Brief Report

Iron Supplementation for the Treatment of Breath-Holding Spells: A Systematic Review and Meta-Analysis

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Introduction

A breath-holding spell (BHS) is a common clinical entity where a young child involuntarily holds their breath until they lose consciousness. An estimated 0.1% to 4.6% of the children younger than the age of 2 years have had one or more episodes of BHS.[1,2] Affected children often begin having such episodes in the first year of life and continue to have them regularly until approximately 4 years of age. BHS episodes are associated with crying and emotional or painful triggers. During the process of breath-holding, a child can turn cyanotic, stiffen, and can jerk their body prior to losing consciousness. The child generally awakens within a minute, is not disoriented, and does not appear postictal.[1,3]

Clinically, BHSs are distinguished from other causes of consciousness loss including cardiovascular or neurological problems by history, electrocardiogram, and electroencephalogram. The course of the disorder is generally considered benign and children develop normally without sequela.[1]

A strong association of anemia and BHS was first reported in 1963 and has since been confirmed by others.[1,4,5] An estimated 23.5% to 69% of children with BHS are iron deficient, and many have anemia.[6] Clinical studies aimed at treating the iron deficiency of subjects with BHS have been performed but have been limited by small sample sizes and inconsistent methodology. We therefore sought to combine these studies into a meta-analysis.

Methods

Article abstracts were located by searching PubMed using the combination of key terms: breath-holding spells AND iron. Abstracts were then screened to identify relevant studies where subjects were enrolled with a diagnosis of BHSs, and subjects were treated with iron supplementation. Acceptable study designs included observational single-arm studies and randomized clinical trials (RCTs). Only studies published after 1990 and reported in English were included.

The main variables of this study were BHSs and iron supplementation. Articles were coded in duplicate to calculate study effects. Discrepancies in coding required agreement between the 2 first authors to be considered resolved. Our effect size measure was risk difference, which was calculated as a 100% event rate at baseline minus the event rate following treatment. We defined treatment success as a $>50\%$ reduction in the frequency of attacks, a definition used in 8 of the 12 studies. An overall summary effect size was estimated by pooling individual study effect sizes weighted by the inverse of its associated variance. We calculated the degree of heterogeneity across studies and tested its significance using the Q-statistic in order to inform whether the analysis should be done with random or fixed effects modeling.

There were methodological and analytical differences among studies that required secondary analysis. For example, 2 studies reported their results with 3×2 contingency tables without using our prespecified definition of treatment success.[5,7] For these studies, we defined treatment success as a reduction of BHS from >5 episodes per week to <5 episodes per week. Another study was a RCT against the active comparator, piracetam.[8] We treated this study as a single-arm observational study consistent with the other studies used. This study

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Table 1. Characteristics of the Studies Included in the Present Meta-Analysis.

Study	Year	Age at Baseline (Months)	Sample	Study Type	Dose of Fe (mg/kg/day)	Duration (Weeks)	Subjects (n)	Risk Difference
Daoud et al[9]	1997	15 (mean)	Both	RCT	5	16	33	82%
Abosdera et al[7]	2016	4 to 48	IDA	Pre-post	6	12	40	77%
Bhat et al[16]	2006	Up to 36	IDA	Pre-post	6	12	35	77%
Dai and Demiryürek[17]	2019	12 to 48	IDA	Pre-post	3	12	146	58.80%
Ghareib et al[8]	2017	6 to 72	IDA	Pre-post	6	12	35	66%
Gurbuz et al[10]	2018	1 to 48	Both	Pre-post	4	12	312	86%
Handan et al[11]	2005	3 to 48	ID	Pre-post	5	4	22	100%
Hussain et al[18]	2016	6 to 72	IDA	Pre-post	NP	12	45	89%
Jain et al[12]	2017	6 to 36	Both	Pre-post	3	12	100	96%
Mocan et al[19]	1999	6 to 30	IDA	Pre-post	6	12	63	84%
Tonekaboni et al[13]	2006	3 to 60	Both	Pre-post	6	12	35	83%
Ziaullah et al[5]	2005	6 to 60	IDA	Pre-post	6	8	50	78%

Abbreviations: RCT, randomized clinical trial; IDA, iron deficiency with anemia; ID, iron deficiency without anemia; Both, iron deficiency without anemia and iron deficiency with anemia; NP, not provided.

