltrials.gov, ISRCTN, which is a clinical trial registry for the BioMed Central publisher and the International Clinical Trials Registry Platform of the WHO [WHO-ICTRP] were searched for the protocols of the registered trials that may not have published their results yet. A search was also carried out in the list of references for all the primary studies included at the end of the PRISMA flow-chart, the

systematic reviews and other review articles on the medicinal plant interventions for neonatal jaundice. No language restrictions were applied in any of the stages of the search or for the information resources.

Search processes until the inclusion of the primary studies

After searching all the resources, the possible primary studies/papers were selected through a review of their titles and abstracts. The full text of all the screened studies was then accessed. Two authors (F and H) received the full texts independently and reviewed them all. Based on the inclusion and exclusion criteria, F and H classified these primary studies into a group that met the inclusion criteria and a group that did not. In the next step, the two authors reached a consensus on those of the papers/studies that they did not agree on and thus determined all the eligible papers/studies.

Assessing the methodological quality (risk of bias) of the primary studies

After determining the included studies/papers, the two authors (F and H) independently assessed all the primary studies using the Cochrane Collaboration's tool for assessing the risk of bias in the randomized trials (Higgins et al., 2011). The checklist has seven different items, each of which assesses one of the aspects or the major biases in the clinical trials. Each item on the checklist offers three choices for the response, including 'high-risk of bias', 'low-risk of bias', and 'unclear'. After completing the assessment of the risk of bias in all the studies, the cases of disagreement on the response chosen for the items were assessed in each study/paper and then the two reviewers reached a consensus and agreed on a single option.

Data extraction and statistical analysis (meta-analysis)

First, a data extraction form was designed for the primary studies/papers based on the objectives of the systematic review, the intended main outcome of clinical trials and other features of the primary studies. After completing this form based on at least one primary study, two copies of the data extraction form were prepared for each primary study and distributed among the same two reviewers (F and H) to ensure the adequacy of the data predicted in the form. The reviewers were asked to independently extract the data required by the forms from the studies/papers. Upon the completion of this step, the main author of the study first determined the cases of incomplete data and lack of agreement between the two reviewers and; then, by reaching a consensus, these cases were modified to reach a single fixed status. If one of the primary articles/papers had not reported the required data, the required data was requested through correspondence with its author. If the corresponding author of the paper did not respond to the email, the request was repeated up to three times on three different occasions (at least every five days); otherwise, if the data in question was related to the primary outcome (total bilirubin distribution in one or both the intervention and control groups), the study was excluded from the systematic review. But if the data was not related to the primary outcome, the study was not excluded and the data was used as missing data in the meta-analysis. A meta-analysis was performed in this systematic review using Stata-12.1. Due to the quantitative nature of the primary outcome in the clinical trials, the mean difference (i.e. a difference of at least two means in the bilirubin index in the intervention and control groups) was calculated as the measure of the effectiveness of the interventions (effect size). As all the studies had been designed to incorporate at least two groups (the intervention and control groups) and since all the trials had repeatedly measured the outcome (bilirubin level) at different intervals of time, including at baseline (time zero) and on other occasions (with a regular interval of 12 hours), two indexes could be calculated: A within-group mean difference (i.e. the mean bilirubin difference at a select time and at baseline) and the between-group mean difference (i.e. the mean bilirubin difference between the intervention and control groups at a select time). From a methodological point of view, there are two different measures of mean difference (with two different interpretations or applications) in the meta-analyses of trials with quantitative outcomes, which are called the Weighted Mean Difference (WMD) and the Standardized Mean Difference (SMD). The WMD is a simple measure of the mean difference that is combined with a weighted combination of each of the primary studies. This measure is used when the effectiveness of an intervention needs to be interpreted based on the mean difference in a quantitative outcome measure and the application needs to be shown to an audience or a group who benefits from the evidence. For example, if the WMD is estimated at 7 mmHg for systolic blood pressure in a meta-analysis of clinical trials of a new drug to lower blood pressure, it means that, on an average, and based on the combined estimate in the meta-analysis, the intervention reduces systolic blood pressure by 7 mmHg. The SMD, however, is a classic effect size measure that shows the achieved strength of the relationship between the intervention and the outcome in question. The closer is the index to zero, the lower is the strength of the relationship, and the closer it is to 1 and above, the stronger is the relationship (Deeks et al., 2001). It should be noted that the SMD is calculated in three different ways, including through the Cohen's method, Hedges' method and Glass' method with the first being the most popular (Cohen, 1988). The difference between these three methods is in the denominator of the SMD. Many experts have recommended against the use of the Cohen's method

