Original Article

Use of iron sucrose injection in anemia patients with reduced serum iron concentration during hospitalizations of digestive and liver diseases

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Background: Anemia is one of the most common disorders in the world. Serum iron is an essential element for the synthesis of hemoglobin and contribution of the oxygen-carrying ability of red blood cells (RBCs). Iron sucrose injection may effectively correct iron deficiency, increase iron storage, and then improve anemia. The aim of the present study was to evaluate the therapeutic effect of iron sucrose injection in anemia patients with reduced serum iron concentration.

Methods: Overall, 95 anemia patients with digestive and/or liver diseases were included. They were divided according to the infusion of iron sucrose injection during hospitalization. The paired sample *t* test was used for comparison between last and baseline hemoglobin concentration. The independent sample *t* test was used for comparison of a dynamic change of hemoglobin concentration between patients who received and did not receive infusion of iron sucrose injection.

Results: Iron sucrose injection was infused in 74 (77.90%) patients. Mean hemoglobin concentration after infusion of iron sucrose injection was significantly increased (91.61 *vs.* 94.98 g/L, P=0.011). Δ Hemoglobin concentration was significantly different between patients who received and did not receive infusion of iron sucrose injection (P=0.007). Mean hemoglobin concentration after infusion of iron sucrose injection remained significantly increased in subgroup analyses of patients with cirrhosis (88.30 *vs.* 91.98 g/L, P=0.035) and gastrointestinal bleeding (85.70 *vs.* 92.63 g/L, P<0.01).

Conclusions: Iron sucrose injection can significantly increase the hemoglobin concentration in anemia patients with serum iron concentration below the lower limit of the normal range.

Keywords: Iron; iron sucrose injection; hemoglobin; liver cirrhosis; gastrointestinal bleeding

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Introduction

Anemia, which is characterized by a decrease in the concentration of hemoglobin, a protein in red blood cells (RBCs) with an oxygen-carrying capacity, is one of the most common disorders in clinical practice (1). A common etiology of anemia is bleeding which can occur from various sources (2). In addition, the presence of anemia is associated with a significant deterioration of hyperdynamic circulation and increased gastric blood flow in cirrhosis with portal hypertension (3). Acute or chronic bleeding, disease severity, hypersplenism, malnutrition, and inflammation are thought to contribute to the development of anemia in such patients (4-6). Serum iron is an essential element for the synthesis of hemoglobin and contribution to the oxygen-carrying ability of RBCs (2,7). Treatment options for iron deficiency anemia include blood transfusion, oral iron supplementation, and intravenous iron supplementation. Intravenous iron supplementation has been considered an efficacious alternative to blood transfusion in colon cancer patients with anemia (8). On the other hand, intravenous iron supplementation can be superior to oral iron supplementation for the treatment of iron deficiency (9-11), because oral iron supplementation often leads to gastrointestinal side effects and some patients cannot respond to oral iron supplementation rapidly (12). Preliminary evidence suggests that intravenous iron, which may correct iron deficiency and increase iron storage, thereby improving anemia (6), seems to be effective and safe in patients with cancer, end-stage kidney disease undergoing hemodialysis (13), inflammatory bowel disease (11,14), and liver disease with iron deficiency anemia. The only intravenous iron entity available for over 40 years is iron dextran. But it is associated with rare but severe adverse effects, such as anaphylaxis, which greatly limits its use. Several different intravenous iron salts are commercially available without dextran moiety and are thought to be much less likely to cause hypotension or anaphylaxis (15). Notably, the side effects of iron sucrose injection are rare according to its product label information sheet. It has been also reported that iron sucrose injection is stable and causes less anaphylactic reactions. Iron sucrose has been utilized in the treatment of iron deficiency anemia due to chronic kidney disease with or without dialysis and is much less likely to cause hypotension or anaphylaxis (16).

