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Research Article

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The Effectiveness of Venesection Therapy for Haemochromatosis Symptoms

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Abstract

Background: Symptoms of hereditary haemochromatosis (HH) include fatigue and arthritis, and iron overload can result in liver cirrhosis and cardiomyopathy. Treatment is venesection, to prevent end organ damage. It is unclear if normalisation of iron stores reverses symptoms.

Aim: To determine if fatigue and arthritis improve with venesection therapy, and to determine the number of venesections needed to reach target ferritin levels.

Methods: Eighty eight clinic patients with HH answered a questionnaire within 6 months of diagnosis, regarding symptoms including the modified fatigue impact scale (MFIS). A follow up questionnaire was used to resample the same population, of which 67 replied (76% retention). Patients were stratified by baseline serum ferritin: Group A-ferritin<300 µg/l; Group B-ferritin 300-1000 µg/l, and Group C-ferritin>1000 µg/l. Fatigue was measured objectively (MFIS) and subjectively, and arthritis subjectively.

Results: There was no significant difference between patient subgroups at baseline in fatigue (MFIS score), or arthritis. At follow up, there was a small trend in improvement of self-reported fatigue in Group A and B, and a trend to worsening fatigue in Group C. Following therapy, 46% felt better, 47% no different, and 5% felt worse. The prevalence of arthritis had a non-significant decline across all groups.

Conclusion: Symptoms of iron overload in haemochromatosis do not correlate with serum ferritin. Reduction in iron stores with venesection may result in a feeling of improvement, but this is not reflected in objective tests.

Keywords

Hereditary haemochromatosis; Venesection; Efficacy of therapy; Symptom resolution

Introduction

Hereditary haemochromatosis (HH) is an autosomal recessive disorder, characterized by iron overload, and it is the commonest genetic condition affecting people of northern European ancestry. In most HH cases (>90%), a homozygous C282Y missense mutation on the HFE gene is the cause [1-3]. Disease penetrance in C282Y homozygotes is not complete, and there is a spectrum of phenotypes ranging from unaffected with normal iron studies, iron overload without symptoms, iron overload with symptoms, and iron overload with organ damage [4]. Twenty eight percent of male C282Y homozygotes and 1% of females are at risk of iron overload related disease, as demonstrated by a large Melbourne cohort [4]. Symptoms attributed to HH include fatigue, arthritis and loss of libido. Iron overload can cause significant end-organ damage, in particular cirrhosis, cardiomyopathy and diabetes [2]. If untreated, there is a risk of progressive disease, resulting in portal hypertension, hepatocellular carcinoma and cardiac failure.

The mainstay of treatment is venesection, which removes approximately 200 mg of iron per 450 ml blood donation. Current recommendations are to decrease ferritin to between 50-100 mg/L, as at this level, iron stores have been depleted [5-8]. The arthritis of HH appears to be unrelated to serum ferritin levels, and does not appear to respond to venesection therapy [4,6]. Anecdotally, many patients report feeling significantly less fatigued following venesection, although this has never been formally studied using objective tools [9]. It remains unclear whether venesection therapy is effective in managing HH-related morbidity; even if target ferritin levels are reached. This may affect patient compliance with venesection, and result in higher than acceptable ferritin levels. The number of venesections required to reduce the ferritin to the target level is not well documented.

The aim of this study was to determine if (1) the main symptoms of haemochromatosis, fatigue and arthritis, are improved by venesection therapy, and (2) to determine the number of venesections required to reach the target ferritin level.

Methods

Eighty-eight patients homozygous for the C282Y mutation of the *HFE* gene were invited to answer a primary questionnaire, either prior to the diagnosis of HH (57 patients), or shortly after diagnosis (31 patients). The former were recruited from the HealthIron study, a population based longitudinal study [4], and the latter from the clinic of a hepatologist. They were re-evaluated with a second questionnaire at a second time point (mean of 31 months later).

The baseline questionnaire gathered basic demographics, data on dietary intake of red meat; alcohol history; oral iron supplements and multivitamins; menstrual and pregnancy history; blood loss, blood transfusion and blood donation; self-reported symptoms of fatigue, arthritis, and any family history of haemochromatosis. Most of the participants (50/88, 57%) had also filled out the Modified Fatigue Impact Scale (MFIS) [10-12]. This is scored on a scale of 0-84, where a higher score indicates a higher level of impairment from fatigue. The MFIS was completed as part of the Healthiron study [4]. At the time of the baseline questionnaire, HealthIron participants were unaware of the diagnosis of haemochromatosis or their serum ferritin levels [4].

