Introduction

Post-gastrectomy anemia is a common long-term complication following gastric cancer surgery that mainly results from iron, folate, and cobalamin deficiency. Anemia can result in various adverse outcomes including immune dysfunction, gastrointestinal disturbance, and neurocognitive impairment.

The gastric cancer patients are at greatest risk for anemia not only postoperatively but also preoperatively based on several etiologies such as gastrointestinal blood loss, chronic gastritis, H2 blocker usage, H. pylori infection, and poor oral intake. To the best of our knowledge, as compared to the abundant studies about post-gastrectomy anemia, no studies have been performed about the relationship of preoperative, perioperative and postoperative hematological profile changes in gastric cancer patients.

In this study, we have analyzed the hematological profile changes during the preoperative stages, immediate postoperative recovery phase and long-term outpatient follow-up phase in patients who underwent a gastrectomy. For 227 gastric cancer patients, three risk factors were identified based on the use of multivariate analysis.

Materials and Methods

Patients

From April 2006 to September 2008, 296 patients with stomach cancer underwent gastrectomy. Among them, 69 patients with the following conditions were excluded: (a) intraoperative or immediately postoperative transfusion; (b) incomplete hematological profile; (c) other diseases related to anemia such as end-stage renal disease; (d) neoadjuvant chemotherapy. Finally, 227 patients were enrolled in this study. There were 158 male and 69 female. Their mean age and body mass index (BMI) were 58.19 ± 11.68 years and 23.17 ± 3.07 kg/m2, respectively. Fifty seven patients underwent a subtotal gastrectomy with gastrroduodenostomy, 73 underwent a subtotal gastrectomy with gastrojejunostomy and 97 underwent a total gastrectomy with Roux-en Y esophago-jejunostomy.

Monitoring parameters

The reference range of hematological profiles for the hematorcrit (Hct), hemoglobin (Hb) level, mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) were 40.0-52.0%, 13.0-17.0 g/dL, 27.0-33.0 pg and 80.0-100.0 fL, respectively. The reference range of iron profiles for the serum ferritin level, serum iron level, total iron binding capacity (TIBC), transferrin level, and transferrin saturation were 15.0-200.0 ng/mL, 54.0-180.0 µg/dL, 275.0-450.0 µg/dL, 200.0-360.0 µg/dL, and 16-90%, respectively. Transferrin saturation was calculated as the ratio of the serum iron level and TIBC multiplied by 100. The reference range for the levels of folate and cobalamin were 4.0-16.7 µg/mL and 200-1320 µg/mL, respectively. Each parameter was measured preoperatively (PS), at postoperative day 4 (POD4), postoperative day 7 (POD7) and during outpatient follow-up. The duration from the time of surgery to the diagnosis of anemia was observed for each subject.

Diagnosis and treatment of anemia

Anemia was defined as an Hb level less than 13g/dL in men and 12g/dL in women. Iron deficiency anemia (IDA) was diagnosed in these patients when the MCV was less than 80 fL or transferrin saturation was less than 19% 

Megalooblastic anemia (MBA) was diagnosed when the MCV was over 100 fL and either the folate level was less than 4ng/mL or the cobalamin level was less than 200 pg/mL. Anemia not otherwise specified (NOS) was defined when preoperative anemic patients had no iron, folate and cobalamin deficiency.

Statistical analysis

All results were expressed as mean ± standard deviations. The chi-squared test was performed for categorical data. The independent t-test was performed for the comparison of monitoring parameter values between normal and anemic patients. Cox regression survival analysis was performed for risk factor identification of anemia. Kaplan–Meier survival analysis was performed for the evaluation of risk factor relevance.

Results

Preoperative anemia

Of the 227 patients, 99 (44.2%) patients were diagnosed as anemic. Of the 99 anemic patients, 24 had iron deficiency anemia and 75 were regarded as having anemia NOS. There was no megalooblastic anemia in a patient diagnosed preoperatively (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Chronological change of the anemic status of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative status</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Preoperative Anemia</td>
</tr>
<tr>
<td>Non-anemic</td>
</tr>
<tr>
<td>Non-anemic</td>
</tr>
</tbody>
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Sources of NOS, anemia of the otherwise specified (IDA), iron deficiency anemia (IDA), and megalooblastic anemia (MBA) were defined when the MCV was over 100 fL and either the folate level was less than 4ng/mL or the cobalamin level was less than 200 pg/mL.
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Diagnosis and treatment of anemia

