International Journal of Medical and Health Research
ISSN: 2454-9142, Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 3; Issue 3; March 2017; Page No. 72-74

Estimation of the number of venesections needed in acquired haemochromotasis patients

John S Croucher

Professor of Statistics and Management, Macquarie University, Sydney, Australia

Abstract
Acquired or secondary haemochromatosis can be the result of another disease or condition that causes an overload of iron from multiple blood transfusions, along with certain types of anemia, chronic liver diseases, oral iron pills and long term kidney dialysis. For those who receive numerous transfusions, it is not unusual for the ferritin level to rise to higher than normal, indicating that the body is storing too much iron in various tissues that can cause morbidity or even mortality.
High levels of ferritin do not affect the amount of iron in the body, although a single unit of transfused blood contains approximately 250 mg of iron and when the ferritin level is too high a series of venesections may be required to reduce it. In this case, blood is removed from the circulatory system, up to 500ml at a time, until the ferritin level returns to within the normal range
The models derived here enable the medical practitioner to estimate the number of venesections that are likely to be required based on the current ferritin level, gender, height, weight, the amount of blood removed at each session and the desired ferritin level. It is found that the drop in ferritin level after a series of venesections follows a negative exponential distribution and numerical examples are provided to illustrate the equations.

Keywords: haemochromotasis, ferritin, venesection, iron, chelation therapy

Introduction
Ferritin is an iron-containing protein stored in virtually all body cells with normal levels subject to variation due to many conditions, the greatest amount being found in liver cells and cells of the immune system. It is such a large molecule that just a single one holds up to 4,500 atoms of iron [1]. With only a very small amount of ferritin being found within the blood, it is possible to have elevated amounts of ferritin in the body while iron levels remain normal. Ferritin is carried in the blood by the protein transferrin and signals cells to release it, making iron available for the production of haemoglobin and red blood cells. As such, the primary role of ferritin is to store iron in cells and deliver it to the areas where it is required, providing a balance iron overload and deficiency.
About 65–80% of the body's iron is bound up in haemoglobin molecules in red blood cells while around 15–30% is stored as ferritin (or *hemosiderin*, a ferritin complex) in the spleen, bone marrow and the liver. The remaining iron is mainly found in myoglobin molecules while a small amount of iron can be found in other molecules in cells throughout the body.

Reference ranges
The reference range of ferritin is usually defined as the prediction interval between which 95% of values of a reference group fall into, in such a way that 2.5% of the time a sample value will be below the lower limit of this interval, and 2.5% of the time it will be above the upper limit, whatever the distribution of these values. In other words, it represents those values within a 95% prediction interval for the mean [2].
Each individual pathology testing laboratory declares what they consider an appropriate reference range for ferritin, usually being quite general and varying quite markedly. Examples include ranges of 23–336 ng/mL for males and 11–306 ng/mL for females [3]; 18–270 ng/mL for males and 18–160 ng/mL for females [4] and 12–300 ng/mL for males and 12–150 ng/mL for females [5]. The mean of just these three would be 18–302 ng/mL for males and 14–205 ng/mL for females.
One study found that ferritin level in Caucasian patients has risen significantly between 1995 and 2005 with age adjusted levels increasing 21% for males and 10% for females during this period [6]. It also concluded that more than 30% of men had a ferritin level above the standard 300ng/mL cut-off and that reference levels should be amended to take into account To be an accurate measure, these intervals should consider the age, height, weight and gender of the individual.

Elevated ferritin levels
Excess iron is toxic to cells, an effect mediated through the production of free radicals and the Fenton reaction where iron and hydrogen peroxide can of oxidize a wide range of substrates to cause biological damage [7]. On those occasions when ferritin levels are elevated, tests may be performed to provide more information about the body's iron stores, the most common being serum iron and Total Iron Binding capacity (TIBC) that reflects the level of transferrin.
A single unit of transfused blood contains approximately 250 mg of iron, and patients who receive numerous transfusions may become transfusion dependent with the excess iron from the transfused erythrocytes gradually accumulating in various tissues, possibly causing heart failure, liver damage and pancreatic or endocrine disorders such as diabetes [8]. For those who receive numerous transfusions, it is not unusual for the ferritin level to rise to higher than normal, indicating that the body is storing too much iron in various tissues [9].
There are a number of reasons why an individual may have raised ferritin levels, but 90% of elevated serum ferritin is not due to iron overload. An investigation into causes of iron overload besides haemochromatosis, presenting a possible approach to patients with hyperferritinemia but normal transferrin saturation [10]. After as few as ten blood transfusions

the signs and symptoms of iron overload can be seen in some people. No physiologic mechanism of iron excretion exists, but absorption alone regulates body iron stores [11].

Chelation therapy

One technique to rid the body of excess iron is chelation therapy which operates by binding to the iron and allowing the body to excrete the bound particles. It is a good option for those who cannot have routine blood removal of iron via venesection and can be taken by means of a dissolvable tablet or as a slow infusion until the iron levels are at normal levels. However, there have been clinical trials that have shown conflicting efficacies.