for measuring the within-group SMD and have instead recommended the Hedges' method (Hedges, 1982; Deeks et al., 2001). See Appendix 1 for more information on these methods. In the majority of the clinical trials conducted on the newborns with jaundice, more than two measurements were performed of the outcome at regular intervals in addition to the presence of at least two groups (i.e. repeated measures; in this review, the primary outcome was measured in the studies at 12 hours intervals); as a result, selecting an effect size measure is more complicated than usual and all the methodological considerations should be taken into account. In other words, if the intention is to uniquely rely on each of the within or between-group mean difference measures as the main measure of the effect size, some of the features of the studies will be ignored. In this meta-analysis, the method proposed by Mooris and DeShon (Morris et al., 2002) was used to calculate or estimate the effect size in order to avoid such limitation. Overall, three measures were estimated for all the primary studies, including the WMD, the within-group SMD (using the Hedges' method) and the Standardized Mean Change (SMC), and then, using the random effect model, the meta-analysis was performed with a combination of these measures for the primary studies that entered the meta-analysis. In the SMC measure, based on the proposed method of Mooris and DeShon, the absolute value of the within-group mean difference of the control arm is subtracted from the absolute value of the within-group mean difference of the intervention arm. As a result, the positive sign in this standardized measure indicates the stronger effect of the intervention arm (manna of cotoneaster and phototherapy) compared to the control arm, while the negative sign indicates the contrast, i.e. the stronger effect of the control arm (phototherapy or phototherapy + placebo). Based on the Mooris and DeShon method (Morris et al., 2002) as well as Hedges' recommendations (Hedges, 1982), the estimation/calculation of two standardized effect size measures is performed by applying the bias correction coefficient. A forest plot was used for the visual representation of the combined primary studies, and Cochran's Q test and I^2 measure were used to assess the heterogeneity and its amount (Higgins et al., 2002). The potential reasons for this heterogeneity were also examined using a subgroup analysis and meta-regression. Since the number of primary studies combined for the meta-analysis was less than 10, Begg's and Egger's statistical tests (Thornton et al., 2000) were used for assessing the publication bias instead of using funnel plots (Egger et al., 1997). If the distribution bias was deemed non-negligible based on these methods, the Trim and Fill method was used to modify it (Duval et al., 2000).

Results

Description of the primary studies

Of the 116 primary studies retrieved from the discussed databases, eight were included in this systematic review (n= 862 infants). Figure 2 is a flow-chart that presents the different stages of the search carried out in the electronic databases and in grey literature, the screening of the primary studies and also the process of selecting the eligible studies based on their full text. All the eligible primary studies were clinical trials; however, one of them was designed and conducted to examine the effects of the manna of cotoneaster in the prevention of neonatal jaundice, and in another one, the primary outcome evaluated was inconsistent with the primary outcome defined, i.e. serum bilirubin levels in newborns (the mean and standard deviation of this variable). In that study, only the frequency of the discharged newborns based on the serum bilirubin levels less than 12 mg/dL was evaluated as the primary outcome. As a result, the meta-analysis of the outcome of serum bilirubin levels in newborns combined the data from six randomized clinical trials, which examined a total of 686 newborns. Table I presents the properties of the primary studies included in this systematic review, the important features used as the inclusion criteria for newborns and the other features of the included trials. All the newborns in the reviewed trials were term infants (gestational age 37 weeks and above); however, they were different in terms of their age and weight to some extent. Also, in terms of the level of total bilirubin as an inclusion criterion, the minimum level of bilirubin varied from 14 to 18 mg/dL. Regarding the criterion of breastfeeding, only one study had also examined the newborns on formula feeding, while the rest of the studies had exclusive breastfeeding or breastfeeding as an inclusion criterion.

Table II presents the findings regarding the assessment of the methodological quality of the primary studies (or the risk of bias) based on the seven domains of the Cochrane Collaboration's tool for assessing risk of bias. Just like many other quality or the risk of bias assessment tools, this tool offers three choices for the response, including 'low-risk of bias', 'high-risk of bias', and 'unclear'. In this systematic review, a low-risk of bias was given 1 point and the other two choices were given zero points so as to obtain a total score for the methodological quality of each study. After adding the scores, the quality score of the primary studies entering the analysis was summarized in the last column of the table. Two trials received a score of zero and the highest score of quality (a score of five) was given to the study by Fallah et al. (Fallah et al., 2014).