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When the monitoring parameters were analyzed by
operation type, the serum iron level on postoperative day 4 (p < 0.01) and postoperative day 7 (p < 0.01) was significantly different, specifically between patients that underwent a total gastrectomy and subtotal gastrectomy. However, no other significant differences were observed during the immediate postoperative recovery phase. The incidence of post-gastrectomy anemia during the long- term follow-up phase for patients who underwent a STBG

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Normal patients (n = 187)</th>
<th>Anemic patients (n = 48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>134:53</td>
<td>24:16</td>
<td>0.146</td>
</tr>
<tr>
<td>Age (year)</td>
<td>56±11.79</td>
<td>55±11.25</td>
<td>0.576</td>
</tr>
<tr>
<td>BMI (g/m²)</td>
<td>22±3.08</td>
<td>20±2.6</td>
<td>0.022**</td>
</tr>
<tr>
<td>Preoperative anemia (Y/N)</td>
<td>73/114</td>
<td>26/14</td>
<td>0.022**</td>
</tr>
<tr>
<td>Preoperative DA (Y/N)</td>
<td>7:180</td>
<td>17:23</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>H. pylori (Y/N)</td>
<td>44/59</td>
<td>10/8</td>
<td>0.312</td>
</tr>
</tbody>
</table>

Table 2. Clinical variables, acute hematological and iron profile changes in normal and anemic patients.

<table>
<thead>
<tr>
<th>Hematological profiles</th>
<th>Normal patients (n = 187)</th>
<th>Anemic patients (n = 48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct (%)</td>
<td>39.96±1.5</td>
<td>38.16±2.6</td>
<td>0.011**</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.7±1.6</td>
<td>12.0±2.9</td>
<td>0.001**</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>30.3±1.26</td>
<td>29.2±3.22</td>
<td>0.001**</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>30.7±1.96</td>
<td>29.9±3.83</td>
<td>0.001**</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>30.5±1.92</td>
<td>29.4±2.82</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iron profiles</th>
<th>Normal patients (n = 187)</th>
<th>Anemic patients (n = 48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin (ng/mL)</td>
<td>96±7.98</td>
<td>68±10.22</td>
<td>0.117</td>
</tr>
<tr>
<td>TIBC (ug/dL)</td>
<td>31.02±145.67</td>
<td>150.86±121.98</td>
<td>0.001**</td>
</tr>
<tr>
<td>TIBC (ug/dL)</td>
<td>192±137.86</td>
<td>170±117.64</td>
<td>0.381</td>
</tr>
<tr>
<td>Serum Iron (ug/dL)</td>
<td>71.38±39.75</td>
<td>64.±46.65</td>
<td>0.265</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>37.6±23.79</td>
<td>37.5±24.09</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

Only the data for total gastrectomized patients was plotted in representative graphs. The solid line indicates normal patients and the dotted line indicates anemic patients.

Fig. 1. Hematological and iron profile changes in total gastrectomized patients

Hemoglobin level, mean cell volume, mean cell hemoglobin, ferritin level, serum iron level, total iron binding capacity, transferrin level and transferrin saturation.

Pre- and post-gastrectomy anemia in gastric cancer patients

STBG and TG5R was 5.3%, 15.1%, and 26.8%, respectively. When the patients were grouped as postoperatively anemic and normal patients, many parameters showed significant differences (Table 2). These significant differences were more apparent in patients who underwent a total gastrectomy (Figure 1). Based on a hematological profile analysis, as compared to normal patients, anemic patients showed a significantly low POD4 hematocrit. 0.97% versus 35.50%, p < 0.01, the hemoglobin level was also significantly low on POD4 and POD7 0.123 g/dL versus 12.24 g/dL, p < 0.01 on POD4 and 11.28 g/dL versus 12.07 g/dL on POD7, p < 0.05. The MCH was also low on POD4 and POD7 for POD4, 24.40 pg versus 30.50 pg, p < 0.05, and POD5, 24.4 pg versus 30.50 pg, p < 0.05. In contrast, iron profiles, specifically ferritin and serum iron levels, TIBC, transferrin levels and transferrin saturation showed wide variations for anemic patients as compared to normal patients with few significant differences. The TIBC on
operation type, the serum iron level on postoperative day 4 \( (p < 0.01) \) and postoperative day 7 \( (p < 0.01) \) was significantly different, specifically between patients that underwent a total gastrectomy and subtotal gastrectomy. However, no other significant differences were observed during the immediate postoperative recovery phase. The incidence of post-gastrectomy anemia during the long-term follow-up phase for patients who underwent a STHB, and TGRY was 5.3%, 15.1%, and 26.8%, respectively.