The present study aimed to evaluate the therapeutic effect of iron sucrose injection on hemoglobin concentrations in patients with anemia with iron concentration <11 mmol/L with an emphasis on the patients with liver cirrhosis and those with gastrointestinal bleeding. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-19-499).

Methods

Study design

The present study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command [No. k (2019) 41]. Because of the retrospective nature of the research, the requirement for informed consent was waived. We reviewed the patients who were admitted to the General Hospital of Northern Theater Command from January 2016 to March 2019 and were treated by a primary investigator of this study. Patients would be eligible if they met the following inclusion criteria: (I) anemia diagnosed at admission or during the hospitalizations; (II) serum iron concentration lower than the normal range; and (III) hemoglobin concentration was re-tested during the hospitalizations. Exclusion criteria were as follows: (I) active bleeding during hospitalizations; and (II) RBCs transfusion during the hospitalizations. Patients with gastrointestinal bleeding at admission were included. Age, gender, and repeated admissions were not limited.

Data collection

The following data was collected: demographic data (i.e., age and gender), presence of liver cirrhosis, malignancy, and gastrointestinal bleeding at admission, infusion of iron sucrose injection and laboratory tests [i.e., RBC, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), hematocrit (HCT), white blood cell, platelet count, total bilirubin, direct bilirubin, albumin, blood urea nitrogen, serum creatinine, potassium, sodium, prothrombin time, activated partial thromboplastin time, international normalized ratio, and serum iron].

Definitions and classifications

Anemia is defined as a decreased number of circulating RBCs and/or hemoglobin concentration. In details, according to the World Health Organization, anemia refers

to a hemoglobin concentration of <130 g/L or an HCT of <41% in men and a hemoglobin concentration of <120 g/L or an HCT of <36% in women. The morphologic approach categorizes anemia by RBC size using the MCV, as follows: (I) microcytic anemia, in which the MCV is less than 80 fL; (II) normocytic anemia, in which the MCV is within the normal range of 80–100 fL; and (III) macrocytic anemia, in which the MCV is greater than 100 fL.

The normal range of serum iron concentration at our hospital is 11–30 mmol/L. Thus, iron deficiency is defined as serum iron concentration of <11 mmol/L.

As for patients who did not receive iron sucrose injection, baseline hemoglobin concentration was defined as the value of hemoglobin obtained at the time of the diagnosis of anemia during the hospitalizations, and the last hemoglobin concentration was defined as the last value of hemoglobin obtained during hospitalizations.

As for patients who received iron sucrose injection, baseline hemoglobin concentration was defined as the value of hemoglobin obtained at the time of the diagnosis of anemia and before the infusion of iron sucrose injection, and the last hemoglobin concentration was defined as the value of hemoglobin obtained before stopping iron sucrose injection.

Δ Hemoglobin concentration was defined as the dynamic change from the last hemoglobin concentration to baseline hemoglobin concentration.

Response was defined as a positive Δ hemoglobin concentration. Otherwise, no response was defined, which referred to no change or further decrease in the last hemoglobin concentration as compared to baseline hemoglobin concentration.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation and median (range). Categorical variables were expressed as frequency (percentage). The paired sample *t* test was used for comparison between last and baseline hemoglobin concentration. The independent sample *t* test was used for comparison of Δ hemoglobin concentration between patients who received and did not receive iron sucrose injection infusion. The Chi-square test was used for comparing of response rate between patients who received and did not receive iron sucrose injection infusion. A two-tailed P<0.05 was considered statistically significant. Subgroup analyses were conducted for patients with liver cirrhosis and gastrointestinal bleeding at admission. All statistical analyses were performed with IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) statistical package.

Results

Patient selection

A total of 442 patients had anemia during the study period. Among them, 84 patients received RBC transfusion during their hospitalizations; 140 patients did not have their hemoglobin concentrations re-tested; 38 patients had active bleeding during their hospitalizations. Finally, 95 patients with anemia who had serum iron concentration of <11 mmol/L were included in our study.

