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META-ANALYSIS

The cost-effectiveness of hypertonic saline inhalations for infant bronchiolitis: a decision analysis

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Abstract

Background This study evaluated the cost-effectiveness of hypertonic saline (HS) inhalations for infant bronchiolitis, compared to normal saline inhalations or standard treatment without inhalations as controls.

Methods The decision tree in the decision analysis was used to calculate the expected costs. Actual cost data were obtained from our retrospective case-control study on bronchiolitis treatment. The effectiveness of treatment, based on the hospitalization rate of those admitted to the emergency department and the length of stay (LOS) of those who were hospitalized, was collected from previous studies. For the effectiveness estimations, we made a meta-analysis summarizing the results of the meta-analysis of the Cochrane review in 2013 and the results of 10 studies published after it.

Results The mean hospitalization rate was 24.7% in the HS inhalation group and 32.6% in the control group [risk ratio: 0.80, 95% confidence interval (CI) 0.67–0.96] and the mean LOS was 3.736 (HS group) and 4.292 (controls) days (mean difference: − 0.55 days, 95% CI − 0.96 to − 0.15), respectively. The expected costs per patient, when both inpatients and outpatients were included, were €816 ($1111) in the HS inhalation group and €962 ($1310) in the control group. The expected costs per hospitalization, when only inpatients were included, were €2600 ($3540) in the HS inhalation group and €2890 ($3935) in the control group.

Conclusions HS inhalations slightly reduced the expected hospitalization costs of infant bronchiolitis. However, the low effectiveness, rather than the cost, is the factor that will limit the use of HS inhalations in infant bronchiolitis.

Keywords Bronchiolitis · Cost-effectiveness · Decision analysis · Hospitalization costs · Hypertonic saline

Introduction

Bronchiolitis is the most common infection requiring hospital care in western infants [1]. A third of all children present with wheezing under two years of age [2], 1–5% of the infants are hospitalized for bronchiolitis [3–5], and 6–9% of the hospitalized infants need intensive care [6–9].

Bronchiolitis is diagnosed clinically [10]. The symptoms and signs get worse for five days on average and then gradually improve [9]. Treatment is supportive and consists of oxygen administration, fluid supplementation and ventilator support, if needed [1, 3, 10, 11].

Over the last decade, many studies provided evidence that hypertonic saline (HS) inhalations may be beneficial in bronchiolitis by reducing mucosal swelling [12] and improving mucus clearing [13]. In the 2013 Cochrane review, the length of stay (LOS) in hospital was shorter and the clinical severity scores were lower in those treated with HS compared to normal saline (NS) [12]. When the data of 11 subsequent studies were added to supplement the 2013 review, the LOS was shorter only in patients who stayed ≥ 3 days in hospital, and the hospitalization rates were reduced only in those treated with multiple inhalations [14].

Bronchiolitis causes an outstanding disease burden in society, leading to marked financial costs [15]. In our recent study, the estimated annual direct hospitalization costs were between €1.5 million and €4.4 million ($2 million and $6 million) in Finland, which has a population of five million people [16].

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Economic considerations have an increasing role in health care at all stages from planning to management [17]. Decision analysis is a formal modeling process, which uses mathematical relationships to define all possible consequences that can result from the treatments being evaluated [18]. In this study, we used decision analysis to evaluate the cost-effectiveness of the HS inhalations in infant bronchiolitis compared to the NS inhalations or no inhalations.

Methods

Design

This study evaluated the cost-effectiveness of the HS (3–7%) inhalations for infant bronchiolitis versus NS (0.9%) inhalations or standard care with no inhalations (controls), by comparing expected costs obtained from the decision tree in decision analysis. The effectiveness measures were the differences in hospitalization rates between patients admitted to the emergency department (ED) and the differences in LOS in hospital between the HS inhalation and control groups. Information for both measures were obtained from the previously published randomized controlled studies (RCT) on HS inhalations in infant bronchiolitis. For the effectiveness estimations, we made a meta-analysis including the results of the Cochrane 2013 meta-analysis [12] and the results of later studies. The costs for ED, ward and pediatric intensive care unit (PICU) settings were real hospitalization costs obtained from our recent study [16].

