Do Blood Tests Cause Anemia in Hospitalized Patients?

The Effect of Diagnostic Phlebotomy on Hemoglobin and Hematocrit Levels

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OBJECTIVE: To determine whether phlebotomy contributes to changes in hemoglobin and hematocrit levels in hospitalized general internal medicine patients.

DESIGN: Retrospective cohort study.

SETTING: General internal medicine inpatient service at a tertiary care hospital.

PARTICIPANTS: All adult patients discharged from the Toronto General Hospital's internal medicine service between January 1 and June 30, 2001. A total of 989 hospitalizations were reviewed and 404 hospitalizations were included in our analysis.

MEASUREMENTS AND MAIN RESULTS: Mean (SD) hemoglobin and hematocrit changes during hospitalization were 7.9 (12.6) g/L ($P<.0001$) and 2.1% (3.8%) ($P<.0001$), respectively. The mean (SD) volume of phlebotomy during hospital stay was 74.6 (52.1) mL. On univariate analysis, changes in hemoglobin and hematocrit were predicted by the volume of phlebotomy, length of hospital stay, admission hemoglobin/hematocrit value, age, Charlson comorbidity index, and admission intravascular volume status. The volume of phlebotomy remained a strong predictor of drop in hemoglobin and hematocrit after adjusting for other predictors using multivariate analysis ($P<.0001$). On average, every 100 mL of phlebotomy was associated with a decrease in hemoglobin and hematocrit of 7.0 g/L and 1.9%, respectively.

CONCLUSIONS: Phlebotomy is highly associated with changes in hemoglobin and hematocrit levels for patients admitted to an internal medicine service and can contribute to anemia. This anemia, in turn, may have significant consequences, especially for patients with cardiorespiratory diseases. Knowing the expected changes in hemoglobin and hematocrit due to diagnostic phlebotomy will help guide when to investigate anemia in hospitalized patients.

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Hospitalized patients frequently have considerable volumes of blood drawn (phlebotomy) for diagnostic testing during short periods of time.[1] This may cause hemoglobin and hematocrit levels to fall, as commonly observed during hospitalization.[2–4] Low hemoglobin and hematocrit levels may result in significant morbidity for patients with underlying cardiorespiratory diseases.[5–7]

The relationship between phlebotomy volume and drop in hemoglobin/hematocrit has been established in adult and pediatric intensive care unit patients.[8–11] Unfortunately, these findings cannot be easily extrapolated to less acute but more common settings, such as general medical wards.[11–13] Studies that have focused on general internal medicine (GIM) inpatients have had limited sample sizes, did not adequately control for the impact of other sources of blood loss on hemoglobin values, or did not use conventional measures of anemia.[2,11,14–16] Therefore, we sought to more thoroughly estimate the impact of diagnostic phlebotomy on changes in hemoglobin and hematocrit levels in this important patient group.

METHODS

Patient Population

All adult patients discharged from the Toronto General Hospital's GIM service from January 1 to June 30, 2001 were potentially eligible for this study. We excluded patients who 1) had acute medical conditions that may have caused or contributed to anemia, either upon admission or during hospital stay (e.g., occult or active gastrointestinal bleed, hemolysis, hematuria, hemoptysis, hemorrhagic stroke, hemothorax, bleeding cutaneous ulcers, hemarthrosis, retroperitoneal bleed, or hematological malignancies); 2) were on therapy that could affect hemoglobin/hematocrit levels (iron, chemotherapy, or erythropoietin); 3) were on dialysis (due to changes in volume status); 4) had fewer than 2 hemoglobin/hematocrit values during admission; 5) received a red blood cell (pRBC) transfusion; or 6) were hospitalized for more than 21 days. The study was approved by the University Health Network's Research Ethics Board.

Data Extraction

The Shared Information Management Services department provided the following data for all potentially eligible patients: age, gender, admission and discharge dates, serum urea, creatinine, sodium, glucose, hemoglobin and hematocrit values, and the number and type of blood tests performed, including types of collection tubes used for each blood draw. The Performance Measurement department provided the Charlson comorbidity index (CCI). All charts were reviewed by one investigator (PT) to identify discharge diagnoses, chronic diseases that may cause anemia, and the presence of any exclusion criteria. Two hundred random hospitalizations from the

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989 total hospitalizations (20%) were reviewed by a second investigator (AB) and the data compared for consistency of extraction. When the two reviewers disagreed, the chart was rereviewed together and consensus was obtained.