Overall analyses

Patient characteristics at admission are shown in *Table 1*. Median age was 60.00 years (range, 20.00–84.00 years); 65 (68.40%) patients were male; 15 (15.80%) patients had malignancy; 54 (56.80%) patients had liver cirrhosis; 39 (41.10%) patients had gastrointestinal bleeding at admission. Median RBC was 3.30×10^{12}/L (range, 1.95×10^{12}–4.86×10^{12}/L). Median hemoglobin concentration was 97.00 g/L (range, 58.00–129.00 g/L). Median MCV was 89.10 fL (range, 65.10–123.00 fL); MCV <80 fL was observed in 21 (22.10%) patients and MCV >100 fL in 11 (11.60%) patients. Median serum iron concentration was 4.90 mmol/L (range, 0.56–10.99 mmol/L).

Iron sucrose injection was infused in 74 (77.90%) patients. The paired sample *t* test revealed that hemoglobin concentration after iron sucrose injection infusion was significantly increased (91.61 *vs.* 94.98 g/L, P=0.011). Mean Δ hemoglobin concentration was +2.21 g/L in patients who received iron sucrose injection.

Iron sucrose injection was not infused in 21 (22.10%) patients. The paired sample *t* test revealed no statistically significant difference between baseline and last hemoglobin concentration (110.57 *vs.* 107.57 g/L, P=0.177). Mean Δ hemoglobin concentration was –3.00 g/L in patients who did not receive iron sucrose injection. The independent sample *t* test revealed that Δ hemoglobin concentration was significantly different between patients who received and did not receive iron sucrose injection (P=0.007).

Subgroup analyses of liver cirrhosis

There were 54 cirrhotic patients (*Table 2*). Iron sucrose

Table 1 Patients with anemia and serum iron <11 mmol/L after excluding active bleeding during hospitalization

Variables	No. Pts	Overall
Age (years)	95	60.00 (20.00–84.00); 57.86±15.25
Gender (male) (%)	95	65 (68.40)
Liver cirrhosis (%)	95	54 (56.80)
GIB at admission (%)	95	39 (41.10)
Malignancy (%)	95	15 (15.80)
Laboratory tests		
RBC (10^{12}/L)	95	3.30 (1.95–4.86); 3.33±0.64
Hb (g/L)	95	97.00 (58.00–129.00); 95.56±19.25
MCV (fL)	95	89.10 (65.10–123.00); 88.37±10.98
MCV <80 fL (%)	95	21 (22.10)
MCV >100 fL (%)	95	11 (11.60)
MCHC (g/L)	95	327.00 (300.00–354.00); 326.00±11.18
HCT (%)	95	29.70 (18.50–39.70); 29.21±5.55
WBC (10^9/L)	95	5.20 (1.00–23.20); 6.05±4.05
PLT (10^9/L)	95	121.00 (19.00–549.00); 156.97±113.42
TBIL (μmol/L)	88	15.25 (3.10–217.30); 24.07±29.91
DBIL (μmol/L)	88	6.35 (1.10–168.00); 13.22±22.41
ALB (g/L)	86	32.70 (17.70–48.50); 33.20±5.89
BUN (mmol/L)	90	5.49 (0.68–28.05); 6.25±3.87
Scr (μmol/L)	90	65.05 (34.51–607.97); 81.45±70.02
K (mmol/L)	90	3.89 (2.72–4.99); 3.89±0.43
Na (mmol/L)	90	137.65 (125.50–145.70); 137.49±3.83
PT (seconds)	87	15.00 (12.10–22.50); 15.67±2.50
APTT (seconds)	87	38.90 (16.80–71.30); 39.87±7.60
INR	87	1.18 (0.92–1.97); 1.26±0.26
Iron (mmol/L)	95	4.90 (0.56–10.99); 5.42±2.70
Infusion of iron sucrose injection (%)	95	74 (77.90)
Response of iron sucrose injection (%)	74	48 (64.90)
No response of iron sucrose injection (%)	74	26 (35.10)

The data are shown as median (range) and mean ± standard deviation or frequency (percentage). Pts, patients; GIB, gastrointestinal bleeding; RBC, red blood cell; Hb, hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; HCT, hematocrit; WBC, white blood cell; PLT, platelet count; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; K, potassium; Na, sodium; PT, prothrombin time; INR, international standardization ratio; APTT, activated partial thromboplastin time.