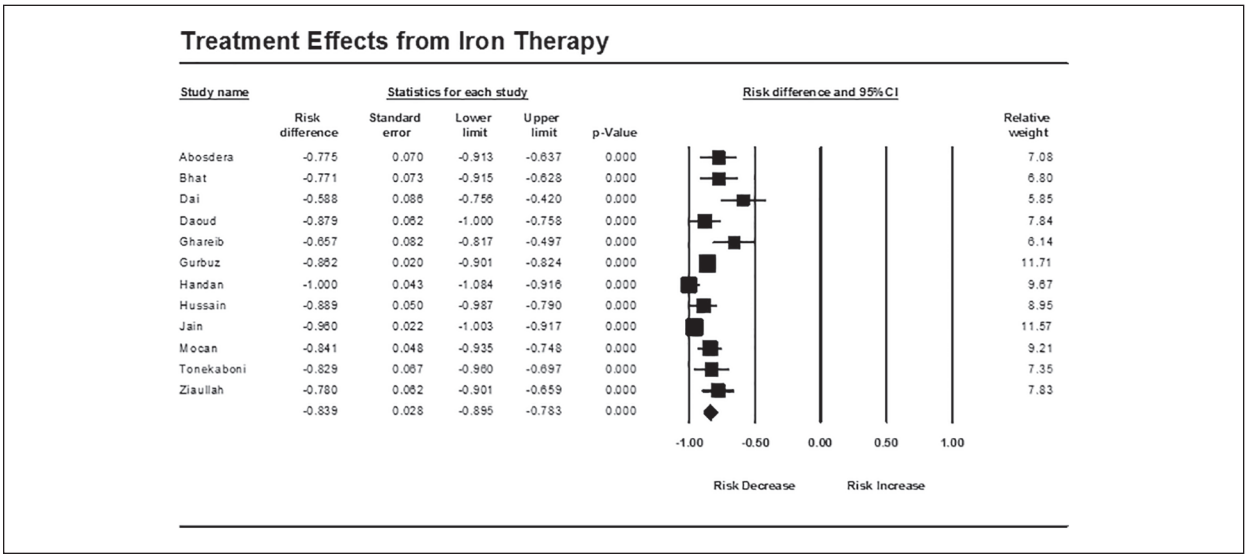

Figure 1. Forest plot of observational studies following treatment of breath-holding spells with iron.

also reported the mean reduction in episodes. The study by Daoud et al was RCT with a placebo group. In order to include this study in a meta-analysis of observational studies, we treated the treatment arm as a single-arm observational pretest, posttest study.[9]

Results

Our search yielded 35 abstracts from PubMed, of which 8 full texts were then retrieved and more fully evaluated. Forward and backward searches through references and citations discovered an additional 4 studies (Table 1).

The Q-statistic for the 12 studies was 49.52 with a degree of freedom of 11 ($P < .001$), suggesting we should reject the null hypothesis of homogeneity across studies and determine the average effect size using the random-effects model. Under the random-effects model, the risk difference comparing pretreatment frequency of BHS episodes and the frequency of events posttreatment was an 84% (95% confidence interval = 0.78-0.90) reduction, suggesting a highly significant treatment effect of iron on the occurrence of BHS episodes (Figure 1).