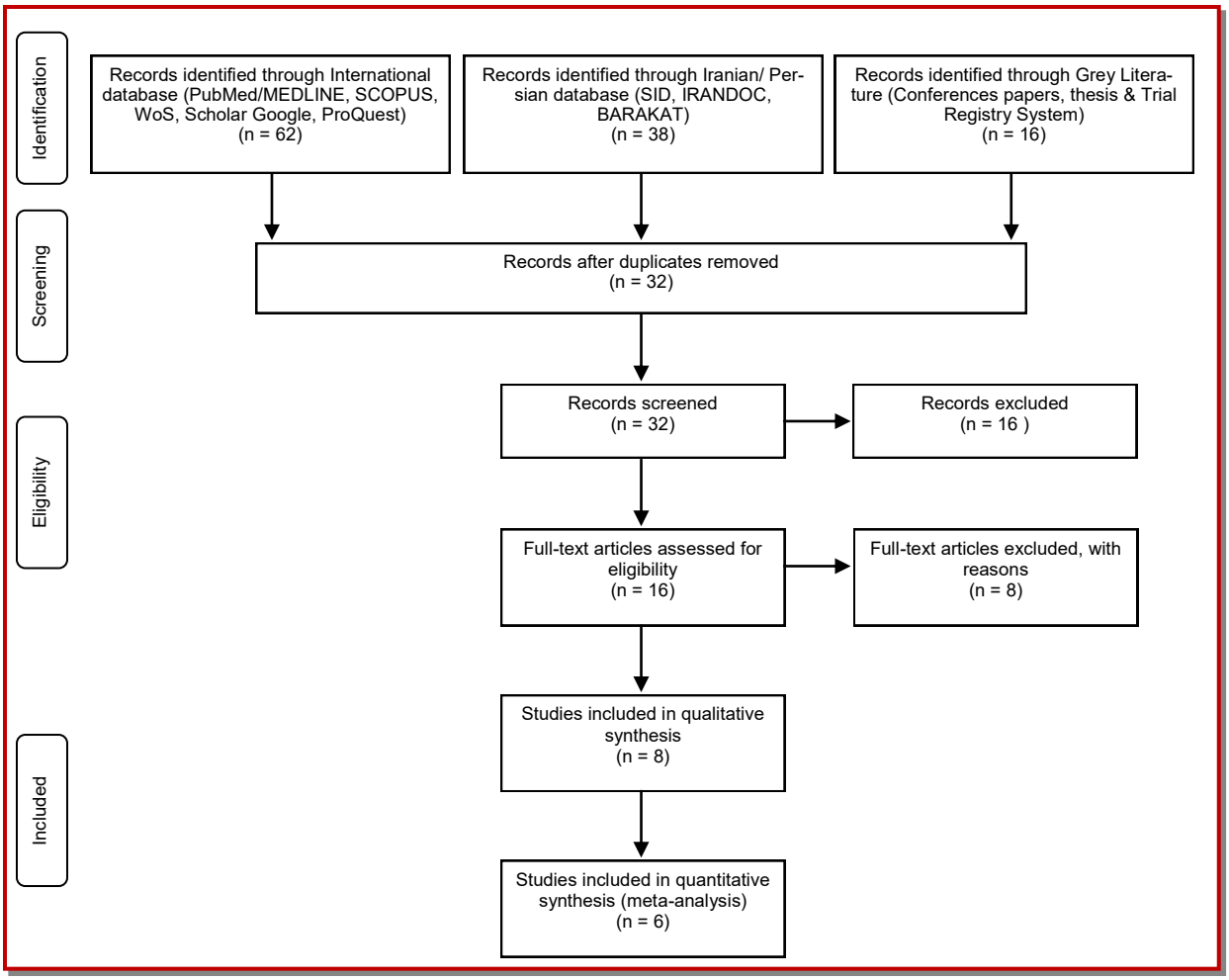

Figure 2: Search flowchart for articles (as described in the PRISMA statement)

Table I

Characteristics of included primary studies (clinical trials)

Author year	Location/ city	Weight criteria	Age criteria (day)	Bilirubin criteria (mg/dL)	Manna of manna of cotoneaster product type	Newborn feeding type as inclusion criteria
Ghotbi et al., 2007	Tehran	2500-4000	3-11	15-20	Extract	Exclusive BF
Shah Farhat et al., 2005	Mashad	>2500	NR§	18-29	Extract	NR
Rafieian-Kopaei et al., 2016	Shahrekord	2500-4000	>1	14-20	Bilineaster	BF
Azadbakht et al., 2006	Mazandaran	Any weight	Any age	NR	Extract	NR
Ameli et al., 2016	Mashad	>2000	2-14	>17	Bilineaster	Exclusive BF
Fallah et al., 2014	Yazd	2500-4000	3-7	15-20	Bilineaster	Exclusive BF
Mansouri et al., 2012	Sanandaj	NR	3-5	NR	Bilineaster	NR
Reshadmanesh and Kamali, 2001	Sanandaj	Any weight	>1	>15	Extract	BF/ formula