Calculation of Blood Phlebotomy Volume

Total phlebotomy volume (whole blood) per patient was calculated based on the number and type of blood tubes collected during hospitalization. We sampled blood specimens over 5 random days during a 3-month period for each type of specimen tube and used a standardized ruler to measure the height to which each tube was filled. The mean of the heights was then used to calculate the volume of blood in each tube. Pediatric tubes are not used at our institution. A total of 568 tubes were sampled. Fill volumes ranged from 36% to 80% of maximum fill volume, with a mean (SD) of 63% (13%) and median (interquartile range) of 60% (46%–74%).

Calculation of Hospitalization Length

Hospitalization length was defined as the number of days between the first and last hemoglobin/hematocrit drawn. This was done for 2 reasons: 1) some patients stayed in hospital beyond their last hemoglobin/hematocrit value and had no further phlebotomy; and 2) others had blood tests after their last hemoglobin/hematocrit value (e.g., International Normalized Ratio [INR] levels), making it impossible to account for the impact of the extra phlebotomy.

Assessment of Intravascular Volume Status

Patients were classified as intravascular volume depleted on admission if they had a serum Blood Urea and Nitrogen [BUN] (mg/dL) to creatinine (mg/dL) ratio of greater than 25 and calculated osmolality greater than 295 mOsmol.[17,18]

Data Analysis

Descriptive statistics were used to summarize baseline characteristics of the study cohort. Paired *t* test was used to assess the change in hemoglobin/hematocrit from admission to discharge. The impact of phlebotomy volume on changes in hemoglobin/hematocrit was assessed using univariate and multivariate linear regression. Potential confounders in our analysis included patient age, gender, length of hospitalization, admission intravascular volume status, baseline hemoglobin/hematocrit level, CCI (classified into categories of 0, 1, or ≥ 2), and presence of chronic diseases that may cause anemia (e.g., chronic renal failure, malignancies, endocrine and inflammatory disorders, and infectious disease). Variables significant on univariate analysis at $P<.2$ were included in the multivariable model. After preliminary multivariate analysis, predictors not significant at $P<.05$ were removed. Confounding was evaluated by sequentially reintroducing nonsignificant predictors. On this basis, none of the nonsignificant variables were re-added to our model. Noncollinearity of the remaining variables was confirmed using tolerance and variance inflation factors. Two-way interactions between volume and all other candidate predictors were then evaluated but were not included in the final model as none were significant. Finally, residual plots confirmed the appropriateness of the assumptions of least-squares regression. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 962 patients, accounting for 1,064 hospitalizations, were discharged during the study period. Information was missing, incomplete, or inaccessible for 75 hospitalizations and therefore 989 hospitalizations (898 patients) were reviewed. Of these, 585 hospitalizations were excluded for the following reasons: medical conditions or treatment affecting hemoglobin/hematocrit levels ($n=266$); patients on dialysis ($n=26$); fewer than 2 hemoglobin/hematocrit values during admission ($n=177$); pRBC transfusion upon admission or during stay ($n=55$); length of stay greater than 21 days ($n=51$); and inability to calculate phlebotomy volume for technical reasons ($n=10$). The remaining 404 hospitalizations (381 patients) formed our study sample. Patient characteristics and the most common discharge diagnoses are presented in Table 1. The κ value for the interrater reliability of data extraction was .92.

Change in Hemoglobin/Hematocrit Values During Hospitalization

The mean (SD) hemoglobin values on admission and discharge were 125.6 (18.2) g/L and 117.6 (19.2) g/L, respectively, reflecting a mean (SD) change of 7.9 (12.6) g/L ($P<.0001$). The corresponding mean (SD) change in hematocrit was 2.1% (3.8%) ($P<.0001$).

Predictors of Change in Hemoglobin and Hematocrit During Hospitalization

Predictors of hemoglobin change on univariate analysis were: total volume of phlebotomy, length of hospitalization, admis-

Table 1. Characteristics of the Patients Included in the Study

Mean age, y*	68.7 ± 16.6
Female, %	44.8
Mean hemoglobin at admission, g/L*	125.6 ± 18.2
Mean hematocrit at admission, %*	37.2 ± 5.3
Mean volume of phlebotomy, mL*	74.6 ± 52.1
Mean length of stay, days*	5.6 ± 4.2
Prevalence of anemia at hospital admission, %	
Women	40.9
Men	49.8
Proportion of patients with chronic disease that may cause anemia, %	42.1
Proportion of patients who became anemic during admission, %†	15.8
Proportion of patients with CCI of 0, 1, or ≥2, respectively, %	30.7, 20.1, 49.3
Most common discharge diagnoses, %	
Pneumonia	19.9
Acute coronary syndrome	11.1
Congestive heart failure	6.4
Chest pain with no cause identified	4.7
Stroke syndrome	4.4

*Mean ± SD; divide by 10 to convert g/L to g/dL.
†Anemia was defined as <120 g/L in women and <130 g/L in men.[26]
CCI, Charlson comorbidity index.