The follow up (post venesection therapy) questionnaire included repeat administration of the MFIS; venesection history; diagnosis of other co-morbidities, including malignancy; arthritis and fatigue.

Fatigue was assessed at baseline and follow-up by response to

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the question "(Have you ever had fatigue?)", and by the MFIS. At follow-up, patients who had undergone venesection were asked a separate subjective question on well-being categorised whether they felt better, worse or no different, since the initiation of treatment. Arthritis was assessed at baseline by response to the question "(Have you ever suffered from any of the following? (yes/no))", and at follow up, the same question was used to determine patients with new onset of arthritis. Past arthritis sufferers were asked if symptoms had improved.

Serum ferritin (SF) was measured at baseline and follow-up. Analysis was stratified by baseline ferritin, consistent with the risk of iron overload causing disease; group A: ferritin <300 µg/l (defined as normal serum ferritin); group B: ferritin 300-1000 µg/l (moderate iron overload); group C: ferritin >1000 µg/l (severe iron overload). One patient did not have a baseline ferritin measure and was excluded from analyses stratified by baseline SF. Not all participants answered every question on both questionnaires (Table 1).

Prevalence of symptoms at baseline was stratified by SF group and compared between the 3 groups. Also, the proportion of symptoms that resolved at follow-up among those who had disease at baseline was compared between the SF groups. The p-values pertain to comparison of these proportions between each SF group.

Results

Eighty eight participants responded to the baseline questionnaire. There were 41 men and 47 women, with a mean age 60.6 years (range 22-82) (median age 59.6). Sixty seven (78%) of these also completed the follow up questionnaire and had follow up ferritin measurements; a mean of 31.6 ± 28 months later. Sixty of the 67 (90%) who responded to the follow up questionnaire had had venesection therapy, and the

Table 1: Characteristics of the total HH cohort (n=88) at baseline (diagnosis of HH) and at follow up.

	Baseline	Follow Up
	n=88	n=67
Age at follow up (mean) (median) (range)		 60.6 years 59.6 years 22-82 years
Men : Women	47% (41): 53% (47)	47% (32): 53% (35)
Period of follow up Mean median		 31.6 (± 28) months 23 months
Average number of pregnancies (n=36)	2.2 (11 nulliparous)	
Known family history of HH	45% (40/88)	
Fatigue (self reported)	64% (50/78)	57% (38/67)
Blood donor (self reported)	64% (52/81)	
Arthritis (self reported)	46% (36/78)	44% (26/59)
Ever taken iron tablets	34% (24/70)	
Liver biopsy (self reported)	12% (9/78)	
Skin pigmentation (self reported)	10% (8/76)	
Infertility (self reported)	10% (8/77)	
Sexual dysfunction		19% (12/66)
Heart disease (self reported)	9% (7/77)	
Liver disease (self reported)	7% (6/78)	
Diabetes (self reported)	6% (5/79)	
Non-drinkers at baseline, male	7% (3/41)	
Non-drinkers at baseline, female	17% (8/47)	
Decreased alcohol intake		26% (17/66)
Hypertension		31% (21/66)
Pneumonia		19 % (12/66)
Breast cancer		5% (3/65)
Colon cancer		0 (0%)
Other cancer		14% (9/66)
Thyroid disease		11% (7/66)
Diabetes		11% (7/66)
Cardiac disease		3% (2/66)
Coeliac disease		2% (1/66)
Number of venesections (mean) Group A (no iron overload) Group B (moderate iron overload) Group C (severe iron overload)		 16 (n=13) 21 (n=23) 35.5 (n=20)
Subjective impression of improvement Better No different Worse		 47% (28/59) 46% (27/59) 5% (3/59)

majority (68%) had reduced their ferritin to less than 200 µg/l. The other 32% had more modest reductions in ferritin, and were still having venesection therapy (Table 1).