NR: Not reported, BF: Beast-feeding

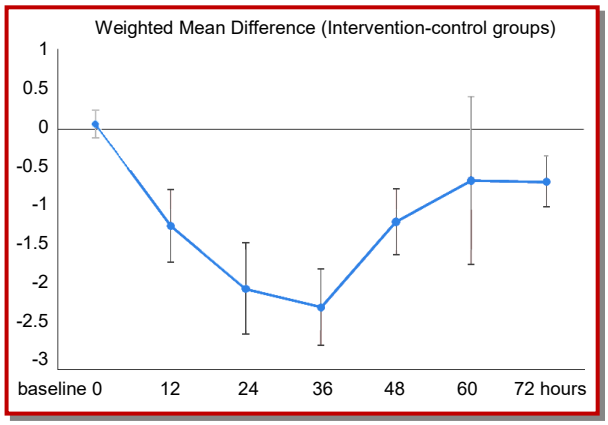

Figure 3: The summary or combined Weighted Mean Difference (WMD) of bilirubin in intervention versus comparison groups across different assessed times 0-72 hours

subtracted from the weighted mean in the intervention group). As shown in the figure, the mean difference between the two groups is very close to zero at baseline. Twelve to 36 hours after the intervention, the difference gradually grows, but the trend does not continue after the 36th hour, and the mean bilirubin level gradually becomes similar in the two groups, such that the mean difference between the two groups is no longer statistically significant 60 hours after the intervention. The findings of this meta-analysis also showed that the maximum reduction in bilirubin levels in the intervention group compared to the control group was observed 36 hours after the intervention and was calculated as -2.2 mg/dL (confidence interval = 95%; WMD = -0.3 to -4.1). Figures 4 as the forest plots presents a summary of the combination of the within-group SMD in the intervention arm (manna of

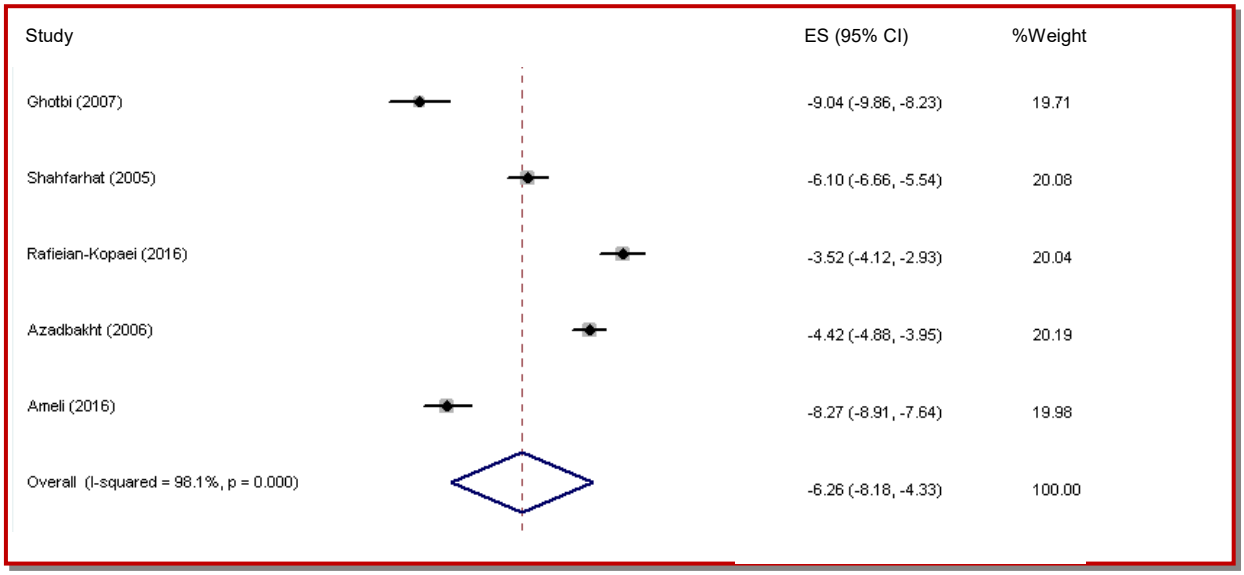

Figure 4: Forest plot Standardized Mean Difference (Hedges method) of within intervention arm (cotoneaster and phototherapy) in 36 hours after the intervention versus baseline

Meta-analysis

As shown in Figure 2 (the flow-chart of the systematic eview process), of the eight trials that entered this systematic review, two were excluded from the combination of the primary studies in the meta-analysis, including one study by Mansouri et al., (2012) that aimed to evaluate the preventive effect of the manna of cotoneaster products, and another study by Reshadmanesh and Kamali, (2001) that did not contain the minimum data required for the meta-analysis of the primary outcome (i.e. the mean and standard deviation of bilirubin levels in the two groups). Only six studies entered the meta-analysis stage. Figure 3 shows the combination of the WMDs of the bilirubin between the intervention and the control groups in all the studies (the weighted mean of bilirubin in the control group

cotoneaster and phototherapy) 12, 24, 36 and 48 hours after the intervention compared to the baseline and Figure 5 presents the combination of this measure in the control arm (phototherapy alone or phototherapy + placebo) at the same time points.