Table 2. Predictors of Change in Hemoglobin During Hospitalization

Variable	Univariate Analyses		Final Multivariate Analysis	
	Parameter Estimate (SE)	*P* Value	Parameter Estimate (SE)	*P* Value
Volume of blood draw, mL	0.073 (0.012)	<.0001	0.070 (0.011)	<.0001
Age, y	−0.069 (0.038)	.0704	−0.8211 (0.036)	.0247
Gender, male vs female	0.770 (1.266)	.5432	*	*
Length of hospitalization, days	0.468 (0.150)	.0019	§	§
Hemoglobin level on admission, g/L†	0.184 (0.033)	<.0001	0.168 (0.032)	<.0001
CCI score (0, 1, or ≥2)	−0.987 (0.719)	.1705	§	§
Intravascular volume depletion at admission‡	2.472 (1.255)	.0496	2.615 (1.203)	.0303
Chronic diseases that may cause anemia	0.833 (1.275)	.5142	*	*

**Not included in multivariate model as it was not a univariate significant predictor (P<.2).*
†To convert g/L to g/dL, divide by 10.
‡BUN (mg/dL) to creatinine (mg/dL) ratio >25 and a calculated osmolality >295 mOsmol.
§Not included in final multivariate model as variable was not a significant predictor after controlling for other factors.
CCI, Charlson comorbidity index; BUN, Blood Urea and Nitrogen.

sion hemoglobin value (patients with higher hemoglobin values on admission had a more significant change), age (younger patients had a greater change), admission intravascular volume depletion (patients who were intravascular volume depleted had a greater change), and CCI (patients with a smaller CCI score had a greater change) (see Table 2). The same variables predicted changes in hematocrit levels (data not presented). Volume of phlebotomy remained a highly significant predictor of change in hemoglobin/hematocrit after adjusting for other significant predictors ($P<.0001$; Table 2). For every 1 mL of phlebotomy, the mean (SD) decrease in hemoglobin and hematocrit were 0.070 (0.011) g/L and 0.019% (0.003%), respectively. Other significant predictors of change in hemoglobin/hematocrit levels on multivariate analysis were admission hemoglobin/hematocrit levels, intravascular volume depletion at admission, and age.

Consequences of Iatrogenic Anemia

Among the 404 hospitalizations, 56 (13.9%) had investigations for anemia including iron studies and fecal occult blood. Eleven (19.6%) of these patients were not anemic on admission and were not admitted for conditions that cause anemia.

DISCUSSION

Our study of internal medicine inpatients demonstrates that the volume of blood taken for diagnostic testing strongly predicts hemoglobin and hematocrit changes during hospitalization. For every 1 mL of phlebotomy, mean (SD) decreases in hemoglobin and hematocrit values were 0.070 (0.011) g/L and 0.019% (0.003%), respectively. Accordingly, for 100 mL, hemoglobin and hematocrit levels would be expected to change by 7.0 g/L and 1.9%, respectively.

While small changes in hemoglobin may be clinically inconsequential, a clinically significant change has been reported to be between 6.6 and 10 g/L.[19,20] In our population, the mean drop in hemoglobin during admission was 7.9 g/L, and larger volumes of phlebotomy resulted in larger falls. Expected changes in hemoglobin and hematocrit corresponding to volumes of phlebotomy due to hypothetical clinical settings are presented in Table 3. Changes larger than predicted warrant further investigation.

Our findings are consistent with prior studies that have assessed the impact of diagnostic phlebotomy on hemoglobin/hematocrit changes in internal medicine patients. Studies by Colimon et al. and Joosten et al. found changes similar to ours,[2,4] although Colimon et al., in contrast to our study, did not find a significant decrease in hemoglobin until the length of hospitalization was greater than 4 weeks and the phlebotomy volume was greater than 100 mL.[2] Our study was larger and therefore had greater power to detect changes in hemoglobin/hematocrit levels with smaller phlebotomy volumes. In addition, we better controlled for other factors that may cause changes in hemoglobin/hematocrit, such as intravascular volume status, and comorbid and chronic illnesses.