Five studies also reported responses among those patients with iron deficiency and without iron deficiency anemia.[9-13] In those studies, the meta risk reduction, 87% (95% confidence interval = 0.76-0.98), was approximately equivalent for both groups, suggesting that iron deficiency anemia is not a necessary

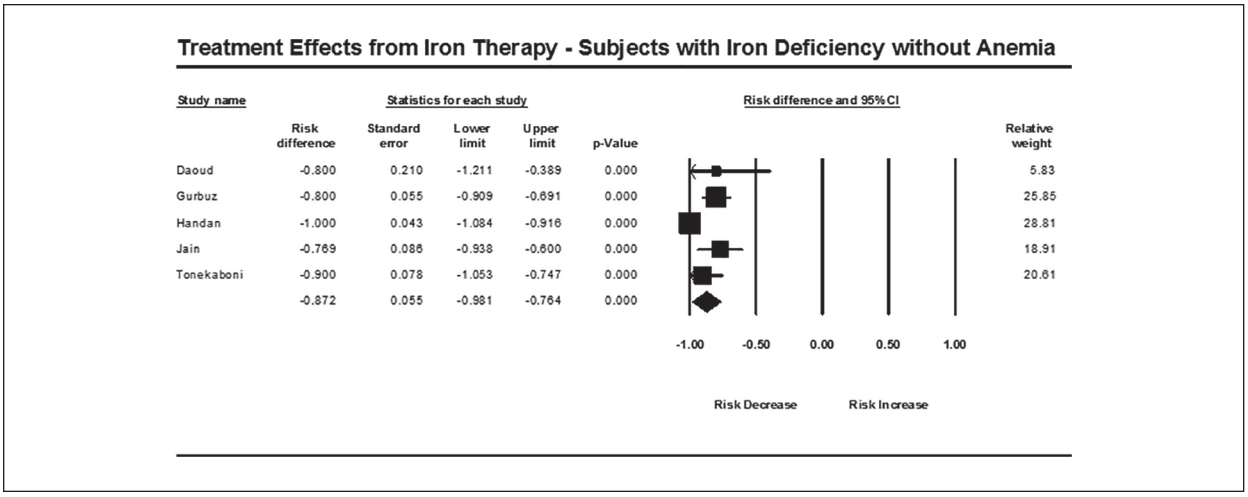

Figure 2. Forest plot of subset of observational studies following treatment of breath-holding spells with Iron.

prerequisite for iron therapy in patients who are mildly iron deficient and have BHSs (Figure 2).

Discussion

In this meta-analysis of observational studies, we found that the use of iron supplementation in subjects with BHS who were iron deficient reduced the frequency of BHS episodes, with an estimated 84% of children experiencing >50% reduction in episodes. These results were also consistent across studies, with all studies reporting substantial reductions in BHS following iron therapy.

This study has several limitations. First, the studies included in this analysis were single-arm observational studies that compared subjects with their baseline assessment. Because most studies did not utilize a control arm, we cannot be certain that individuals selected in these studies were not already trending toward less episodes over time as is seen by the natural history of the illness. One included study in the analysis was a placebo-controlled RCT, and in this study, 87% of the treatment group had a complete or partial reduction in BHS, compared with fewer than 6% in placebo group.[9] Another limitation is that the number of pretreatment episodes varied across studies, ranging from several per month to dozens per month. Also, no Western European or US studies were found in our search, suggesting the epidemiology of BHS might differ between regions of the world. Finally, there is the possibility of publication bias where negative studies might be less likely to be published and found.[14] A funnel plot (not shown) did not suggest publication bias.

Our study suggests that it is the correction of iron deficiency and not iron deficiency anemia that is instrumental in treating BHSs. Of interest is the study by Handan where the investigators detected iron deficiency in subjects with BHSs through the use of the transferrin receptor diagnostic test when standard measures of iron store assessment was normal, and no anemia was present.[11] This suggests that subclinical forms of iron deficiency might be associated with BHSs and corrected by iron therapy. Perhaps the association between iron deficiency and BHSs is better attributed to iron deficiency, particularly in the brain where iron plays a key role in neuronal and glial energy metabolism, myelin synthesis, and neurotransmission.[15]

These data suggest that in children with BHS and iron deficiency, iron therapy reduces the frequency of BHSs. Children with BHSs should be tested for iron deficiency and treated accordingly. Additional studies investigating iron supplementation in BHS without iron deficiency anemia or iron deficiency are warranted.

Author Contributions

EMH conceived the research question and contributed to the manuscript. MRL performed the analyses and contributed to the manuscript. GAA contributed to the development of the research question and contributed to the manuscript.

Declaration of Conflicting Interests

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