Iron indices

The baseline and follow up serum ferritin results are shown in table 2. Ferritin results were available on 87 participants at baseline and 67 participants at follow up. Overall, the mean serum ferritin at baseline was 1106 ± 910 µg/l in men and 513 ± 490 µg/l in women. At the time of entry into this study, twenty seven (31%) had iron indices within the normal range (group A); 35 (40%) had moderately elevated ferritin (group B), and 25 (29%) had severely elevated SF (group C). In group A, 5 participants had a normal ferritin due to previous venesection therapy or self-initiated blood donations (either due to previous diagnosis, or as regular blood donors). The mean serum ferritin at follow up was 189 ± 260 µg/l in men and 159 ± 185 µg/l in women, and 22 (32%) were below 50 µg/l. These results are shown in table 2.

Nineteen patients (9 in Group A, 6 in Group B and 4 in Group C) did not participate at follow-up. Group A had a follow up ferritin of 72 mg/l, Group B was 174 ± 197 mg/l, and the follow up ferritin of those with severe iron overload at baseline (Group C) was a mean of 258 ± 352 µg/l. In Group B, 2 patients also had a significant drop in serum ferritin from over 300 µg/l to <30 µg/l at follow-up, which may have resulted in fatigue from overzealous venesection.

Fatigue

At baseline, a total of 64% (50/78) self-reported fatigue (subjective assessment, Table 1). Comparison of the prevalence of fatigue at baseline between Group B and C versus Group A (the latter considered as the near normal ferritin group), did not show any significant difference (p =0.304 and 0.331 respectively). The proportion of fatigue resolution at follow up was 46% in Group A, 43% in Group B and 20% in Group C. The proportions were not significantly different between the groups (Table 3).

No significant difference in mean fatigue score was seen as measured by the MFIS, between baseline and follow up in groups A, B or C (Figure 1). Despite a large reduction in the serum ferritin at follow up in group C, the MFIS demonstrated a small increase in fatigue (Figure 1). Eleven patients in Group C had a significant drop in ferritin from >1000 µg/l to <100 µg/l over 54.7 months. Of these 11 patients, 6 had initial and follow up MFIS measuring fatigue, and all 6 of these patients had a higher follow up MFIS, consistent with worse fatigue. Of the remaining 5 who either who had neither initial or follow up MFIS, all had fatigue present as a symptom at follow up. Three patients had a follow up ferritin <30 µg/l, which may contribute to fatigue due to low iron levels.

Arthritis

There was no difference in the prevalence of self-reported arthritis in patients between groups A, B and C at baseline (overall 46%). At

Table 2: Serum ferritin results for patients at baseline and follow up.

	Baseline µg/l		Follow up µg/l		p
	n	(mean ± SD)	n	(mean ± SD)	
Serum ferritin all patients	87	785 ± 769	67	173 ± 222	0.00
Serum ferritin (males)	40	1106 ± 910	32	189 ± 260	0.00
Serum ferritin (females)	47	513 ± 490	35	159 ± 185	<0.001
Baseline SF group:					
Group A: no iron overload (<300 µg/l)	27	131 ± 94	18	72 ± 41	0.02
Group B: moderate overload: (300-1000 µg/l)	35	680 ± 197	29	174 ± 197	0.00
Group C: severe overload: (>1000g/l)	25	1639 ± 895	21	258 ± 352	0.00

Serum ferritin results compared between groups at baseline and follow up, (n=number of patients in each group). The lowest baseline ferritin was seen in Group A and the highest in Group C, both at baseline and follow up.

Table 3: Prevalence of clinical symptoms at baseline and proportion of clinical symptom resolution at follow-up, by group.

	Self-reported Fatigue*			Self-reported Arthritis		
Baseline		%	*p*		%	*p*
Group A SF<300	13/24	54%		8/23	35%	
Group B SF 300-1000	21/31	68%	*0.304*	14/30	47%	*0.384*
Group C SF>1000	16/22	67%	*0.331*	13/23	56%	*0.139*
Follow up		%	*p*		%	*p*
Group A SF<300	6/13	46%		2/8	25%	
Group B SF 300-1000	9/21	43%	*0.851*	4/14	29%	*1.000*
Group C SF>1000	3/15	20%	*0.139*	1/13	8%	*0.271*

No significance difference in self reported fatigue and fatigue in patients in Group A (near normal ferritin levels), as compared to patients with higher baseline ferritin levels in Group B and C. There was also no significant difference between the groups in the proportion of symptom resolution at follow up.

follow up, all groups had a small, but non-significant reduction in the reporting of subjective arthritis symptoms (Figure 2). Prevalence of arthritis in groups B and C was not statistically significant; as compared to Group A. Proportion of resolution at follow up was 25% and 29% in Group A and B, with minimal (8%) resolution in Group C (Table 3).