In our study, patients with higher admission hemoglobin/hematocrit values had greater falls in hemoglobin/hematocrit

Table 3. Volumes of Blood Draw and Predicted Drops in Hemoglobin and Hematocrit Based on Clinical Scenarios

Volume of Blood Draw, mL	Expected Change in Hemoglobin, g/L (95% CI)*	Expected Change in Hematocrit, % (95% CI)	Scenarios Resulting in the Volume of Blood Draw
10	0.7 (0.5 to 0.9)	0.19 (0.13 to 0.25)	Routine labs (CBC, electrolytes, renal and coagulation profiles)
50	3.5 (2.4 to 4.6)	0.95 (0.65 to 1.25)	Routine labs for 5 days
100	8.0 (4.8 to 10.2)	1.90 (1.30 to 2.50)	Routine labs for 5 days, acute anemia workup, 3 sets of cardiac enzymes
200	14.0 (9.6 to 18.4)	3.80 (2.60 to 5.00)	Routine labs for 10 days, 3 sets of cardiac enzymes, 3 sets of liver profile, transaminitis work-up

**Divide by 10 to convert g/L to g/dL.*
CBC, Complete Blood Count.

during hospitalization. There are two potential explanations for this finding. First, patients with higher hemoglobin/hematocrit levels will lose more red blood cells per mL of phlebotomy than those with lower levels, hence accounting for the larger drop. Second, patients with higher hemoglobin/hematocrit values on admission may have been "hemoconcentrated" and a drop on the basis of rehydration, in addition to phlebotomy, would be expected. While we adjusted for intravascular volume status in our multivariable analysis, it is possible that our results regarding admission hemoglobin/hematocrit levels represent residual confounding for this variable, that is, volume contraction not captured by our BUN/Cr ratio and osmolality definition. We also found that younger patients had larger hemoglobin/hematocrit changes during hospitalization. We do not have a clear explanation for this effect. It is possible that younger patients received more volume resuscitation because physicians are generally less concerned about fluid administration to younger patients.

Interestingly, post hoc analysis of our cohort revealed that investigations for anemia, including iron indices and fecal occult blood, were performed during 56 (13.9%) hospitalizations. During 11 of these 56 (19.6%) hospitalizations, patients were neither anemic on admission nor admitted for conditions that may have caused anemia. These investigations were likely, at least in part, attributable to changes in hemoglobin values caused by phlebotomy.

Our study has several limitations. First, our results were based on medical record reviews and therefore information pertinent to the inclusion or exclusion criteria may have been incompletely recorded, thereby resulting in misclassification. Second, because our study was retrospective, establishing causation is challenging. It is possible that large falls in hemoglobin/hematocrit, for other reasons, may have triggered investigations requiring large volumes of phlebotomy. We think this is unlikely because anemia-driven blood testing would have been expected to increase daily phlebotomy volumes during the later stages of admission. Our results (not shown), however, indicate that the average daily volume of phlebotomy per patient decreases over time. Third, we only included approximately 38.4% of the hospitalizations due to stringent exclusion criteria. While this may limit the generalizability of our results, we believe that our explicit inclusion and exclusion criteria allow us to make a more accurate assessment of the impact of phlebotomy on hemoglobin/hematocrit levels. Fourth, we were unable to control for the use of medications that may idiosyncratically affect red cell homeostasis (e.g., antibiotics) or cause subclinical blood loss (e.g., Nonsteroidal Antiinflammatory Drugs [NSAIDSs]). We believe any unmeasured effect is likely small and would not significantly affect our results. Finally, accurately controlling for intravascular volume status was difficult and, as mentioned above, our results regarding admission hemoglobin/hematocrit may reflect residual confounding. Also, volume status is likely not a dichotomous variable as it pertains to changes in hemoglobin/hematocrit levels, that is, the relationship is likely more continuous. Our definition is based on those used by others in the literature[17,18] and is easy to interpret, in contrast to small changes in BUN/Cr ratios or osmolalities.

Our results highlight the need to perform blood testing judiciously. Physicians do not always check the blood work ordered for the management of their patients.[21] Therefore, education of physicians and nurses about the potential risk of anemia as a consequence of phlebotomy should be the first step.[16] In addition, other techniques such as reporting of cumulative volumes of phlebotomy to physicians and the use of pediatric-sized blood collection tubes[22–25] that have been shown to decrease volumes of phlebotomy in the critical care setting could easily be adapted to general medical wards.