The values of these measures of effect varied from -2.7 to -6.3 in the intervention arm and from -1.5 to -4.1 in the control arm. As shown by these figures and the combined standardized effect sizes, the strength of bilirubin reduction was higher in the intervention arm (manna of cotoneaster and phototherapy) than in the control arm (phototherapy alone or with placebo) 36 hours after the intervention compared to the same at baseline. Figure 6 presents the combined between-group SMC 36 hours after the intervention. The positive sign in the combined measure in these forest plots indicates the superior effect of the bilirubin changes in

Table II

Methodological quality of included primary studies in according to cochrane risk of bias assessment tool

Author year	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting bias	Other bias (baseline imbalance)	Quality score
Ghotbi et al., 2007	UC	UC	UC	UC	Low	Low	Low	3
Shah Farhat et al., 2005	UC	UC	Low	UC	High	UC	UC	1
Rafieian-Kopaei et al., 2016	UC	UC	UC	UC	UC	Low	UC	1
Azadbakht et al., 2006	UC	UC	UC	UC	Low	Low	Low	3
Ameli et al., 2016	UC	UC	High	High	UC	UC	High	0
Fallah et al., 2014	Low	Low	Low	High	UC	Low	Low	5
Mansouri et al., 2012	UC	Low	Low	UC	UC	UC	High	2
Reshadmanesh and Kamali, 2001	UC	High	UC	UC	UC	High	High	0

UC: Unclear, Low: Low-risk of bias, High: High-risk of bias

the intervention group compared to the control group and vice versa (i.e. negative values indicate the superiority of the control group). Twelve hours after the intervention, the results of the comparison of the two groups were in favor of the intervention arm, although the SMC of this measure was not statistically significant (Figure 6). Nonetheless, 24 and 36 hours after the intervention, the results of the comparison of the two groups were in favor of the intervention group and the measure was statistically significant. In addition to the significance of this combined measure, the point values of this measure showed an ascending trend 12 to 24 hours after the intervention (Figure 6), while the comparison of the two groups 48 hours after the intervention showed another reduction in this combined measure that was not significant similar to the 12 hours time point (Figure 6). Figure 7 summarizes the changes in this combined measure 12-48 hours after the intervention in all the studies.

Heterogeneity assessment

The combination of the within-group SMD in both the intervention and control arms had a significant heterogeneity based on the Cochran's Q-test ($p<0.001$) and the I^2 value in the eight discussed effect measures were consistently above 90%. Nonetheless, the combination of the SMC 12, 24, 36 and 48 hours after the intervention had the least heterogeneity ($I^2= 0.0\%$) and its result for the Cochran's Q-test was also not significant ($p>0.05$). In combining the within-group SMDs, a subgroup analysis was used to assess the impact of the methodological quality measure of the clinical trials on the homo-

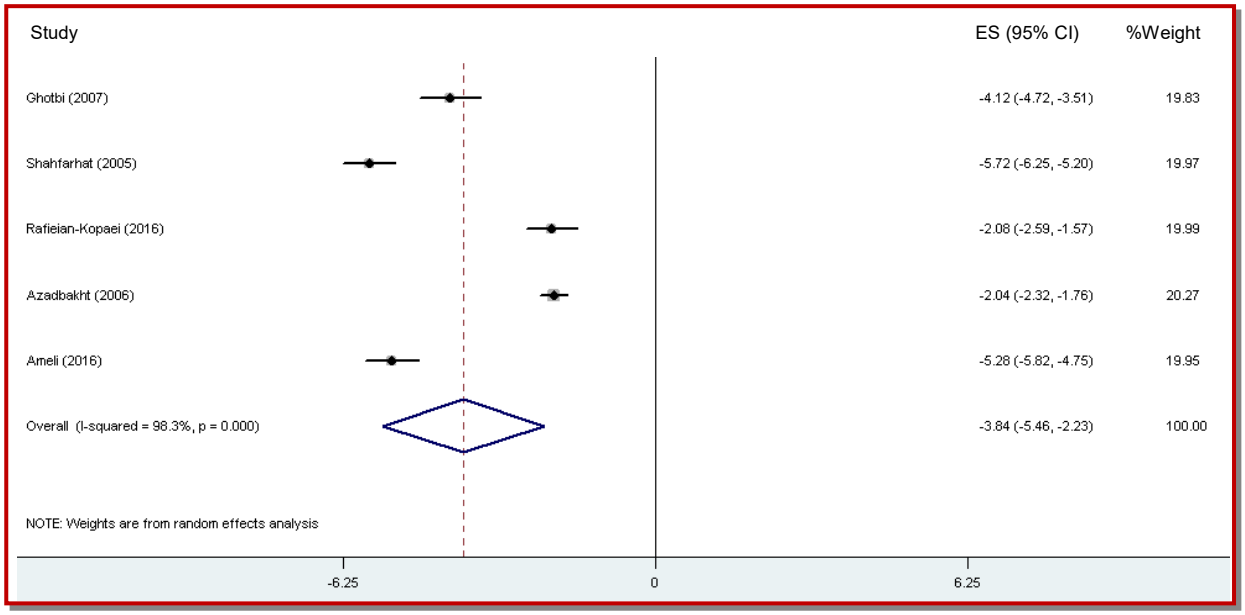

Figure 5: Forest plot Standardized Mean Difference (Hedges method) of within arm control (phototherapy alone or phototherapy + placebo) in 36 hours after the intervention versus baseline