When the patients were grouped as postoperatively anemic and normal patients, many parameters showed significant differences (Table 2). These significant differences were more apparent in patients who underwent a total gastrectomy (Figure 1). Based on a hematological profile analysis, as compared to normal patients, anemic patients showed a significantly low POD4 hematocrit (32.97% versus 35.50%, \( p < 0.00 \)), the hemoglobin level was also significantly low on POD4 and POD7 (11.23 g/dL versus 12.24 g/dL, \( p < 0.01 \) on POD4 and 11.28 g/dL versus 12.07 g/dL on POD7, \( p < 0.05 \)). The MCH was also low PRE and on POD4 for PRE, 28.40 pg versus 30.58 pg, \( p < 0.05 \) for POD7, 28.4 pg versus 30.59 pg, \( p < 0.05 \). In contrast, iron profiles, specifically ferritin and serum iron levels, TIBC, transferrin levels and transferrin saturation showed wide variations for anemic patients as compared to normal patients with few significant differences. The TIBC on

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#### Hematological profiles

**Hct (%):**
- PRE: 39.96 ± 2.84
- POD4: 36.92 ± 2.69
- POD7: 35.81 ± 2.57
- **p < 0.01**

**Hb (g/dL):**
- PRE: 13.87 ± 1.82
- POD4: 12.34 ± 1.4
- POD7: 12.43 ± 1.4
- **p < 0.01**

**MCH (pg):**
- PRE: 30.43 ± 2.26
- POD4: 29.94 ± 2.32
- POD7: 30.54 ± 2.92
- **p < 0.01**

**MCH (%)**
- PRE: 68.74 ± 6.55
- POD4: 67.31 ± 6.00
- POD7: 68.47 ± 6.26
- **p < 0.01**

#### Iron profiles

**Ferritin (ng/mL):**
- PRE: 96.77 ± 19.35
- POD4: 201.67 ± 145.67
- POD7: 192.62 ± 173.86
- **p < 0.01**

**Serum Iron (ug/dL):**
- PRE: 71.36 ± 59.74
- POD4: 20.44 ± 10.94
- POD7: 36.62 ± 73.78
- **p < 0.01**

**TIBC (ug/dL):**
- PRE: 297.61 ± 54.77
- POD4: 208.46 ± 40.87
- POD7: 233.42 ± 52.49
- **p < 0.01**

**Transferrin (mg/dL):**
- PRE: 219.74 ± 43.46
- POD4: 158.29 ± 26.59
- POD7: 176.95 ± 34.95
- **p < 0.01**

**Transferrin saturation (%):**
- PRE: 24.62 ± 13.49
- POD4: 10.23 ± 5.96
- POD7: 15.08 ± 8.38
- **p < 0.01**

### Notes

1. BMI: Body Mass Index, EDA: iron deficiency anemia, POD: postoperative day, PRE: preoperative; POD4, postoperative day 4; POD7, postoperative day 7; *p < 0.05, **p < 0.01
2. Statistically significant differences were observed between the preoperative and postoperative state.
3. The comparison used the Student’s t-test or Wilcoxon signed-rank test for skewed data. *p < 0.05, **p < 0.01
Table 3. Multivariate risk factor analysis for postgastrectomy anemia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquiring preoperative IDA</td>
<td>4.965</td>
<td>2.408-10.31</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>P0D7 Hb ≥ 12 g/dL versus &lt; 12 g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STBI versus TGRY</td>
<td>0.319</td>
<td>0.093-1.096</td>
<td>0.070</td>
</tr>
<tr>
<td>STBI versus TGRY</td>
<td>0.455</td>
<td>0.223-0.927</td>
<td>0.030*</td>
</tr>
</tbody>
</table>

P0D7 and P0D7 was significantly different (241.19 g/dL versus 208.39 g/dL on P0D1, p < 0.05: 260.61 g/dL versus 223.05 g/dL on P0D7, p < 0.05). The transferrin level was significantly different on P0D4 and P0D7 (74.86 mg/dL versus 155.60 mg/dL on P0D1, p < 0.05: 188.30 mg/dL versus 168.94 mg/dL on P0D7, p < 0.05). These values are plotted as shown in Figure 1 for patients who underwent a total gastrectomy.