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REFERENCES

1. **Wisser D, van Ackern K, Knoll E, Wisser H, Bertsch T.** Blood loss from laboratory tests. Clin Chem. 2003;49:1651–5.
2. **Colimon L, Souadjian JV, Longpre B.** [Effects of collection of blood samples on hemoglobin levels in the hospital environment]. Union Med Can. 1972;101:705–7.
3. **Eyster E, Bernene J.** Nosocomial anemia. JAMA. 1973;223:73–4.
4. **Joosten E, Hiele M, Pelemans W, Haesen E.** Blood loss from diagnostic laboratory tests in elderly patients. J Am Geriatr Soc. 1992;40:298.
5. **Arant CB, Wessel TR, Olson MB, et al.** Hemoglobin level is an independent predictor for adverse cardiovascular outcomes in women undergoing evaluation for chest pain: results from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation Study. J Am Coll Cardiol. 2004;43:2009–14.
6. **Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM.** The prognostic importance of anemia in patients with heart failure. Am J Med. 2003;114:112–9.
7. **Sarnak MJ, Tighiouart H, Manjunath G, et al.** Anemia as a risk factor for cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol. 2002;40:27–33.
8. **Lin JC, Strauss RG, Kulhavy JC, et al.** Phlebotomy overdraw in the neonatal intensive care nursery. Pediatrics. 2000;106:E19.
9. **Vincent JL, Baron JF, Reinhart K, et al.** Anemia and blood transfusion in critically ill patients. JAMA. 2002;288:1499–507.
10. **Corwin HL, Gettinger A, Pearl RG, et al.** The CRIT Study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. Crit Care Med. 2004;32:39–52.
11. **Smoller BR, Kruskall MS.** Phlebotomy for diagnostic laboratory tests in adults. Pattern of use and effect on transfusion requirements. N Engl J Med. 1986;314:1233–5.
12. **Muakkassa FF, Rutledge R, Fakhry SM, Meyer AA, Sheldon GF.** ABGs and arterial lines: the relationship to unnecessarily drawn arterial blood gas samples. J Trauma. 1990;30:1087. discussion 1093–5.
13. **Greenwood M.** Blood gas analysis may lead to iatrogenic anaemia in intensive care. Aust Crit Care. 2000;13:30.
14. **Buckley-Sharp MD.** Anemia of investigation. Lancet. 1971;1:916.
15. **Miller ES.** Blood lost because of phlebotomy. N Engl J Med. 1975;292:319.
16. **Dale JC, Pruett SK.** Phlebotomy—a minimalist approach. Mayo Clin Proc. 1993;68:249–55.
17. **Thomas DR, Tariq SH, Makhdomm S, Haddad R, Moinuddin A.** Physician misdiagnosis of dehydration in older adults. J Am Med Dir Assoc. 2004;5(suppl):S30–S34.
18. **Eaton D, Bannister P, Mulley GP, Connolly MJ.** Axillary sweating in clinical assessment of dehydration in ill elderly patients. BMJ. 1994;308(6939):1271.

19. **Wiesen AR, Hospenthal DR, Byrd JC, Glass KL, Howard RS, Diehl LF.** Equilibration of hemoglobin concentration after transfusion in medical inpatients not actively bleeding. Ann Intern Med. 1994;121:278–30.
20. **Kjeldsberg CR.** Principles of hematologic examination. In: Wintrobe's Clinical Hematology, 9th ed. Philadelphia: Lea & Febiger; 1993:10.
21. **Frye EB, Hubbell FA, Akin BV, Rucker L.** Usefulness of routine admission complete blood cell counts on a general medical service. J Gen Intern Med. 1987;2:373–6.
22. **Foulke GE, Harlow DJ.** Effective measures for reducing blood loss from diagnostic laboratory tests in intensive care unit patients. Crit Care Med. 1989;17:1143–5.
23. **Smoller BR, Kruskall MS, Horowitz GL.** Reducing adult phlebotomy blood loss with the use of pediatric-sized blood collection tubes. Am J Clin Pathol. 1989;91:701–3.
24. **Dech ZF, Szaflarski NL.** Nursing strategies to minimize blood loss associated with phlebotomy. AACN Clin Issues. 1996;7:277–87.
25. **Dale JC, Ruby SG.** Specimen collection volumes for laboratory tests. Arch Pathol Lab Med. 2003;127:162–8.
26. **World Health Organization.** Nutritional Anemias: Report of a WHO Scientific Group. Technical Report Series no. 405. Geneva, Switzerland: World Health Organization; 1968.