Number of venesections

Sixty of the 67 patients had venesection therapy, with an average of 25 venesections per person. Target ferritin was 50 µg/l; however only 22 participants had achieved this at the time of follow up. In group A, 13 patients were venesected with an average of 16 venesections per person, to reach an average follow up ferritin of 77 µg/l, (from 131 µg/l). In group B, all but one patient (who had a drop in follow up ferritin despite no treatment), were venesected with an average of 21 venesections, from a baseline of 680 µg/l to a follow up ferritin of 167 µg/l. In group C, all patients had venesection therapy, with a mean of 35 venesections per person. The follow up average ferritin was 248 µg/l, down from a baseline of 1639 µg/l.

Overall symptom improvement

Fifty nine patients responded to a general well-being question at follow up, with options of: better; no different, or worse, since having venesection therapy. Twenty eight (47%) felt no different, 27 (46%) felt better, and 3 (5%) felt worse. Those who reported feeling no different had a higher post-venesection ferritin (mean 239 µg/l); compared to those who felt better, with a mean follow up ferritin of 119 µg/l. The three patients who reported feeling worse had a mean baseline ferritin of 690 ± 212 µg/l (range 562-935 µg/l), with a mean follow up ferritin 224 µg/l (range 62-359 µg/l).

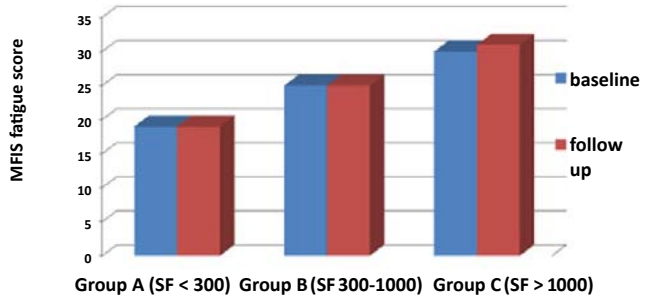

Figure 1: Comparison of mean MFIS (fatigue) score between group A, B and C at baseline and follow up. Patients in group A-no iron overload at baseline and Group B-moderate iron overload (ferritin (SF) 300-1000 µg/l), had no decrease in the MFIS score (purple bar), while patients in Group C-high initial ferritin (>1000 µg/l), experienced worsening of fatigue. There is no significant difference from baseline to follow up in any of the groups or between groups A (p=0.89), B (p=1) or C (p=0.73).

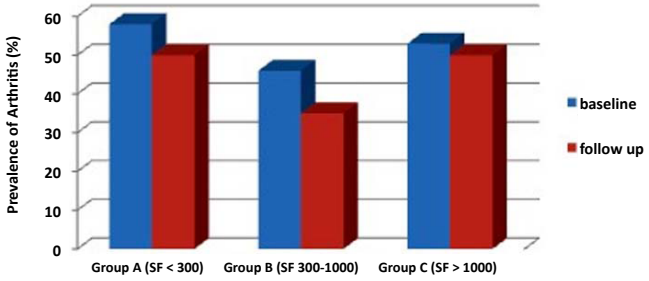

Figure 2: Comparison of arthritis (%) at baseline and follow up between groups A, B and C. Prevalence of arthritis in group A (no iron overload), group B (moderate iron overload) and group C (severe iron overload), at baseline (light bars) and follow up (dark bars). SF=serum ferritin. There was no significant difference between the three groups at baseline (p=0.384 for Group A *vs.* Group B, and p=0.139 Group A *vs.* Group C). There was no significant difference from baseline to follow up.