Literature review

The Cochrane review on HS inhalations in infant bronchiolitis included data until May 2013 [12]. We supplemented that data with RCTs published between May 2013 and April 2016, using the search terms "bronchiolitis" and "hypertonic and/or saline". The inclusion criteria were that the study compared HS (≥ 3%) inhalations to NS inhalations or to standard care without inhalations, and that bronchiolitis was defined as first breathing difficulty induced by respiratory infection at age under 24 months. We found 111 studies and accepted 29 based on the title, 16 after reading the abstract and finally 10 after reading the full text. Thus, the data on the effectiveness of HS inhalations in infant bronchiolitis of the present study consisted of the Cochrane 2013 review [12] and 10 RCTs published after the review (Table 1) [19–28].

The 2013 Cochrane review included 560 infants who had received HS inhalations (503 of them 3% saline) for bronchiolitis [29–34]. They had significantly lower LOS in hospital than those treated with NS inhalations, the mean difference (MD) being − 1.15 days and the 95% confidence interval (95% CI) − 1.49 to − 0.82 [12]. Four studies reported hospitalization rates [35–38], which were 8.4% in 191 infants who received HS inhalations and 13.2% in 189 infants who received NS inhalations (pooled risk ratio: 0.63, 95% CI 0.37–1.07) [12].

Ten RCT studies [19–28] published after the Cochrane review included 1615 infants with bronchiolitis; nine studies compared HS inhalations with NS inhalations [19–27] and one with standard care without inhalations [28]. The LOS was reported in 6 studies and varied from 1.87 to 5.6 days in 441 infants who received HS and from 1.82 to 5.4 days in 252 infants who received NS inhalations [21–26]. The hospitalization rates in those admitted to the ED were reported in two studies being 42 and 71% in 83 infants who received HS inhalations, and 49 and 65% in 80 infants who received NS inhalations [19, 20].

A RCT from the USA [27] included 408 infants with bronchiolitis and reported a significantly reduced hospitalization rate favoring HS over NS inhalations (28.9 vs. 42.6%, respectively). The odds ratio was 0.55 (95% CI 0.36–0.83). The LOS in hospital did not differ between these groups [27].

A study from the UK compared 290 hospitalized infants with bronchiolitis treated with HS inhalations to those treated with standard care without inhalations. In that study, the mean LOS in hospital was 4.2 days in both groups [28].

The analysis strategies

Statistical analyses were performed with Review Manager version 5.3 (the Nordic Cochrane Center, the Cochrane Collaboration, 2014) and with TreeAge Pro version 2015 (TreeAge Software, Inc. Williamstown, Massachusetts, USA). We performed a meta-analysis including 10 recent studies identified via our search strategy and then a further meta-analysis including these 10 studies and those included in the Cochrane 2013 review [12]. We used the decision tree for the cost-effectiveness analysis of the hospitalization rate data (model 1) and the hospital stay data (model 2).

The decision trees were run three times using the means of the hospitalization rate or the LOS, and the effectiveness: first with the details of the studies included in the Cochrane 2013 review [29–38], then with the details of the later studies not included in the Cochrane review [19–28] and finally with the details of all studies [19–38].

Model 1 was constructed using the mean costs per admission. The effectiveness measure for those admitted to the ED (Fig. 1a) was the mean relative reduction in hospitalization rate, calculated from the meta-analysis including the published data [19, 20, 27, 35–38].