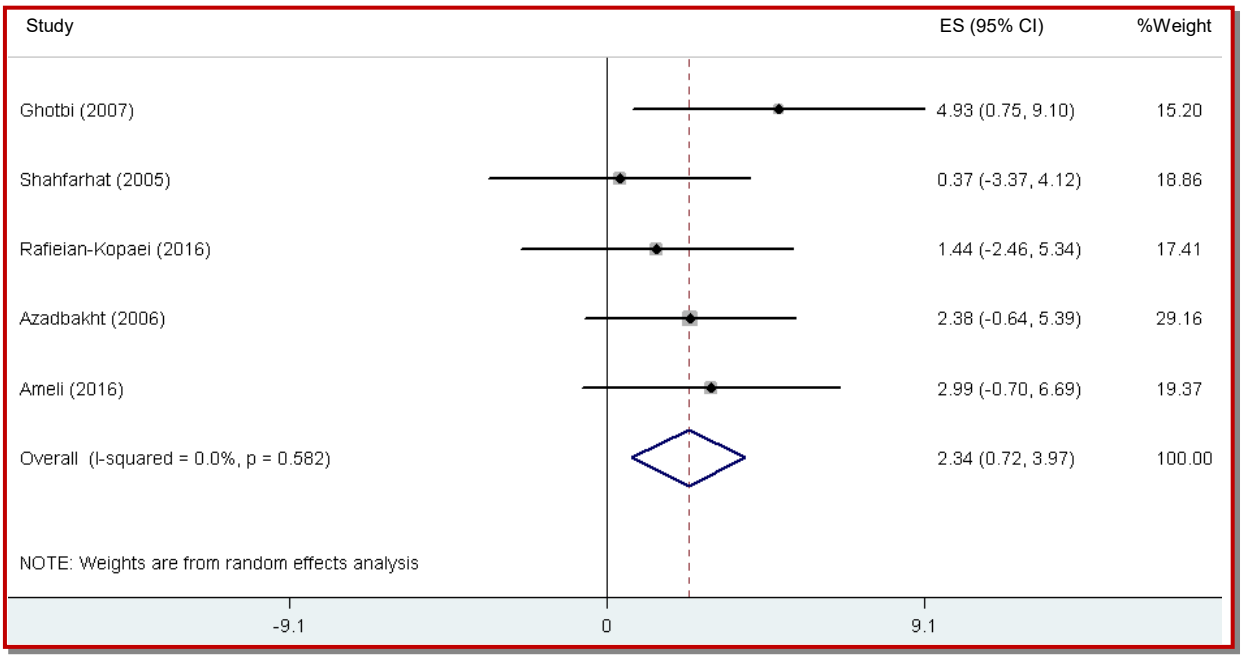

Figure 6: Forest plot Standardized Mean Change (SMC) of between 2 arms (intervention-comparison) in 36 hours after the intervention versus baseline

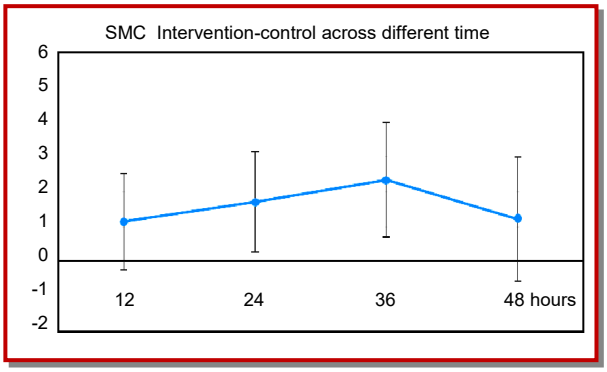

Figure 7: The trend of combined SMCs between 2 arms (intervention-comparison) across assessed times (12-48 hours)

geneity measure as well as the numerical value of the noted effect size. Table III presents the results of this analysis for the within-group measures separately for the intervention and the control arms. This classification (which was based on the quality measure) did not have a great effect on the numerical value of the I^2 and the related statistical test. Nonetheless, in the majority of these measures, the numerical value of the relationship strength index was larger (signifying a stronger relationship) in the low-quality trials subgroup (quality score less than 3) while it was smaller (signifying a weaker relationship) in the high-quality trials subgroup (quality score of 3 or more). A meta-regression was used to evaluate the effect of the baseline neonatal bilirubin level on the effectiveness of the manna of cotoneaster in the clinical trials. For this purpose, the minimum amount of bilirubin defined in the studies (as a quantitative variable) and the relationship strength index were entered into the meta-regression model as a univariate and based on the inclusion criteria of the primary studies.