Table 2 Cirrhotic patients with anemia and serum iron <11 mmol/L after excluding active bleeding during hospitalization

Variables	No. Pts	Overall
Age (years)	54	59.00 (36.00–84.00); 58.24±11.17
Gender (male) (%)	54	36 (66.70)
GIB at admission (%)	54	25 (46.30)
Laboratory tests		
RBC (10^{12}/L)	54	3.25 (1.95–4.86); 3.29±0.70
Hb (g/L)	54	91.00 (58.00–127.00); 90.65±18.73
MCV (fL)	54	87.25 (65.10–123.00); 85.99±12.11
MCV <80 fL (%)	54	17 (31.50)
MCV >100 fL (%)	54	5 (9.30)
MCHC (g/L)	54	324.00 (300.00–346.00); 323.41±11.38
HCT (%)	54	27.95 (18.50–39.70); 27.97±5.44
WBC (10^9/L)	54	3.55 (1.00–23.20); 4.66±3.72
PLT (10^9/L)	54	79.50 (19.00–470.00); 109.94±88.60
TBIL (μmol/L)	53	18.20 (5.60–80.90); 25.33±18.69
DBIL (μmol/L)	53	9.90 (2.60–53.50); 13.53±11.74
ALB (g/L)	52	31.05 (21.30–42.40); 31.12±5.47
BUN (mmol/L)	53	5.81 (1.88–20.20); 6.12±3.10
Scr (μmol/L)	53	64.70 (34.51–314.00); 74.64±44.07
K (mmol/L)	52	3.95 (2.72–4.99); 3.98±0.42
Na (mmol/L)	52	137.90 (128.00–144.00); 137.50±3.61
PT (seconds)	51	16.10 (12.10–22.50); 16.80±2.65
APTT (seconds)	51	41.60 (16.80–71.30); 41.90±7.75
INR	51	1.30 (0.90–1.97); 1.37±0.28
Iron (mmol/L)	54	5.14 (1.19–10.99); 5.69±2.80
Supplement of iron sucrose injection (%)	54	46 (85.20)
Response of iron sucrose injection (%)	46	30 (63.00)
No response of iron sucrose injection (%)	46	16 (34.80)

The data are shown as median (range) and mean ± standard deviation or frequency (percentage). Pts, patients; GIB, gastrointestinal bleeding; RBC, red blood cell; Hb, Hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; HCT, hematocrit; WBC, white blood cell; PLT, platelet count; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; K, potassium; Na, sodium; PT, prothrombin time; INR, international standardization ratio; APTT, activated partial thromboplastin time.

injection was infused in 46 (85.20%) patients. The paired sample *t* test revealed that hemoglobin concentration was significantly increased in patients who received iron sucrose injection (88.30 *vs.* 91.98 g/L, P=0.035). Mean Δ hemoglobin concentration was +3.67 g/L in patients who received iron sucrose injection.

Iron sucrose injection was not infused in 8 (14.80%) patients. The paired sample *t* test revealed no statistically significant difference between baseline and last hemoglobin concentrations (104.13 *vs.* 104.75 g/L, P=0.740). Mean Δ

hemoglobin concentration was +0.62 g/L in patients who did not receive iron sucrose injection. The independent sample *t* test revealed that Δ hemoglobin concentration was not significantly different between patients who received and did not receive infusion of iron sucrose injection (P=0.200).