Model 2 was constructed using the mean costs per day multiplied by the LOS. The effectiveness measure for those treated in hospital (Fig. 1b) was the relative reduction in LOS, calculated from the meta-analysis including

Table 1 The designs and results of the available studies on hypertonic saline inhalations in infants with bronchiolitis

Basic data provided by the studies	The study protocol	Results of the main effects
Zhang et al. [12]	Cochrane review 11 RCT or quasi-RCT ($n = 1090$) Infants under 24 mon of age Compared ≥ 3% HS, with or without bronchodilators, to 0.9% NS	Significantly reduced LOS (2.6–6 vs. 3.5–7.4; 1.15 days shorter) in HS group. Significantly reduced clinical severity score on first 2 days. Reduced admission rate, but not significantly (16/191 vs. 25/189, risk ratio = 0.63)
Florin et al. USA [19]	RCT, blinded HS ($n = 31$), NS ($n = 31$) Infants under 24 mon of age Compared 3% HS to 0.9% NS. Both HS and NS doses were 8 mL once in ED.	No significant difference on hospital admission rate (71 vs. 65%) or in clinical severity scores
Jacobs et al., USA [20]	RCT, blinded HS ($n = 52$), NS ($n = 49$) Infants from 6 wk to 18 mon of age Compared 7% HS to 0.9% NS, both with adrenaline. Both HS and NS doses were 3 mL once in ED and then every 6th h if admitted for the first 24 h in hospital	No significant difference between hospital admission rates (42 vs. 49%), ED or inpatient LOS or in clinical severity score
Nenna et al., Italy [21]	RCT, double-blind HS with HSHA ($n = 21$), NS ($n = 18$) Infants under 7 mon of age Compared 7%/0.1% HSHA to 0.9% NS. Both HS and NS doses were 2.5 mL twice a d for 3 days	No significant differences in LOS (4.1 vs. 4.8 days) or in the clinical severity score
Ojha et al., Nepal [22]	RCT, double-blind HS ($n = 28$), NS ($n = 31$) Infants under 24 mon of age Compared 3% HS to 0.9% NS. Both HS and NS doses were at least 4 mL every 8th h	No significant differences in LOS (44.82 vs. 43.6 h) or normalization of clinical severity score
Sharma et al., India [23]	RCT, double-blind HS ($n = 125$), NS ($n = 123$) Infants under 24 mon of age Compared 3% HS to 0.9% NS. Both HS and NS doses were 4 mL every 4th h	No significant differences in LOS (63.93 vs. 63.51 h) or in clinical severity score
Teunissen et al., The Netherlands [24]	RCT, double-blind, multi-center 3% HS ($n = 84$), 6% HS ($n = 83$), 0.9% NS ($n = 80$) Infants under 24 mon of age Compared both 3% HS and 6% HS to 0.9% NS. Both HS and NS doses were 4 mL every 8th h and the first doses were administered with the salbutamol	No significant differences in LOS (69 or 70 vs. 53 h) or in clinical severity score
Flores et al., Portugal [25]	RCT, double-blind HS ($n = 33$), NS ($n = 35$) Infants under 12 mon of age Compared 3% HS to 0.9% NS, both with salbutamol. Both HS and NS doses were 3 mL every 6th h	No significant differences in LOS (5.6 vs. 5.4 days) or in the clinical severity score

Table 1 (continued)

Basic data provided by the studies	The study protocol	Results of the main effects
Tinsa et al., Tunis [26]	RCT, double-blind HS (n = 31), HS with epinephrine (n = 36), NS (n = 26) Infants under 12 mon of age Compared both 5% HS alone and 5% HS with epinephrine to 0.9% NS. Both HS and NS doses were 4 mL every 4th hour	No significant differences in LOS (3.6 or 3.5 vs. 4.48 days) or in clinical severity score
Wu et al., USA [27]	RCT, double-blind HS (n = 211), NS (n = 197) Infants under 24 mon of age Compared 3% HS to 0.9% NS. Both HS and NS doses were 4 mL with salbutamol up to 3 times in ED and every 8th h on ward	Significantly reduced hospital admission rate when given in ED: 28.4% HS compared to 42.6% NS, odds ratio = 0.55 (95% CI = 0.36-0.83). No significant differences in LOS (3.16 vs. 3.92 days) or in clinical severity scores
Everard et al., UK [28]	RCT, multi-center HS (n = 158, 141 analyzed) SC (n = 159, 149 analyzed) Infants under 12 mon of age Compared 3% HS to SC. HS doses were 4 mL every 6th hour	No significant differences in hospital LOS (100.6 vs. 101.3 h) or admission to PICU (8.5 vs. 10.1%) between the groups