According to the data, the higher the neonatal bilirubin level before the intervention, the greater was the effectiveness of the manna of cotoneaster in reducing it. However, this reducing trend was not statistically significant ($p>0.20$).

In addition to following, a similar reducing trend seen in the intervention arm, the relationship strength was higher in this group (the effect of phototherapy) and the relationship was significant at all the four time points from 12 to 48 hours after the intervention ($p<0.20$).

Assessment of publication bias

As described in the Materials and Methods section, since the number of the primary studies entering this meta-analysis was less than 10, the visual method of funnel plot was not used to assess the publication bias; rather, Egger's and Begg's methods were used. The publication bias was not statistically significant for any of the relationship strength indexes using either of the two methods and all the p values were more than 0.20.

Discussion

Although, this study is not the first systematic review to assess the effectiveness of the manna of cotoneaster on reducing bilirubin in neonatal jaundice, two features differentiate this systematic review and meta-analysis

Table III

Subgroup analysis in according to methodological quality and by two arms (intervention versus comparison)

Groups	Effect size measures	High quality trials (quality score≥3)			Low quality trials (quality score<3)			All trials		
Quality sub-groups		Estimate (CI 95%)	Hetero-genity c^2 (p value)	I^2	Estimate (CI 95%)	Hetero-genity c^2 (p value)	I^2	Estimate (CI 95%)	Hetero-genity c^2 (p value)	I^2
Interven-tion group	SMD_w 12-0	-2.22 (-2.90 : -1.54)	15.2 (0.001)	86.8	-3.08 (-4.47 : -1.68)	50.9 (<0.001)	96.1	-2.65 (-3.40 : -1.90)	88.2 (<0.001)	94.3
	SMD_w 24-0	-4.05 (-4.66 : -3.45)	8.1 (0.02)	75.3	-5.19 (-7.38 : -3.01)	89.0 (<0.001)	97.8	-4.64 (-5.72 : -3.56)	127.2 (<0.001)	96.1
	SMD_w 36-0	-6.72 (-11.25: -2.19)	93.4 (<0.001)	98.9	-5.96 (-8.58 : -3.35)	115.7 (<0.001)	98.3	-6.26 (-8.18 : -4.33)	210.6 (<0.001)	98.1
	SMD_w 48-0	-4.29 (-5.05 : -3.53)	2.8 (0.09)	64.3	-5.57 (-8.57 : -2.57)	163.0 (<0.001)	98.8	-5.06 (-6.86 : -3.27)	179.6 (<0.001)	97.8
Compar-ison group	SMD_w 12-0	-1.09 (-1.96 : -0.21)	32.9 (<0.001)	93.9	-1.83 (-2.94 : -0.73)	43.3 (<0.001)	95.4	-1.46 (-2.24 : -0.69)	131.8 (<0.001)	96.2
	SMD_w 24-0	-2.79 (-4.62 : -0.97)	93.2 (<0.001)	97.9	-3.56 (-5.59 : -1.54)	102.9 (<0.001)	98.1	-3.18 (-4.54 : -1.81)	277.8 (<0.001)	98.2
	SMD_w 36-0	-3.06 (-5.10 : -1.03)	277.8 (<0.001)	97.3	-4.36 (-6.64 : -2.09)	113.6 (<0.001)	98.2	-3.84 (-5.46 : -2.23)	240.9 (<0.001)	98.3
	SMD_w 48-0	-3.56 (-5.18 : -1.93)	20.9 (<0.001)	95.2	-4.45 (-6.42 : -2.47)	83.4 (<0.001)	97.6	-4.09 (-5.41 : -2.78)	147.3 (<0.001)	97.3

from the previous secondary studies (systematic reviews or review articles). First, as far as the search revealed, the present study is the first systematic review that has combined only primary studies (clinical trials) on this subject. Second, it is the only systematic review or even secondary study that has combined the findings of the primary studies using quantitative/statistical meta-analysis.

Based on the results obtained using a combination of the primary studies, the manna of cotoneaster was effective in reducing serum bilirubin levels in the neonates and this effectiveness reached its peak about 36 hours after the intervention. These findings are consistent with the results of the other clinical trials using this particular form of intervention(Azadbakht et al., 2005; Rafieian-Kopaei et al., 2016; Ameli et al., 2017).