Among the reported positive outcomes of chelation therapy was a conclusion that long-term deferoxamine iron chelation therapy is effective not only in retarding but, in some cases, even reversing organ damage caused by transfusional iron overload [12]. A similar result found that iron chelation was a suitable treatment option not only for thalassemia patients, but also for those with lower-risk myelodysplastic syndrome who can be expected to need several years of transfusion therapy [13].

However, uncertainty exists with regard to the optimal approach to iron-chelating therapy, especially with respect to the optimal hepatic iron concentrations for minimising the risk that hepatic fibrosis will progress to cirrhosis and its ultimate complication, hepatocellular carcinoma [14].

This paper concentrates only on those cases where the ferritin level is lowered by venesection as described below.

Venesection

A common technique for removing blood from the circulatory system is venesection (phlebotomy), usually preformed through a cut (incision) or puncture for the purpose of analysis, blood donations or treatment for blood disorders. One study considered whether the main symptoms of haemochromatosis, fatigue and arthritis, are improved by venesection therapy [15] while others discuss therapeutic phlebotomy and the related disorders, along with offering guidelines for establishing a therapeutic phlebotomy program [16].

The models in the following sections are based on patients who have acquired haemochromatosis and are lowering their ferritin levels by means of venesection.

Estimated blood volume

To use the models effectively it is necessary to estimate the amount of blood in the patient. Nadler's method employs separate non-linear multiple regression equations, separately for males and females, each based on their height and weight [17]. These are shown in Equations (1) and (2).

In each case:

Height = height in centimetres

Weight = weight in kilograms

Estimated Total Blood Volume (TBV) in ml for males:

$$TBV(ml) = 604 + 0.0003668(height)^3 + 32.2(weight) \quad (1)$$

Estimated Total Blood Volume (in ml) for females:

$$TBV(ml) = 183 + 0.000356(height)^3 + 33.1(weight) \quad (2)$$

Nadler's method will be used for the purposes of this paper.

Estimated number of venesections

In this section a model is derived for the number of venesection sessions required based on a patient's gender, height, weight, current ferritin level, desired ferritin level and the amount of blood removed at each venesection session.

Let F = the current amount of ferritin (measured in a blood test) in ng/mL

Let M = the amount of blood (in ml) removed at each venesection session

Let p = the proportion of blood taken

Height is in centimetres

Weight is in kilograms

Using Equations (1) and (2), the values of p can be found:

For males:

$$p = \frac{M}{604 + 0.0003668(height)^3 + 32.2(weight)} \quad (3)$$

For females:

$$p = \frac{M}{183 + 0.000356(height)^3 + 33.1(weight)} \quad (4)$$

In each case:

Amount of ferritin removed = pF ng/mL

Amount of ferritin remaining after 1 venesection = $F - pF = (1 - p)F$ ng/mL

Amount of ferritin removed = $p(1 - p)F$ ng/mL

Amount of ferritin remaining after 2 venesections

$= F - pF = (1 - p)F - p(1 - p)F = (1 - p)^2F$ ng/mL

In general, after r venesections:

Amount of ferritin remaining = $(1 - p)^rF$ ng/mL

Suppose it is desired to reduce the ferritin level to below L ng/mL.

Then we require:

$$(1 - p)^rF < L$$

Solving for r yields:

$$r > \frac{\log(L/F)}{\log(1 - p)} \quad (5)$$

Equation (5) provides the minimum number of venesections, r, required to reduce the ferritin level to L ng/mL.

Example 1

A male patient presents with a ferritin level of 3000 ng/mL and it is desired to reduce the level to 400 ng/mL by taking 500ml of blood per venesection session. He weighs 78.0kg and is 180cm tall. To calculate how many venesection sessions will be required, first use Equation (6) with the parameter values:

M = 500, *height* = 180 and *weight* = 78.0

This yields:

$$p = \frac{500}{604 + 0.0003668(180)^3 + 32.2(78.0)} = 0.095 \quad (6)$$

(Note that the denominator of Equation (6) estimates his total blood volume to be 5.25 litres.)

Now use this value of p in Equation (6) with L = 400 and F = 3000. This yields:

$$r > \log(400/3000)/\log(0.905) = 20.2$$

or about 20.

After 20 venesections, the ferritin level would be $(0.905)^{20}3000$ = 407 ng/mL. Figure 1 shows the way in which the ferritin level decreases after each of the first 25 venesections. It is

exponential in shape, meaning that the amount of ferritin decrease is much greater in the beginning sessions than in the final sessions. For example, after the first five sessions the level drops by 1179 ng/mL, while in the final five sessions it drops by only 160 ng/mL.

Menstruation

Women who are pre-menopausal lose an average of 30–40ml per period [18] while menstruation increases the average daily iron loss to about 2 mg per day in premenopausal female adults [19]. As such, this amounts to an equivalent of around one extra venesection session per fourteen or so sessions. And so, for example, if a female was still menstruating, her number of venesection sessions required would reduce by 1 for every 14 sessions provided by Equation 6.