RCT randomized controlled trial, *HS* hypertonic saline, *NS* normal saline, *LOS* length of stay, *ED* emergency department, *PICU* pediatric intensive care unit, *CI* confidence interval, *SC* standard care, *HSHA* hyaluronic acid

the published LOS data [21–26, 29–34]. The probability of being treated in the PICU after hospitalization was set to 6% in both HS inhalation and control groups in both models, based on the two recent Finnish studies [8, 9].

Effectiveness

The measure of effectiveness (E) was the change in the hospitalization rate or LOS in hospital of the HS inhalation group, in relation to respective figures in controls: $E = 1 + \left(\left(\int_c - \int_{hs}\right) / \int_c\right)$, where $\int_c$ was the admission rate (%) or LOS (days) in controls and $\int_{hs}$ the admission rate (%) or LOS (days) in the HS inhalation group. In controls, the effectiveness was set to be 1.0. The effectiveness was only calculated if the difference in the hospitalization rate or LOS in hospital between the HS inhalation and control groups was statistically significant in the meta-analysis. If there was no statistically significant difference, the effectiveness was set to be 1.0 in both groups.

Cost data

Data on the costs of bronchiolitis treatment were obtained from our recently published study [16] of 80 infants treated in the PICU, 104 treated on the ward and 56 treated in the ED at age under 12 months.

The costs are expressed in Euros as the year 2012 value of money. They were then converted to US dollars using the average conversion rate (€1 = $1.3615) in 2012.

The costs consisted of daily municipal billing for every patient. When we analyzed the hospitalization rates (model 1), we used the mean total direct costs, including the costs for ED treatment (all infants) and for ward and PICU treatments (hospitalized infants) [16]. The mean costs for just ED treatment were €359 ($489) and for hospital treatment €1834 ($2497) if intensive care was not needed and €8061 ($10 975) if intensive care was needed.

When we analyzed the inpatient treatment (model 2), we used the mean total direct costs per day per the patient multiplied by LOS, and included ED, ward and PICU costs. These costs were €223 ($304) for the ED attendance, €232 ($316) for the ED attendance and €556 ($757) for the ward days if intensive care was not needed, and €533 ($726) for the ward days and €961 ($1308) for the PICU days if intensive care was needed [16].

Because HS inhalations mean low-cost treatment, we included the same costs for HS inhalation and control groups. The difference in costs between HS and NS inhalations per dose was only €0.02 ($0.03).

The incremental cost effectiveness ratio (ICER) was calculated as, part of the decision tree analysis. The ICER describes the monetary expenses or savings to gain one additional unit of effectiveness: $\text{ICER} = \left(C_{\text{intervention}} - C_{\text{control}}\right) / \left(E_{\text{intervention}} - E_{\text{control}}\right)$, where C was the cost and E was the effectiveness [39].