According to Iranian traditional medicine, the manna induces the excretion of bile from the liver and the gallbladder and it suggests the mechanism of manna in the subsequent decrease in the level of serum bilirubin. In addition, the main compound of the manna is mannitol which induces the most therapeutic effects (Azadbakht et al., 2005; Fakhri et al., 2017). These traditional medicine practices help in the understanding of the mechanism of action by which the manna is effective in the treatment of neonatal jaundice.

Combining the SMC showed that the effectiveness of the manna of cotoneaster was higher compared to phototherapy at least 24 and 36 hours after the intervention. This result is inconsistent with the results of some of the clinical trials. This disparity of findings can be attributed to two reasons. First, all the clinical trials conducted in this field have examined the effectiveness of this intervention (whether the between-group or the within-group effectiveness) only with statistical tests (the independent or paired t-test) and the p value. Given the small sample size in most of the trials, the possibility of false negative responses is evidently too high due to the low statistical power of the tests. Second, and not completely irrelevant to the first reason, no relationship strength indexes were used or measured in these studies.

Although measuring relationship strength indexes can resolve the weakness of using solely statistical tests in clinical trials with a low statistical power, the reviewed researchers had not used these indexes in their studies. The disparity between the results of the present systematic review/meta-analysis and the results

phototherapy (as the standard or routine treatment in neonatal jaundice) may thus be attributed to the higher strength of the meta-analyses and the present study's measurement of the relationship strength index, especially from different perspectives, i.e. within-group and between-group. The limitations of this systematic review and meta-analysis can be summarized as follows. The first and foremost limitation was the relatively small number of primary studies extracted in this systematic review.

Although there were six clinical trials in some meta-analysis combinations, in some of the combinations, especially in the 48 hours post-intervention combination, only two studies were qualified and a meta-analysis combination with such small number of primary studies cannot improve the problem of the low strength of the majority of the clinical trials reviewed. Neither can it increase the generalizability of their results (by increasing the number and variety of studies with different underlying and clinical conditions, etc.). Although in many cases, the researchers of secondary studies have to combine a very small number of primary studies, the smaller the number of primary studies used, the more will be the limitations faced for performing the statistical tests in the meta-analysis (such as subgroup analysis, sensitivity analysis, publication bias assessment, etc.). Certainly, in this systematic review and meta-analysis, which analyzed various subgroups for the quality of the primary studies as one of its subgroup analyses, the presence of only three studies and even less (i.e. two) in each subgroup was a serious weakness for the interpretation and application of the analysis. And even in the methods such as meta-regression, which are less restrictive with even a small number of primary studies (compared to subgroup analysis), such a small number of studies as 10 can be a serious drawback for the interpretation of the analysis results. The second limitation of this systematic review was the very low geographical diversity of the eligible clinical trials.

Despite the approach used for the review of the studies and especially the search strategy, which meant that the search for primary studies was carried out in a large number of databases (including international databases), all the studies extracted had been conducted Iran, and even then, their geographical diversity within Iran was relatively low. Moreover, the dependence of some of the contributing factors on the effectiveness of the interventions, such as genetic, cultural and natural attributes, in conditions where the geographical generalizability of the primary studies is also limited, may be considered a serious drawback. Evidently, the limited consumption of the manna of cotoneaster products in some countries and cultures is an obstacle to the design of more primary studies on this subject.

The findings of the ethnographic and cultural studies on traditional medicine in Asian countries have shown that these products are used in different forms among some common cultures in Asia, such as in China, Afghanistan, Pakistan, India, etc. Future studies should pay a greater attention to the role of the primary studies on the subject, especially standard clinical trials, which have been conducted in countries other than Iran. The third limitation of this systematic review was the relatively low methodological quality of the majority of the primary studies reviewed. Although the researchers of these studies had announced that their clinical trials were randomized and double-blind, the Cochrane Collaboration's tool yielded a quality score less than 3 for most of the studies two of the trials even received a quality score of zero. This weakness becomes more discernible when the subgroup analysis performed confirms the relationship between the methodological quality of the trials and the relationship strength index in most of the measures calculated. If this systematic review was not faced with the issue of the small number of primary studies, it would have been able to draw the final conclusion only from the relatively-high-quality trials subgroups.

Conclusion

Although the findings of this systematic review and meta-analysis confirm the effectiveness of the manna of cotoneaster products in the treatment of neonatal jaundice compared to the standard interventions or treatments (phototherapy), the primary studies on the subject, particularly the standard clinical trials of high methodological quality, need to be further encouraged. A higher geographical diversity of primary studies in addition to an increased consistency of the findings, would facilitate further systematic reviews and meta-analyses with a larger number of the primary studies and these two positive factors can largely help resolve the limitations faced in this study.

Conflict of Interest

There is no potential conflict of interest. The authors alone are responsible for the content and writing of the paper.

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