Can We Improve the Detection of Iron Deficiency by Routinely Analyzing Ferritin and TIEBC on All Patients with Non-Macrocytic Anemias?

Aylit Schultz

LAY ABSTRACT

A. Study Purpose

Approximately 7% of adults over 50 years, and 9-11% of adolescent girls and women of childbearing age have iron deficiency, and almost half of them have anemia secondary to their iron deficiency. It is not known exactly how many of these people are being adequately treated for their anemia, but studies have shown that perhaps as many as half of these anemias are undiagnosed. The consequences of undiagnosed, untreated, and underevaluated anemia is undisputed. In pregnant women, untreated iron deficiency has been shown to cause low birthweight infants and prematurity. Studies have also shown that the mortality risk in elderly anemic subjects without obvious clinical disease is more than twice that of nonanemic patients. Additionally, the side effects of iron deficiency are well documented and include: cheilosis, dyspnea on exertion, fatigue, headache, inability to concentrate, irritability, listlessness, neuralgic pain, pallor, palpitations, peripheral parasthesias, pica, spoon-shaped brittle nails, susceptibility to infection, tachycardia, and vasomotor disturbances.

The question that inspired this study is the following: what can we do to improve the detection of iron deficiency anemia? Other investigators have attempted to improve iron deficiency detection by distributing guidelines to physicians with recommendations to send further studies (ferritin levels) on all anemic patients who have small or regular sized red blood cells (patients with large red blood cells, or macrocytic anemia, are more likely to have anemia secondary to causes other than iron deficiency). In one such study, 70% of people with non-macrocytic anemia were not appropriately worked up by their physicians. Afler the new guideline was distributed, there was a 32% improvement in the evaluation of anemia but 59% of patients were still not properly evaluated even after the guidelines were distributed. Our protocol, which automatically analyzes ferritin and TIBC levels (another marker of iron deficiency) on all patients with non-macrocytic anemias will be more effective at evaluating non-macrocytic anemias. The purpose of this study is to evaluate whether such a protocol can also improve the dectection of iron deficiency anemia, and if so by how much.

B. Study Subjects and Method of Recruitment

Study subjects will include all non-pregnant patients greater than 18 years of age who are new to the WEBCIS system, and who have a blood count in WEBCIS which shows a non-macrocytic anemia. People already being treated for anemia, and those with other laboratory values that strongly suggest another etiology for their anemia will be excluded.

C. Study Procedure

The study will follow the lab data for all included patients. If ferritin and TEBC are not ordered for any patient within I month of the first blood count that suggests a nonmacrocytic anemia, then we will run a ferritin and TIBC for that patient on a blood sample saved for us by the lab. Initially, we will not report the results of our extra tests to the physicians, and we will continue to monitor the laboratory data for I month after inclusion into the study, At the end of the study period, results will be reported to physicians.

D. Issues

The main ethical question with this study regards the delay in reporting abnormal results which we detect during the study. In order not to influence physician behavior during the study period, we will withhold results of any ferritin and TEBC tests that we run until the study is completed. Ofcourse, should a physician order the tests independently, the results will be reported as usual in WEBCIS. At the end of the study period we will notify the physicians of the ferritin and TEBC results which we ordered (excluding results for patients who were also tested by their physician during the follow up period). For patients with normal ferritins and TEBCs we will suggest rechecking the CBC and continuing the evaluation of the anemia as they deem appropriate. For patients with abnormal ferritins and TIBCs consistent with iron deficiencv, we will suggest a possible diagnosis of iron deficiency anemia and recommend further tests to verify and evaluate as appropriate. We will also report the ferritin and TEBC results in W`EBClS. Should we be unable to identify a physician for any of the patients with abnormal results, we will send a letter by registered mail, directly to the patient explaining that he/she had abnormal results of tests for anemia and if he/she has not already done so, he/she should contact his/her primary care physician to farther evaluate the condition. We believe that it is appropriate to delay the reporting of our tests in this way because iron deficiency anemia is not an immediately life threatening condition and is routinely worked up on an outpatient, nonurgent basis.

PROTOCOL

E. Study Purpose and Rationale

The prevalence of iron deficiency in the United States has been estimated by the Division of Health Examination Statistics at the CDC (JAMA 1997 Mar 26;277(12):9736) to be up to 7% of people older than 50, less than 1% of teenage boys and young men, and 9-11% of adolescent girls and women of childbearing age. This correlates with 7.8 million women with iron deficiency, approximately 3.3 million (42%) of whom have iron deficiency anemia.