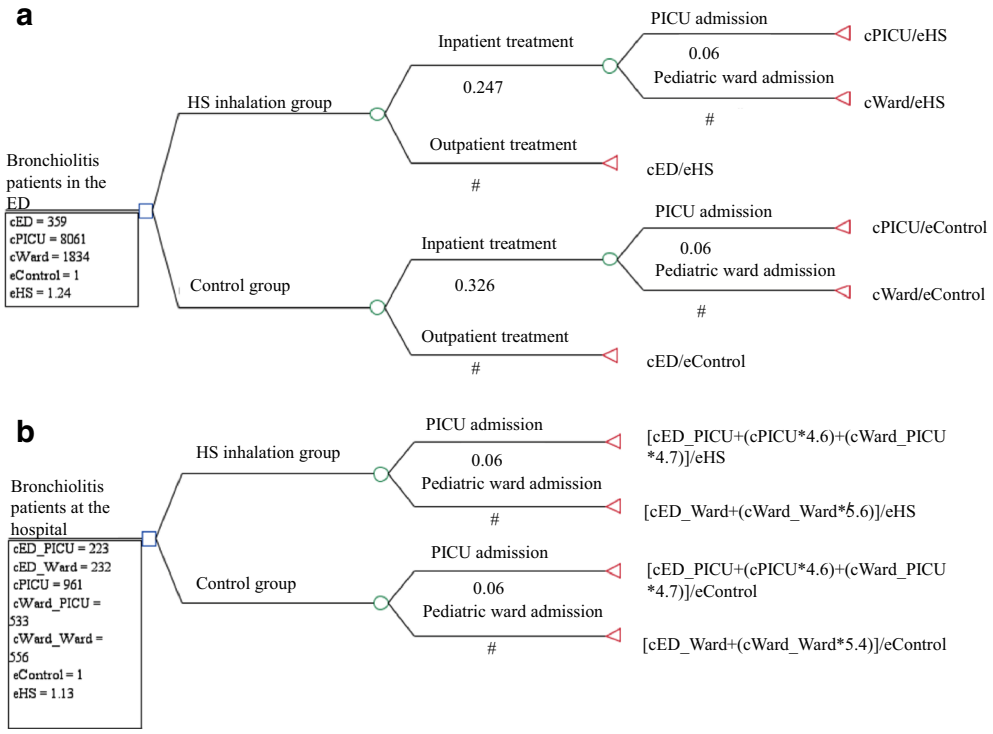

Fig. 1 **a** The decision tree for model 1: hypertonic saline inhalations compared to control treatment in infant bronchiolitis in the emergency department. **b** The decision tree for model 2: hypertonic saline compared to control treatment in infant bronchiolitis in the hospital