Postoperative anemia and risk factor analysis

Patient clinical variables and monitoring parameters (Table 2) were analyzed with determination of odds ratios for becoming anemic postoperatively based on the use of the Cox regression model (Table 3). Accompanying preoperative iron deficiency anemia (IDA), type of surgery and P0D7 Hb level were fitted into the model. When anemia occurrence was analyzed by Kaplan–Meier survival analysis, Figure 2 p-values for each above three factor was 0.001, 0.002 and 0.001, respectively. A comparison of post–gastrectomy anemia occurrence pattern of patients who had or did not have preoperative IDA is shown in Figure 3. Despite an initial steep increase in preoperative IDA, no significant difference was observed (p > 0.303).

Discussion

This study clearly shows that preoperative iron deficiency anemia accounts for post-gastrectomy anemia. First, when we overview patient status chronologically, more than two-thirds (70.89%) of preoperative IDA patients were diagnosed with postoperative anemia again. Second, anemia NOS patients and preoperatively non-anemic patients acquired postoperative anemia only in 12.0% and 10.9% of cases, respectively. Third, preoperative IDA patients showed a steep increased rate of post-gastrectomy anemia during the long-term follow-up phase, even though no significant difference for non-preoperative IDA patients was seen.

Occurrence of post–gastrectomy IDA has been known to have an interval of more than five years. However, the patient populations were different from this study. Previous post–gastrectomy anemia studies mainly examined peptic ulcer24 or morbid obese25 patients who were moderately nourished preoperatively. However, gastric cancer patients have a higher risk24 of pre- and post-operative malnutrition. If preoperative iron deficiency is not properly managed, subsequent postoperative IDA is unavoidable and will occur faster than for the well-nourished population. In this study, post–gastrectomy anemia was diagnosed through two years after gastrectomy and the level of post–gastrectomy anemia reached a plateau over 24 months. As this study only observed a three year follow-up period, more observation is required to obtain sufficient data. Given that cobalamin26 and iron storage26 depletion requires about two and five years, respectively, there should be another peak incidence of anemia with additional observation.

When patients were grouped based on the type of surgery, patients who underwent a TGRY showed the highest IDA incidence followed by patients who underwent Billroth II GSTRY and Billroth I GSTRY reconstruction. This finding is in agreement with the observation that the incidence of anemia is directly correlated with a duodenal bypass and rapid transit. Other clinical variables, specifically sex, age, BMI, H. pylori infection and pathological stage showed no significant difference. A lower P0D7 Hb level was identified as a risk factor for post–gastrectomy anemia. This finding may reflect that a robust high Hb level after surgical stress and a period of poor oral intake indicates good nutritional status. Such a patient would have a low risk of postoperative anemia. Even though the patient might acquire anemia, the time to acquire anemia would still be later as compared to other patients.

Perioperative iron profiles showed disappointing results for the prediction of post–gastrectomy anemia. The serum ferritin level that reflects iron body stores is considered the single best parameter27 for the iron status. However, the usefulness of this parameter is limited only for the preoperative phase, as ferritin is known to act as an acute phase reactant. The serum iron level showed an apparent acute decrease on P0D4. However, the cause and implications of this decrease in the level are unclear. The serum iron level is known to be poorly correlated28 with the levels of ferritin and transferrin. This study also confirmed a poor correlation (data not shown) with other hematological factors during the perioperative period and showed little significant difference for anemic and normal patients. The poor correlation originates from a wide variation of serum iron levels and diurnal changes29. In this regard, the usefulness of the serum iron level and transferrin saturation, which is calculated from TIBC and the serum iron level, have limited value. Even though the TIBC and transferrin level showed a significant difference for postoperative anemic and normal patients, multivariate analysis showed a low predictive value of these parameters.

Practical application of anemia diagnosis and treatment is very difficult. As for the diagnosis, microcytosis and hypochromasia of iron deficiency can be frequently masked by concomitant cobalamin or folate deficiency30. Conversely, macrocytosis of cobalamin and folate...
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<tr>
<td>Accompanying preoperative IDA</td>
<td>0.455</td>
<td>0.911</td>
</tr>
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</table>
| POD7 Hb level | 0.690 | 0.536-0.901 | 0.024 **
| STBI versus TGRY | 0.319 | 0.269-0.371 | 0.001 **
| STBI versus TGRY | 0.455 | 0.223-0.927 | 0.030 **

CL, confidence interval; IDA, iron deficiency anemia; POD, postoperative day 7; STBI, subtotal gastrectomy with gastroduodenostomy; TGRY, total gastrectomy with gastrojejunostomy; TGRY, total gastrectomy with gastrojejunostomy.