It is not known exactly how many of these people are being treated adequately for their iron deficiency anemia. In a retrospective chart review, Smieja et al from McMaster University in Ontario (CMAJ 1996 Sep 15; 15 5(6):691-6) showed that of 183 elderly patients admitted to their hospital, 66 (36%) had anemia, 49 of whom had nonmacrocytic anemia of unknown cause. Only 26 of these 49 patients had adequate investigation of their anemia, leading Smieja et al to conclude that anemia is underrecognized and underevaluated in elderly, hospitalized patients. Likewise, it is probable that anemia is underrecognized and underevaluated, and undertreated in the general US population.

The consequences of undiagnosed, untreated, and underevaluated anemia is undisputed. In pregnant women untreated iron deficiency has been shown to cause low birthweight infants and prematurity. Furthermore, in JAMA 1999 May 12;281(18):17147, Izaks et al presentd results of a study showing that the mortality risk in elderly anemic subjects without obvious clinical disease is more than twice that of nonanemic patients. Additionally, the side effects of iron deficiency are well documented and include: cheilosis, dyspnea on exertion, fatigue, headache, inability to concentrate, irritability, listlessness, neuralgic pain, pallor, palpitations, peripheral parasthesias, pica, spoonshaped brittle nails, susceptibility to infection, tachycardia, and vasomotor disturbances.

The question that inspired this study is the following: what can we do to improve the detection of iron deficiency anemia? Other investigators have attempted to improve iron deficiency detection by distributing guidelines to physicians. loannou et al (Am J Med 2002 Sep; 113(4):281-7) examined the effect of informing university hospital affiliated physicians about a guideline recommending measurement of serum ferritin levels for all anemic patients with an MCV of<95flL. At baseline, 31% of anemic patients with an MCV <95 underwent ferritin testing. After the intervention, 41% of patients underwent ferritin testing. (Approximately 25% of these patients were found to have serum ferritin level

<45.) Although loannou's intervention improved the evaluation of anemia by 32%, 59% of patients were still not properly'evaluated (with a serum ferritin level) even after the Gruidelines were distributed. Our protocol, which automatically analyzes ferritin and TIBC levels on all patients with non-macrocytic anemias will be more effective at evaluating these anemias. The purpose of this study is to evaluate whether such a protocol can also improve the dectection of iron deficiency anemia, and if so by how much.

F. Study Design and Statistical Analysis

The study will consist of two, phases. In the first phase, an observatory phase, the investigators will follow the labs of study subjects (see G. Study Subjects). The proportion of subjects who are worked up for their anemia will be calculated. If, during this phase, it is discovered that all non-macrocytic anemic patients at CPMC are being worked up with ferritins and TIBCs then the study will be aborted and these results reported as much better then the national rate. However, if during phase I it is found that a significant proportion of patients are receiving substandard workups, then the study will continue.

In phase 2, technically also an observatory phase, the study will follow the lab data for all included patients. If ferritin and TIBC are not ordered for any patient within I month of the first CBC, then we will run a ferritin and TIBC for that patient on a blood sample saved for us by the lab. Initially, we will not report the results of our extra tests to the physicians, and we will continue to monitor the laboratory data for 1 month after inclusion into the study. At the end of the study period, results will be reported to physicians as outlined above in the Lay Abstract, Issues section.

Non-macrocytic anemia

MD sends Ferritin and TIBC MD does not send ferritin and TIBC
I (ferritin and TIBC done by investigators)

A. Fe deficiency anemia B. normal C. Fe deficiency anemia D. normal

Iron deficiency anemia will be defined as TIBC > 350 and ferritin < 20.

We will use the Chi-Squared test to determine a statistically significant difference between the level of iron deficiency anemia detected by physicians independently (p 1 =A/A+B+C+D), and that detected by the study (p2=A+C / A+B+C+D). For the purposes of estimating the maximum number of people we will need to study, we generously assume that currently, physicians at CPMC are catching 90% of iron deficiency anemias (this is far better than at McMaster, where they adequately worked up only 50% of people with non-macrocytic anemias). Using our protocol, we think we would be able to catch an additional 2.5% of iron deficiencv ariemias (since we estimate that atleast 25% of non-macrocytic anemias are due to iron deficiency). In order to see such an effect at a significance of p=0.05 (power 80%, p I = 0.9, p2 = 0.925), we will need to include approximately 2100 cases of iron deficiency anemia, for which we estimate we will need to study approximately 8400 non-macrocytic anemias. If MDs send ferritins and TIBCs on 90% of these people, then the study investigators will need to send tests on an additional 2.5% of these people (21 eople~ which at less than 50 cents a test, would cost less than $250.