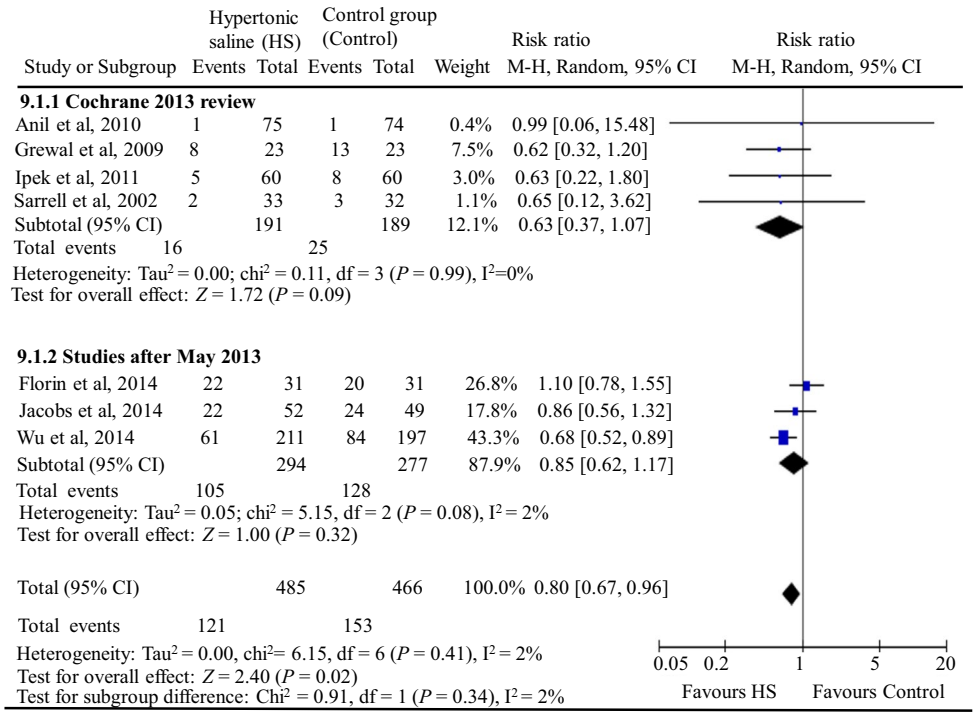

Fig. 2 Meta-analysis on the hospitalization risk of infants with bronchiolitis treated with hypertonic saline inhalations, compared to controls. The figure presents first the results of the Cochrane 2013 review, and then the results of the studies published after it, and last the combined results of all studies

Table 2 The expected costs of bronchiolitis hospitalizations per patient with different hospitalization rates obtained from previous studies, in which hypertonic saline inhalations were given in the emergency department

Hospitalization rate (%), hypertonic vs. normal saline inhalations, effectiveness (*E*) of the treatment	Expected costs as € ($), per patient when the values of the costs [16] were expressed as means	Incremental cost effectiveness ratio, savings per 1% reduction in the hospitalization rate, calculated as € ($)
HS 8.4%, E1	514 (700)	–
Control 13.2%, E1 (from Cochrane review 2013)	603 (821)	
HS 35.7%, E1	1019 (1387)	–
Control 46.2%, E1 (from studies publisher after May 2013)	1213 (1651)	
HS 24.7%, E1.24	816 (1111)	− 6 (− 8)
Control 32.6%, E1 (from all studies)	962 (1310)	

Calculated first separately for hospitalization rates from studies included in the Cochrane 2013 review and from the studies published after May 2013 and not included in the Cochrane review, and then combining all studies. *HS* hypertonic saline inhalation group

Sensitivity analyses

The observed effects of HS inhalations in infant bronchiolitis in the available studies were conflicting. Because of this uncertainty, we performed one-way and two-way sensitivity analyses by varying the costs (the upper and lower limits of 95% CIs), hospitalization rates and LOS in hospital. In addition, we also performed decision tree analysis for every single included study separately.

Results

The risk of hospitalization in the ED was lower in the HS inhalation group than in controls in the meta-analysis including seven RCTs and 951 infants with bronchiolitis. The mean hospitalization rate was 24.7% in the HS inhalation group and 32.6% in controls, and the risk ratio was 0.80 (95% CI 0.67–0.96) (Fig. 2). With these assumptions and applying the mean real costs per admission [16], the expected costs

