Journal of Paediatrics and Child Health

doi:10.1111/j.1440-1754.2010.01790.x

JOURNAL CLUB

Edited by Patrina Caldwell (patrinac@chw.edu.au)

Does iron therapy affect the frequency of breath-holding attacks in children?

Clinical scenario

A two-year-old girl presents with repetitive episodes of facial cyanosis with occasional collapse. The episodes last for less than a minute and occur up to three times a day. She makes a rapid recovery after each episode and her mother states that the episodes are worse when Chloe is tired, irritable or does not get her own way. Her physical examination and past medical history is unremarkable. Blood tests are within the normal range with a low normal haemoglobin result 101 g/L. Her electrocardiogram and electroencephalogram are normal. Breath-holding attacks (BHAs) are diagnosed. It has been postulated that iron may be beneficial for treatment.

Structured clinical question

> In children with BHAs (P), does iron therapy (I) compared to placebo (C) affect the frequency of BHAs (O)?

The clinical question is expressed in the PICO format, where P is the patient population, I is the intervention, C is the comparator and O is the outcome. Further resources detailing this are available online at the Centre for Evidence Based Medicine at www.cebm.net

Search strategy

As BHAs are commonly termed breath-holding spells in some regions, it was decided to use the search term 'breath-holding$.mp' to include both instances. Combining 'breath-holding$.mp' and 'iron' yielded 17 papers in Medline/PubMed (1950–Oct week 2 2009) (the search was also conducted in Excerpta Medica Database [EMBASE] (1980–2009 week 42) and the 17 papers were found within the search results of 21 papers). The papers were filtered to exclude papers irrelevant to clinical practice, duplicate results, breath-holding *per se* and children (Table 1).

Six studies pertaining to iron and breath-holding attacks in children were found. Their attributes and comments relating to methodology and results are detailed in Table 1.

Best paper and critical appraisal

Evaluating those clinically relevant for our patient and with the best level of evidence available (Ib), the paper by Daoud was found to be to be the best available. This paper was critically appraised using the Journal of the American Medical Association (JAMA) guidelines.[1] A simplified checklist for appraising randomised controlled trials (RCTs) as part of the Critical Appraisal Skills Programme is available for use here http://www.phru.nhs.uk/Doc_Links/rct%20appraisal%20tool.pdf

Daoud enrolled all children attending a tertiary children's hospital in Jordan for BHAs over a three-year period and followed each for a period of 16 weeks (weekly for the first eight weeks and every two weeks for the next eight weeks). Blood indices were taken at baseline and at the conclusion of the study. BHAs were diagnosed clinically by a paediatrician and confirmed by a paediatric neurologist.

This population of children, seen at a tertiary children's hospital, may produce referral bias. More severely affected children with BHAs are more likely to be referred, while milder cases may be treated in a local, primary care setting.

A diagnosis of BHAs is usually made clinically and often by excluding other disease processes, such as epilepsy and cardiac arrhythmias. Before the trial was conducted, Daoud established exclusion criteria to omit children with: profound anaemia (haemoglobin < 70 g/L), a history of febrile convulsions or epilepsy, current treatment with anticonvulsant medications, a clinically identified neuromotor delay, growth parameters above or below two standard deviations of standard references and any other serious illness. No children met the exclusion criteria and as the vast majority (67/74; 91%) of the eligible children were enrolled, the sample is felt to be representative of the population of children who have BHA seen at a tertiary children's hospital.

Diagnosis of BHA is a clinical diagnosis made without objective rating scales and as such, is prone to inter-observer variability, which can cause random errors and lead to misclassification bias. To minimise this potential bias, it is often useful to appoint the same operator to conduct all of the diagnoses and interpretation of clinical results or as was performed in this trial, to appoint a 'second opinion' regarding diagnosis because the duration of the trial (three years) made the use of one paediatrician for diagnosis impractical. Even if inter-observer variability existed in this study, this error would not be linked in a systematic way to selection of intervention or comparison groups, which were performed with quasi-randomisation, and as such, should not alter the findings of effectiveness in one direction.