G. Study Procedure

Not applicable.

H. Study Drugs

Not applicable.

I. Medical Device

Not applicable.

J. Study Questionnaires

Not applicable.

K. Study Subjects

Inclusion criteria: - all patients > 18 years of age - with no previous CBC on record in WEBCIS - for whom a CBC is ordered by their physician - if the CBC shows a hematocrit level of < 41% for males or < 36% for females - and an MCV of < 95 - Subjects will start to be included ori January I't 2004 and recruitment will continue until 8400 subjects have accrued.

Exclusion criteria: - patients already being treated with Iron, B 12, folate, or erythropoietin, as determined by a review of the pharmacy and medication lists data in VvTEBCIS - patients whose CBC shows sickle cells, spherocytes, schistocytes (suggestive of hemolytic anemia), or ovalocytes (suggestive of thalassemia) - patients who have abnormal hemoglobin studies in WEBCIS (suggestive of sickle cell, thalassemia, or other hemoglobinopathy) - patients who have WBC < 4000/ul and platelets < 150,000/ul (suggestive of bone marrow disease) - patients with positive betaHCG > 2 in VvEBCIS - patients who do not have a gold top tube (needed to run the ferritin and TEBC) available in the lab within I month of the initial CBC.

L. Recruitment of Subjects

Not applicable.

M. Confidentiality of Study Data

A unique code number will be used.for all study subjects. Data will be stored in a secure location, accessible only to the investigators.

N. Potential Conflict of Interest

Not applicable.

O. Location of the Study

Columbia Presbyterian Medical Center, General Chemistry Laboratory.

P. Potential Risks

The potential risk of being included in the study is that an anemia that would have otherwise been ignored will be treated and/or worked up, in some cases unnecessarily or inappropriately. Xithough one hopes that physicians ,.,~ould use their discretion to ignore the results of the extra tests in cases where they are not relevant, it is conceivable that when faced with a diagnosis of iron deficiency anemia physicians will reflexively treat or order,invasive workups even if not appropriate to the situation. In order to minimize this adverse event, the notification to the physician will remind them to treat the iron deficiency anemia with diet or iron therapy if appropriate and to consider further evaluation including menstrual history, stool 0 & P, FOBT, endoscopy, colonoscopy or stool clotting studies if appropriate.

Q. Potential Benefits

The subject may or may not benefit as a result of being included in the study. The potential benefit of being included in the study is diagnosis of a previously undiagnosed iron deficiency anemia. If the physician chooses to treat the anemia, symptoms/consequences of iron deficiency may improve (see section A, Study Purpose and Rationale). Furthermore, if the physician chooses to further investigate the etiology of the iron deficiency, the patient may benefit from earlier diagnosis of underlying conditions including GI ulceration, neoplasm, bleeding varices, and uterine disorders. Another potential benefit of being included in the study, for those who are not ultimately diagnosed with iron deficiency, is that the physician may be more likely to search for other treatable causes of anemia.

The potential benefit to society is indirect and stems from improved physician education and and awareness of anemia. Additionally, if the study can prove the benefit to patients and physicians of this computer assisted automatic intervention, perhaps it will promote general good will towards other computer assisted diagnosis and decision support systems.

R. Alternative Therapies

Not applicable.

S. Compensation to Subjects

There will be no compensation provided to subjects.

T. Costs to Subjects

There will be no costs to subjects as a result of participating in the study. All ferritin and TIBC analyses that are ordered by the study investigators will be paid for from the study grant.

U. Minors as Research Subjects

Not applicable.

V. Radiation or Radioactive Substances

Not applicable

Decision Analysis: (from evidence based medicine, Daniel Friedland et al, page 36)

Dogmatism	→	this is the best way to do it
Policy	→	this is the way we do it around here
Experience	→	this way worked the last few times
Whim	→	this way might work
Nihilism	→	it doesn't really matter what we do
Rule of least chagrin	→	do hat you will regret the least
Defer to experts	→	what would you do?
Defer to patients	→	how would you like us to proceed?
Pet owners	→	let's do what you can afford