Subgroup analysis of gastrointestinal bleeding at admission

There were 39 patients with gastrointestinal bleeding at admission (*Table 3*). Iron sucrose injection was infused in 35 (89.70%) patients. The paired sample *t* test revealed that hemoglobin concentration was significantly increased in patients who received iron sucrose injection (85.7 *vs.* 92.63 g/L, P<0.01). Mean Δ hemoglobin concentration was +6.91 g/L in patients who received iron sucrose injection.

Iron sucrose injection was not infused in 4 (10.30%) patients. The paired sample *t* test revealed no significant difference between baseline and last hemoglobin concentration (107.25 *vs.* 103.75 g/L, P=0.671). Mean Δ hemoglobin concentration was −3.50 g/L in patients who did not receive iron sucrose injection. The independent sample *t* test revealed that Δ hemoglobin concentration was not significantly different between patients who received and did not receive iron sucrose injection (P=0.071).

Discussion

Our findings were in the support of iron sucrose injection as an effective therapy for anemia. Intravenous iron supplementation might be essential in anemia patients with reduced serum iron concentration for improving hemoglobin concentration in the absence of blood transfusion. Price *et al.* performed a randomized controlled trial and included 19 elderly patients with anemia, of whom 9 received iron sucrose injection and 10 patients did not receive it. At the 12th week, the hemoglobin concentration was increased in the group of intravenous iron sucrose injection, but decreased in the control group (P=0.026) (17). Thus, studies by our team and others demonstrated that iron sucrose injection increased hemoglobin concentration in patients with anemia.

Iron binds to transferrin receptor 1 and synergizes with erythropoietin to promote the differentiation of erythroid precursors into reticulocytes, thereby producing hemoglobin. Because iron is metabolized quickly in the body, the supply of iron is often essential for maintaining hemoglobin concentration (18). Three major cells, including enterocyte, macrophage, and hepatocyte, play an important role in iron homeostasis. First, the absorption of dietary iron occurs in the small intestine, especially in the duodenum, via the divalent metal transporter-1 (DMT-1). The iron is transferred from the gut lumen to the enterocyte, and then is stored as ferritin or enters into the plasma by a transmembrane transporter named ferroportin (FPN)/SLC40A1. The plasma iron is then conjugated to transferrin, which is the major iron transporter in the circulation. Impaired synthesis of any of these participants can inhibit the absorption of iron and dysregulate its homeostasis. Second, macrophages can also provide iron by degrading senescent or damaged erythrocytes through erythrophagocytosis in the spleen, liver, or bone marrow. In addition, macrophages have the ability to store iron as ferritin or to release it into circulation via FPN (19). Third, the liver, a significant site for the storage of iron, absorbs iron through the portal circulation and, in case of increased demand, releases it back to the systemic circulation (20). The liver maintains a subtle physiological iron balance in the body (21). Hepcidin, a master regulator of iron homeostasis, is produced by the liver (22,23). Under physiological conditions, the hepcidin expression is strictly regulated to maintain a normal serum iron concentration. An augmentation in serum iron level increases the hepcidin synthesis, thus impairing the intestinal iron absorption to maintain a normal serum iron concentration. On the contrary, in the case of a reduced serum iron concentration, the hepcidin production will be decreased, which stimulates the intestinal iron absorption, thereby increasing the serum iron concentration (24,25). The hepcidin maintains serum iron levels. In pathological conditions as anemia, the hepcidin expression is inhibited in an attempt to correct the serum iron concentration (26). Iron deficiency can occur due to the inability to regulate hepcidin expression in patients with chronic liver disease (10,11). Disorders of serum iron balance, which are characterized as iron deficiency and hepcidin overload, are frequently observed in patients with chronic hepatitis (27). Our study found that iron sucrose injection may be an effective choice of intravenous iron in patients with liver cirrhosis and reduced serum iron concentration, probably by correcting iron deficiency and increasing serum iron storage (6).