Conclusion

The reasonable assumption made in these equations is that the proportion of ferritin removed from the blood is the same as the proportion of blood removed. They provide an easy to use handy guide for practitioners to give their patients an idea of just how many venesection sessions might be required.

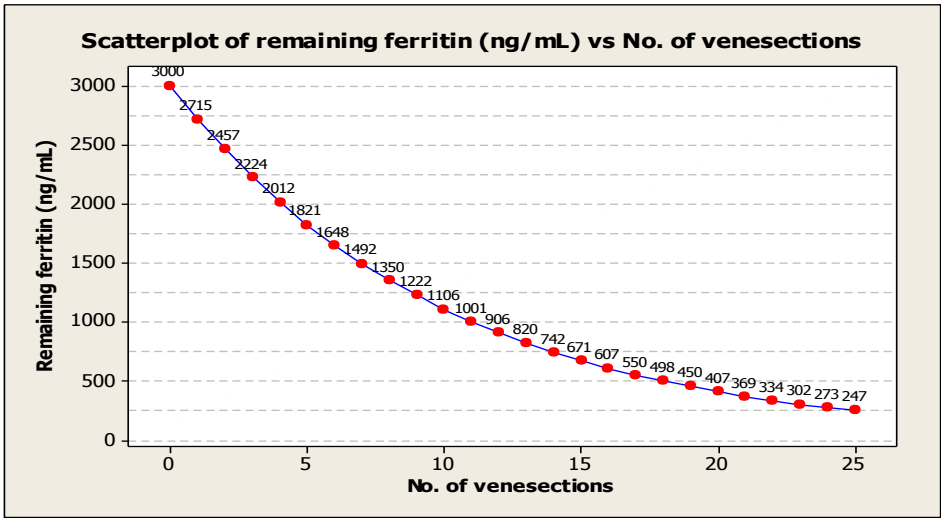

Fig 1: Scatterplot for Example 1 of the remaining ferritin level (ng/mL) versus the number of venesections

References

1. Garrison C. (ed.). Iron Disorders Institute Guide to Hemochromatosis: Sourcebooks Inc. 2009.
2. Bangert SK, Marshall WJ, Marshall WL. Clinical biochemistry: metabolic and clinical aspects. Philadelphia: Churchill Livingstone/Elsevier, 2008, 19.
3. Devkota BP. Ferritin, Medscape, 2014, 16.
4. WebMD, US, Ferritin, (http://www.webmd.com/a-to-z-guides/ferritin#2; 2014 [accessed 28.02.17].
5. Medscape Ferritin, http://emedicine.medscape.com/article/2085454-overview, 2014 [accessed 28.02.17].
6. Lord E. Ferritin ranges need overhaul: study. Medical Observer, 2013.
7. Bacon BR, Britton RS. The pathology of hepatic iron overload: a free radical-mediated process? Hepatology. 1990; 11(1):127-137.
8. Iron overload and iron chelation therapy, Australian Leukaemia Foundation, http://www.leukaemia.org.au/treatments/supportive-care/blood-transfusions/iron-overload/iron-overload-and-iron-chelation-therapy [accessed 28.02.17].
9. Files, B. Brambilla, D, Kutlar, A. *et al.* Longitudinal changes in ferritin during chronic transfusion: A report from the stroke prevention trial in sickle cell Anemia. J Ped Hematol Oncol. 2002; 24:284-289.
10. Makker J, Hanif A, Bajantri B, Chilimuri S. Dysmetabolic Hyperferritinemia. All Iron Overload is not Hemochromatosis Case reports in gastroenterology, Published online. 2015; 9(1):7-14.
11. McCance RA, Widdowson EM. The absorption and excretion of iron following oral and intravenous administration. J Phys. 1938, 94-148.
12. Schafer AI, Rabinowe S, Le Boff, MS, *et al.* Long-term Efficacy of Deferoxamine Iron Chelation Therapy in Adults With Acquired Transfusional Iron Overload, Arch Intern Med. 1985; 145(7):1217-1221.
13. Gatterman N. The Treatment of Secondary Hemochromatosis, Dtsch, Arzteblatt. 2009, 499-504.
14. Brittenham GM. Iron-Chelating Therapy for Transfusional Iron Overload N. Engl. Med. 2011; 364(2):146-56.
15. Niewiadomski O, Rode A, Bertalli N, Gurrin L, Allen KJ, Nicoll AJ. The effectiveness of venesection therapy for haemochromatosis symptoms. Journal of Liver: Disease & Transplantation. 2013, 2(1).
16. Kim KH, Oh KY. Clinical applications of therapeutic phlebotomy, Dove Press. 2016; 7(18):139-144.
17. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962; 51:224-232.
18. NSW Health Advisor, How Much Blood Do You Lose on Your Period? 2017. http://www.newhealthadvisor.com/how-much-blood-do-you-lose-on-your-period.html [accessed 28.02.17].
19. Bothwell TH, Charlton RW. A general approach of the problems of iron deficiency and iron overload in the population at large. Seminars in Hematology. 1982; 19:54-67.