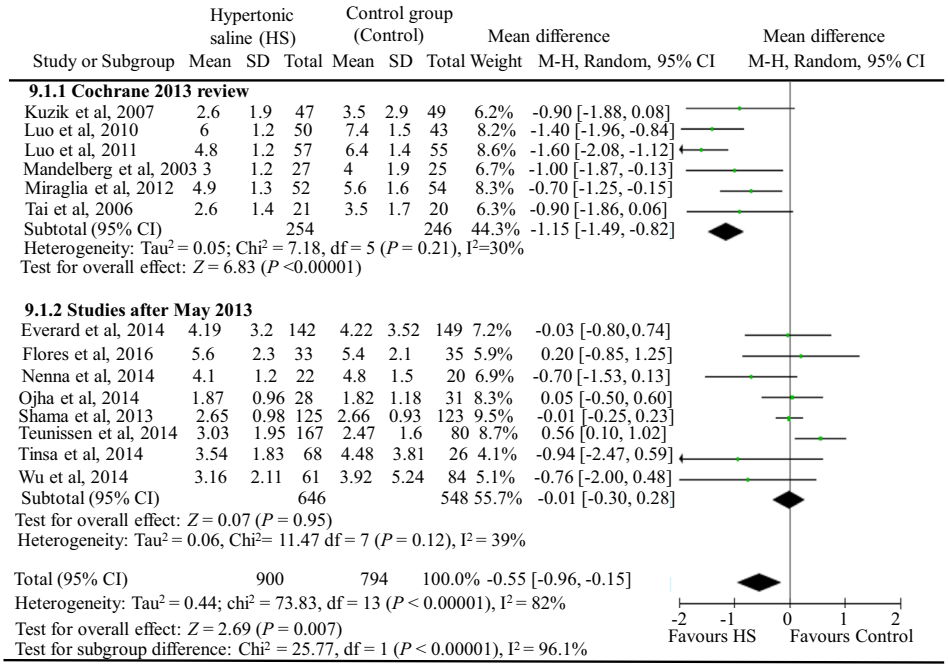

Fig. 3 Meta-analysis on the length of stay in hospital of infants with bronchiolitis treated with hypertonic saline inhalations, compared to controls. The figure presents first the results of the Cochrane 2013 review, and then the results of the studies published after it, and last the combined results of all studies

Table 3 The expected costs and incremental cost effectiveness ratios of bronchiolitis hospitalization per treatment episode in inpatients treated with hypertonic saline inhalations compared to those treated with normal saline inhalations or no inhalations

Length of stay in hospital (d), hypertonic vs. normal saline inhalations, effectiveness (*E*) of the treatment	Expected costs as € ($), per treatment episode when values of the costs [16], per day were expressed as mean	Incremental cost effectiveness ratio, savings per 1-h reduction in the LOS calculated as € ($)
HS 4.442, E1.21	2969 (4042)	− 22 (− 30)
Control 5.597, E1 (from Cochrane review 2013)	3572 (4863)	
HS 3.193, E1	2287 (3114)	–
Control 3.423, E1 (from studies publisher after May 2013)	2291 (3119)	
HS 3.736, E1.13	2600 (3540)	− 22 (− 30)
Control 4.292, E1 (from all studies)	2890 (3935)	

Calculated first separately for mean length of stay in hospital from studies included in the Cochrane 2013 review and from the studies published after May 2013 and not included in the Cochrane review, and then combining all studies. *HS* hypertonic saline inhalation group

per patient were €816 ($1111) in the HS inhalation group and €969 ($1310) in controls (Table 2). The ICER was €-6 ($-8) per one percent reduction in the hospitalization rate. The effectiveness of 1.24 means a 24% reduction in the hospitalization rate, which indicates €146 ($199) savings per patient (Table 2).

The LOS in hospital was shorter in the HS inhalation group than in controls in the meta-analysis including 14 RCTs and 1694 infants with bronchiolitis. The mean LOS was 3.7 days in the HS inhalation group and 4.3 days in controls, and MD was − 0.55 days (95% CI − 0.96 to − 0.15) (Fig. 3). With these assumptions, and applying the mean real hospital costs per day [16], the expected hospitalization costs per treatment episode were €2600 ($3540) in the HS inhalation group and €2890 ($3935) in controls (Table 3). The ICER was €-22 ($-30) per 1 h reduction in the LOS in hospital. The mean difference of − 0.55 days in LOS between the HS inhalation and control groups means a 13.2 h reduction in LOS and a 1.13 effectiveness, which indicates €291 ($396) savings per treatment episode.

Sensitivity analyses

In model 1, the expected costs per patient, when the upper and lower limits of the 95% CIs for the costs [16] were applied, varied from €352 ($479) to €1883 ($2564) in the HS inhalation group and from €352 ($479) to €1757 ($2392) in controls.

In model 2, the expected costs per treatment episode, when the upper and lower limits of the 95% CIs for the costs [16] were applied, varied from €1481 ($2016) to €3769 ($5131) in the HS inhalation group and from €1457 ($1984) to €3658 ($4980) in controls.