Baseline characteristics are comparable between the intervention (iron) and control (placebo) group. There is a slightly higher degree of anaemia in the treatment group (mean Hb 89 g/L) than in the control group (mean 94 g/L), although this did not reach statistical significance ($P = 0.07$). A higher proportion of less frequent attacks at baseline (<five per month) was seen in the treatment group (45%) versus the placebo group (32%), although this difference was again not significant (P value = 0.52). If this difference was significant in the context of the same outcome results, it might imply that iron reduces the frequency of BHA, more so in children who have infrequent

Table 1 Relevant studies of iron supplementation for breath-holding attacks in children

Citation (country)	Study population	Study design	Level of evidence	Intervention	Follow-up duration	Results	Comments
Daoud 1997[4] (Jordan)	67 children (33 treatment group, 34 placebo group)	Quasi-RCT	Ib	Ferrous sulphate 5 mg/kg/day for 16 weeks (5 mg/kg elemental iron or sulphate compound used?)‡	16 weeks	BHA frequency decreased†: Iron treated group by 88% Placebo group by 6% ($P < 0.01$)	Generally an anaemic population (Baseline Hb 89-94 g/L) Consanguinity correlated with response to treatment (P value = 0.07) Treatment group responders had significantly lower Hb and higher TIBC than non-responders
Paul 1969[5] (India)	30 children (21 boys, 9 girls) divided into 3 groups: 10 with Hb < 100 g/L & given intramuscular iron (treatment group), 10 with Hb < 100 g/L & given 'vitamins' & counselling 10 with Hb >100 g/L & given 'vitamins'	Prospective study (possibly a controlled trial but randomisation uncertain)	IIb	Iron dose according to 'Lahey's formula'§ Iron administered by intramuscular (IM) injection (not oral)	3 months	BHA frequency decreased: Iron treated group by 100% ('good' or 'fair' response) Anaemic no iron group by 40% Non-anaemic no iron group by 60%	All received counselling (co-intervention) 28 children described as poor socio-economic status, 1/3 familial background of psychiatric and psychosomatic disorders Minimal study details provided IM iron not blinded/placebo-controlled Vitamins (control) may contain iron
Ahmad Bhat 2007[6] (India)	59 children (31 boys, 28 girls) 35 anaemic (Hb < 2 SD, mean 79 g/L; treatment group) 24 non-anaemic (mean Hb 110 g/L; control group)	Prospective Study	IIb	Oral iron 6 mg/kg/day for 12 weeks for anaemic children	16 weeks	BHA frequency decreased†: Iron treated group by 77% Non-anaemic (control) group by 29% ($P < 0.01$)	Tendency to younger age of BHA peak frequency in anaemic (treatment) group
Ziaullah 2005[7] (Pakistan)	50 children (31 boys, 19 girls) Mild (Hb 8–12 g/dL) and moderate (Hb 5–8 g/dL) anaemia	Prospective Study	IIb	Oral iron 6 mg/kg/day for 8 weeks for all children	8 weeks	Significant rise in Hb level (from 9.79 g/dL to 11.23 g/dL), a significant fall in BHA frequency ($P < 0.001$)	No comparison group Combined mild & moderate anaemia groups for outcome
Khalifa 2004[8] (Saudi Arabia)	126 children (81 boys, 45 girls) 93 anaemic (Hb <105 g/L, MCV <75 fL; treatment group) 33 non-anaemic (control group)	Retrospective study	IIIb	Oral iron (as ferrous sulphate solution) 6 mg/kg/day for 3 months for anaemic children	3 months	BHA frequency decreased†: Iron treated group by 89% Non-anaemic (control) group by 21% ($P < 0.02$)	Iron only given to anaemic children
Mocan 1999[9] (Turkey)	91 children (56 boys, 35 girls) 63 anaemic (Hb < 105 g/L, MCV < 75 fL; treatment group) 28 non-anaemic (control group)	Case series	IV	Oral iron (as ferrous sulphate solution‡) 6 mg/kg/day for 3 months for anaemic children	3 months	BHA frequency decreased†: Iron treated group by 84.1% Non-anaemic (control) group by 21.4% ($P < 0.02$)	Iron only given to anaemic children 10 children had febrile convulsions (6 in iron treatment group)

†Complete or partial [≥50% reduction] remission.
‡Ferrous sulphate contains only approximately 20% elemental iron (so the child may only have received elemental iron 1 mg/kg/day)
§Lahey's formula is bodyweight (Kg) × (13.5 – Hb (g/dL)) × 2.5 = mg elemental iron to give.[10]

Journal club

BHAs anyway (although they are the ones less likely to be referred to a tertiary children's hospital). The trend to have less attacks over time, a key feature of BHA as children grow out of them as they age, aligns with the concept of 'regression to the mean' and would consequently overestimate the beneficial effect of any intervention.