Discussion

This study demonstrates the lack of medium term impact of venesection therapy on the symptoms of HH, particularly fatigue and arthritis, despite effective normalisation of SF in the majority. It also did not show significant differences between patients with low or high ferritin, in regard to the presence of fatigue and arthritis at baseline, or difference in the proportion of patients with resolution of these symptoms at follow up, although there was a trend suggesting that some patients felt "better" after venesection. This study differs from previous studies, in that this well-characterised cohort was examined using a validated objective tool to measure fatigue. Although the objective tests did not show that venesection therapy resulted in any benefit in fatigue, 47% did report feeling better, and only 5% reported feeling worse since venesection therapy.

It is likely that knowledge of the diagnosis of HH resulted in some people obtaining a higher fatigue score at baseline. 64% of our cohort did not know that they had haemochromatosis, or what their serum ferritin level was, until after completing the first MFIS fatigue score, as they were blinded as part of the Healthiron study [4].

Patients in Group C who had a paradoxical increase in their fatigue also had the greatest decline in serum ferritin, which may indicate overzealous iron depletion exacerbating fatigue. Also, for 10 of the patients, the ferritin remained relatively stable, but nearly half of them (40%) complained of fatigue at follow up, making it less likely to be due to their ferritin level.

A previous cross-sectional study of HH symptoms in 1999 showed more promising results, with 54.4% of HH patients having symptom improvement with venesection therapy, while only 17.2% reported worsening fatigue [9]. However, in this study, only one time point was examined, and no objective measurement of fatigue was employed, as compared to the MFIS is a validated objective measure of fatigue, and has been used in many chronic diseases [10-12].

HH-associated arthritis is notoriously difficult to distinguish from other arthritis, and does not correlate well with serum ferritin [4,10]. It often presents in the same age group as age-related osteoarthritis is expected, and is difficult to distinguish from this clinically. In our study, the correction of iron overload did not appear to improve the symptoms of arthritis [4,9], which is not surprising, as the pathogenesis is related to chondrocalcinosis, with no definite evidence of synovial iron deposition and many of these patients may have had osteoarthritis, or combined haemochromatosis and osteoarthritis. The arthritis of HH is reported to be a major determinant of quality of life for many patients [13].

Venesection therapy is proven to prevent and reverse disease due to iron overload [14,15], including hepatic cirrhosis and fibrosis [16]. This results in the reduction of complications such as liver failure and hepatocellular carcinoma. However, its impact on morbidity is less clear [17], and this may affect compliance with therapy. Therapeutic compliance is based on many different factors that include the patient's understanding of the benefit of therapy, but also other therapy-related factors such as treatment complexity, route of administration and duration of the treatment period [18]. Venesection is an invasive

therapy, carried out over a prolonged period of time. Patient-related factors also impact on compliance and these included demographic factors such as age, education level, gender, as well as disease factors such as the impact on morbidity [18]. Lack of improvement in symptoms, such as fatigue and arthritis, can thus impact negatively on patient compliance. Previous studies have shown that compliance is good until serum ferritin normalisation is accomplished (96.6%), and then drops off in the following year to 86% [19], and continues to drop off, with less than 50% of patients at 6 years post initial iron depletion remaining compliant with venesection therapy [20]. Compliance is vital to prevent complications of HH and improve survival [19-21]. Our study has shown that the number of venesections required vary from an average of 13 to 35, depending the baseline ferritin. Of note, only 22 patients reached the suggested ferritin of 50 mg/l, which may reflect the real world ferritin reduction in these patients, given it is an observational study.

The results shown here are consistent with a placebo effect of starting venesection therapy, with almost half of the patients saying that they felt better. However, this could not be confirmed using an objective tool of fatigue measure. Consistent with other studies, the arthritis associated with haemochromatosis did not improve with reduction in serum ferritin. This cohort was slightly older than most, with a mean age of 60 years, and many had been regular blood donors, prior to diagnosis. Further studies to compare sham venesection with venesection may be the only way to determine if subjective improvement in well-being is a placebo effect, or is due to reduction in serum ferritin and tissue iron stores.

Conclusion

Venesection therapy for iron overload in haemochromatosis reduces the incidence of liver disease and improves survival, but the benefit for symptom control is minimal. Although many patients anecdotally report an improvement in well-being following iron removal, this is not confirmed using objective tests.

Conflict of Interest

Associate Professor A Nicoll has received research support from Gilead Sciences, and has been paid speaker fees for Roche, Schering Plough, Bayer and Bristol Myers Squibb Pharmaceuticals.

All other authors have no conflicts of interest to declare.

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