The expected costs were both less and more expensive in the HS inhalation group compared to controls in both model 1 and model 2 sensitivity analyses.

Discussion

We evaluated the cost-effectiveness of HS inhalations compared to NS inhalations or no inhalations and did not find any substantial cost-effectiveness either in the outpatient or inpatient settings. This study suggests that the expected costs for treating infants with bronchiolitis are marginally lower for HS inhalations compared to control treatment. Although the costs were lower, also the effectiveness of HS inhalations was low, and even absent in the latest studies [19–28].

Treating infants with bronchiolitis with HS inhalations in the ED saves costs if this treatment reduces hospitalization rates. Three of four available studies reported such reductions [12, 20, 27]. In the double-blind RCT with over 400 infants, inhalations with 3% HS were repeated three times, and there was a significant 13.7% reduction in hospitalization rates between the HS and NS inhalation groups [27]. In our meta-analysis, the mean reduction in the hospitalization rate was 24%, and this indicates €146 ($199) savings per patient in our theoretical model.

Treating infant bronchiolitis with HS inhalations in hospital saves costs if this treatment reduces the LOS in hospital or the need or duration of intensive care. All six studies included in the 2013 Cochrane review reported such LOS reductions [29–34]. Seven studies, published after the review, compared the HS inhalations with NS inhalations [21–27] in infants hospitalized for bronchiolitis and one study compared the HS inhalations with standard care without inhalations [28], and the results of these studies did not favor HS inhalations.

The mean reduction in the LOS in the studies [21–34] included in the present meta-analysis was 13 h. The ICER caused by HS inhalations was low, and so, the limiting factor for the use of the HS inhalations for bronchiolitis in infants is the low effectiveness. In addition, the 13-h reduction may not implicate any true savings, in particular

if the hospital invoicing is based on the diagnosis and estimated costs per day or per period.

In the two most recent meta-analyses, including selected patients to diminish heterogeneity, HS inhalations did not anymore shorten significantly LOS in hospital. The MD was − 0.22 (95% CI − 0.54 to 0.10) [40] and − 0.26 (95% CI − 0.82 to 0.30) [41], respectively, and these slight differences were not clinically, statistically nor economically significant.

This study has three strengths. Firstly, the decision analysis provided an opportunity to combine different available data in one analysis, including the cost and effectiveness data measured using different outcomes. The reliability of the results was evaluated by sensitivity analyses. Secondly, the costs included in the present analyses represented a real transfer of money from municipalities to the hospital. All costs we included were collected for 13 years and were based on real patients and real daily municipality billings [16]. Thirdly, the results from the latest trials were included in our meta-analyses together with the previous results included in older meta-analyses.

There are some limitations in this study. The cost data were from the years 2000 to 2012 corrected to the year 2012 level [16], and no further corrections were made. Bronchiolitis treatment and the costs in question, including hospital prices, did not markedly change between 2012 and 2017. Furthermore, the difference in costs between the groups is more informative than the absolute costs in the decision analysis. The proportional difference stays at the same level independently from the realized cost level.

In conclusion, the HS inhalations were marginally cost-effective in the outpatient treatment of infant bronchiolitis. The HS inhalations were not cost-effective in the inpatient treatment of infant bronchiolitis.

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Author Contributions PH participated in the designation of the study, collected the data, performed and participated in the interpretation of the analyses and participated in the writing of the manuscript. MM participated in the writing of the manuscript. MK was responsible of the designation of the study, participated in the interpretation of the analyses and participated in the writing of the manuscript. All authors approved the final version of the manuscript.

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Compliance with ethical standards

Ethical approval The data collection on the costs of bronchiolitis was carried out with the permission of the Chief Physician of the Tampere University Hospital. The data of the effectiveness was collected from the PubMed as a literature search.

Conflict of interest None of the authors' declare that they have no conflict of interest.

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