The major scientific flaw with the Daoud study is the lack of randomised allocation and the lack of information regarding any concealment of the allocation process. The trial is quasi-randomised (by alternating assignment) and has the potential for bias. For those recruiting children into the study, there would be a temptation to place children who appeared pale (anaemic) into the intervention group rather than the placebo group. This is partly borne out in the baseline differences where there is an almost significant ($P = 0.07$) difference in Hb between the control and intervention groups.

A truly RCT would have assigned children to treatment groups using a random number generator or by flipping a coin under observation. Alternating assignment has the potential for bias as the sequence may be predicted and patients then allocated to groups through intention rather than randomisation.

It is stated that the intervention administered was ferrous sulphate 5 mg/kg/day, while other studies have used elemental iron at 5 mg/kg/day. Ferrous sulphate contains only approximately 20% elemental iron (so the child may only have received elemental iron 1 mg/kg/day). However, the authors' report an increase in haemoglobin values in the treatment group, which indicates that a clinically adequate dose of iron was used. Compliance with both treatments was also assessed visually by the amount of solution remaining in the bottle at each clinic visit. Close follow-up and monitoring by the treating clinician, no loss of study participants and improvement in haemoglobin values in the treatment group implies good compliance, which maintained the power of the study.

There is no information available on whether the study participants had accessed other forms of iron or other treatments for BHAs, although this is not thought to be the case.

Both the guardian and treating physician were blinded, neither knowing which solution the child received. The solutions were provided in identical bottles supporting the blinding process. However, as the iron usually leads to darker stools, loss of blinding for the guardians is possible. This would only create bias if the guardians reported the frequency of BHA differently if because the child was known to be taking iron or not. Aside from the intervention, the groups were treated equally.

All the patients who entered the trial were accounted for at the end, that is there was no loss to follow-up. Further, patients were analysed in the groups to which they were initially (quasi-) randomised to, an 'intention to treat analysis'.

Outcome measures appeared to be objectively recorded (by guardian record of the number of BHAs), which was then used to generate the average number of BHAs per month. The frequency was then categorised into three levels: complete response (no more attacks), partial response (≥50% reduction in the frequency but not complete disappearance of the attacks) and minimal or no response (<50% reduction in the frequency of the attacks). The first two categories (complete and partial response) were then combined and treated as one result.

Results found that children treated with iron displayed a 14-fold significant reduction ($P < 0.01$) in the frequency of BHAs (88%) compared with the frequency (6%) in the placebo group. For the treatment group, the baseline mean haemoglobin level among those with a favourable response (complete or partial) was lower (86 g/L) than among the children who responded poorly (106 g/L), and the difference was statistically significant ($P = 0.004$). Total Iron Binding Capacity at baseline was higher in patients with a favourable response than in patients with a poor response, and this difference was also statistically significant ($P = 0.05$). These results suggest that the more anaemic a child with BHAs is, the more likely he or she is to respond with iron therapy.

Brief discussion of how to do the research better

Ideally, the study should have been truly randomised using an unpredictable method such as random number production or tossing a coin. The authors comment that the low power of the study did not allow baseline variables, such as sex, age at onset and at presentation, frequency and type of attacks, consanguinity, and family history to be used in an analysis to assess whether they predicted subsequent response to iron therapy. It is unlikely that all of these factors are important predictors of effect but reporting of subgroup analyses of important potential clinical indicators of response to iron therapy, such as frequency of episodes at baseline, type of breath holding attack and age at diagnosis, would be ideal in future trials. Replication of these findings in different populations, such as those with BHA and haemoglobin values well within the normal range (Hb > 110 g/L) and in children without high rates of thalassaemia and consanguinity, which may influence both breath-holding episodes and the effect of iron therapy, may better define the magnitude of effect iron has on BHA frequency reduction.

Nevertheless, despite low quality aspects of the Daoud study, the reduction in the frequency of BHAs in the intervention group is dramatic. Thus, it seems likely the effect is true, rather due to biases within the study.