PONI and POD7 was significantly different (PONI, 94.19 g/dL versus 208.39 g/dL on POD1, p < 0.05; POD7, 206.61 g/dL versus 223.05 g/dL on POD7, p < 0.05). The transferrin level was significantly different on POD4 and POD7 (74.86 mg/dL versus 155.60 mg/dL on POD1, p < 0.05; 188.30 mg/dL versus 168.94 mg/dL on POD7, p < 0.05). These values are plotted as shown in Figure 1 for patients who underwent a total gastrectomy.

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In this regard, the usefulness of the serum iron level and transferrin saturation, which is calculated from TIBC and the serum iron level, have limited value. Even though the TIBC and transferrin level showed a significant difference for postoperative anemic and normal patients, multivariate analysis showed a low predictive value of these parameters.

Practical application of anemia diagnosis and treatment is very difficult. As for the diagnosis, microcytosis and hypochromasia of iron deficiency can be frequently masked by concomitant cobalamin or folate deficiency. Conversely, macrocytosis of cobalamin and folate
deficiency is often masked by iron deficiency. Diagnosis of iron, folate, and cobalamin deficiency would be difficult without additional laboratory testing at an additional expense. As for treatment, because there are no standard guidelines and treatment options are dependent on the individual physician. A study about iron deficiency anaemia treatment reported one-fourth of patients were discharged from the hospital without a proper treatment plan.

Long-term oncological survival is the main treatment goal of gastric cancer surgery. However, quality of life and patient satisfaction are also important. Post-gastrectomy anaemia is one of the common complications that require intensive medical care. Considering the implications of postoperative IDA that were demonstrated in this study, a routine checkup of iron storage, immediate postoperative iron support, and close follow-up of anemic surgical candidate would be imperative.

Conclusions

Risk factors of post-gastrectomy anaemia were accompanying preoperative iron deficiency anaemia, a low postoperative day 7 hemoglobin level and the type of surgery. Furthermore, diagnosis and treatment of preoperative iron deficiency anaemia would have profound implications for post-gastrectomy anaemia.

REFERENCES

Pre- and post-gastrectomy anemia in gastric cancer patients

Department of Surgery, Yonsei University College of Medicine, Seoul, South Korea
Myung-jae Jung, MD, Hyoung-Il Kim, MD, Hyoung won Cho, MD, Ho Young Yoon, Choong Bai Kim, MD

Abstract
Purpose: Post-gastrectomy anemia is a common long-term complication after gastric surgery. However, the relationship of preoperative, perioperative and postoperative hematological changes has not been well studied. We analyzed factors that cause post-gastrectomy anemia including hematological changes.

Materials and Methods: A total of 227 patients who underwent a gastrectomy were analyzed. Hematological and iron profiles were measured preoperatively, post-operative day (POD) 4, POD7, and during outpatient follow-up.

Results: During the preoperative phase, 99 patients were anemic and 24 of the patients had iron deficiency. No folate or cobalamin deficiency was noted. No significant differences were observed during the immediate postoperative recovery phase. During the long-term outpatient follow-up phase, we monitored occurrence of post-gastrectomy anemia and identified three risk factors, including presence of preoperative iron deficiency anemia, low hemoglobin level on POD7 and the type of surgery (p-value 0.001, 0.002, and 0.001).

Conclusions: We showed that patients with preoperative iron deficiency anemia accounted for nearly half of the post-gastrectomy anemia population. Further study on the utility of preoperative treatment of anemia before the surgery should be considered for the quality of life in gastric cancer survivors.

Key Words: Stomach Neoplasms, Gastrectomy, Anemia, Iron-Deficiency, Megaloblastic

Correspondence: Choong Bai Kim, M.D., F.A.C.S.
Department of Surgery, Yonsei University College of Medicine 250 Seogang-daero, Seodaemun-gu, Seoul 120-752, Republic of Korea
Tel: 82-2-2228-2713 (office) / 82-10-2807-5998 (mobile) Fax: 02-351-8289 E-mail: cbbkim@yuhs.ac
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