How to apply the information to the patient

The age range of participants in Daoud's trial is not given. However the mean age within the groups was between 12.4 and 17.3 months. Our patient was aged 24 months, which is slightly older. However, BHAs are known to generally occur between the ages of six months and six years, and our patient's age would not preclude her from being eligible to participate as a study subject of the Doaud trial.

From the data, there is a higher degree of anaemia (mean Hb 89 g/L in the treatment group and 94 g/L in the control group) in the population of children in Jordan. From the finding that the greater degree of anaemia at baseline confers a greater benefit from iron, our patient with a haemoglobin value of 101 g/L may be expected to have a less pronounced treatment effect, if any.

The microcytic and hypochromic picture of iron deficiency anaemia (5% of Jordanian schoolchildren), though, may also be found in thalassaemia. A 10% haemoglobinopathy (including sickle cell anaemia) rate is also prevalent in Jordan.[2] The high degree of consanguinity (70%) and haemoglobinopathy in the study population – and its possible influence on breath-holding – is generally not reflective of the Australian population and consanguinity or a haemoglobinopathy was not present in our patient.

Ultimately, the results of Daoud's trial are applicable and generalisable to our patient.

Our patient was treated with oral iron supplementation (elemental iron dose, not ferrous sulphate) at 5 mg/kg/day for 16 weeks (as per the Daoud study protocol). The child's mother reported almost complete resolution of the BHAs after eight weeks, with an average of one episode of breath-holding occurring every six weeks. The child tolerated the oral iron supplementation well without any adverse gastrointestinal effects.

Clinical bottom line

Iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of BHAs. This is reported to be of particular benefit in children with iron deficiency anaemia, although it may still be of assistance in children who are not anaemic or have low normal haemoglobin levels (as in the case presented here). No studies specifically treating non-iron deficient children with iron for BHAs were found. The expected benefit of the intervention outweighs the low risk of harm (potential gastrointestinal adverse effects), making oral iron a suitable initial therapy for an 'n-of-one' trial in clinical practice, while more research trial evidence is emerging.

Further high-quality trials of iron supplementation to treat BHAs in children are required. A Cochrane Systematic Review to assess the efficacy of iron for BHAs is currently in progress.[3]

Submitted by: Anthony Zehetner, Nigel Orr, Adam Buckmaster, Katrina Williams.

Contact person: Dr Anthony Zehetner, Children's Hospital at Westmead, Westmead, NSW 2145, Australia. Email: anthonyz@chw.edu.au

References

1 Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. *JAMA* 1994; **272**: 1367–71.
2 Babiker MM, Bashir N, Sarsour N. Prevalence of thalassaemia in schoolchildren in North-Eastern Badia, Jordan. *East. Mediterr. Health J.* 1999; **5**: 1165–70.
3 Zehetner AA, Orr N, Buckmaster A, Williams KJ, Wheeler DM. Iron supplementation for breath-holding attacks in children (protocol). *Cochrane Database Syst. Rev.* 2009; (4): CD008132. [doi: 10.1002/14651858.CD008132].
4 Daoud AS, Batieha A, Al-sheyyab M, Abuekteish F, Hijazi S. Effectiveness of iron therapy on breath-holding spells. *J. Pediatr.* 1997; **130**: 547–50.
5 Paul R, Manchanda S. Breath-holding attacks. The role of psychological factors and iron therapy. *Indian J. Pediatr.* 1969; **36**: 271–7.
6 Ahmad Bhat M, Ali W, Mohidin K, Sultana M. Prospective study of severe breath holding spells and role of iron. *J. Pediatr. Neurol.* 2007; **5**: 27–32.
7 Ziaullah Nawaz S, Shah S, Talaat A. Iron deficiency anemia as a cause of breath holding spells. *J Postgrad. Med Inst.* 2005; **19**: 171–4.
8 Khalifa M, Aldoseky S, Shalaby H. Effectiveness of iron therapy on breath holding spells. *Neurosci.* 2004; **9**: S8–S10.
9 Mocan H, Yildiran A, Orhan F, Erduran E. Breath holding spells in 91 children and response to treatment with iron. *Arch. Dis. Child.* 1999; **81**: 261–2.
10 Lahey ME. Iron deficiency anaemia. *Pediatr Clin. North Am.* 1957; **4**: 481–96.