Traditionally, patients with gastrointestinal bleeding often need blood transfusion for the management of anemia. However, blood transfusion brings risks, such as infection and transfusion reactions (28). In addition, blood

Table 3 Patients with anemia and serum iron <11 mmol/L after excluding active bleeding during hospitalizations with gastrointestinal bleeding at admission

Variables	No. Pts	Overall
Age (years)	39	54.00 (20.00–79.00); 53.85±15.07
Gender (male) (%)	39	27 (69.20)
Liver cirrhosis (%)	39	25 (64.10)
Malignancy (%)	39	4 (10.30)
Laboratory tests		
RBC (10^{12}/L)	39	2.98 (2.06–4.41); 3.08±0.61
Hb (g/L)	39	85.00 (58.00–124.00); 87.92±18.07
MCV (fL)	39	89.10 (67.10–104.90); 87.70±9.33
MCV <80 fL (%)	39	7 (17.90)
MCV >100 fL (%)	39	4 (10.30)
MCHC (g/L)	39	327.00 (301.00–354.00); 327.05±12.13
HCT (%)	39	25.90 (18.50–37.20); 26.82±5.15
WBC (10^9/L)	39	4.30 (1.00–12.00); 4.93±2.88
PLT (10^9/L)	39	101.00 (19.00–470.00); 142.64±114.59
TBIL (μmol/L)	36	14.00 (3.50–67.50); 17.72±12.36
DBIL (μmol/L)	36	5.50 (1.10–42.20); 8.63±8.21
ALB (g/L)	35	31.20 (21.30–48.50); 31.68±5.45
ALT (U/L)	36	18.44 (4.82–79.02); 20.97±16.21
AST (U/L)	36	21.50 (7.52–94.04); 28.54±20.64
AKP (U/L)	36	80.61 (8.32–299.81); 124.54±176.61
GGT (U/L)	36	21.54 (8.00–299.81); 49.71±63.59
BUN (mmol/L)	36	5.16 (1.88–13.19); 5.60±2.68
Scr (μmol/L)	36	65.76 (37.22–314.00); 76.39±48.65
K (mmol/L)	36	3.81 (2.72–4.99); 3.91±0.44
Na (mmol/L)	36	139.00 (132.00–144.00); 138.94±2.85
PT (seconds)	35	15.30 (12.60–22.50); 16.34±2.85
APTT (seconds)	35	37.10 (28.90–71.30); 38.92±7.78
INR	35	1.21 (0.94–1.97); 1.33±0.29
Iron (mmol/L)	39	4.48 (1.19–10.71); 4.88±2.70
Supplement of iron sucrose injection (%)	39	35 (89.70)
Response of iron sucrose injection (%)	35	26 (74.30)
No response of iron sucrose injection (%)	35	9 (25.70)

The data are shown as median (range) and mean ± standard deviation or frequency (percentage). Pts, patients; GIB, gastrointestinal bleeding; RBC, red blood cell; Hb, hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; HCT, hematocrit; WBC, white blood cell; PLT, platelet count; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Scr, serum creatinine; K, potassium; Na, sodium; PT, prothrombin time; INR, international standardization ratio; APTT, activated partial thromboplastin time.

transfusion has a substantial cost. Oral iron supplementation is inexpensive and easy to manage, but is associated with gastrointestinal side effects, such as abdominal pain, diarrhea, constipation, and dyspepsia. Intravenous iron supplementation is more effective than oral iron supplementation in ensuring adequate iron storage. Bager *et al.* performed a randomized controlled trial and enrolled 97 patients with non-variceal gastrointestinal bleeding and anemia, who were randomized into three groups: oral iron supplementation, intravenous iron supplementation, or placebo groups. At the 4th week, hemoglobin levels were significantly higher in patients treated with iron supplements than in patients treated with placebo (P<0.01). Intravenous iron supplementation seems to be more effective than oral iron supplementation (29). In accordance with these findings, our study also confirmed that iron sucrose injection increased hemoglobin concentration in patients with gastrointestinal bleeding.

Several limitations should not be neglected. First, because this was a retrospective study, the selection bias of patients cannot be ignored. Second, because serum iron and hemoglobin concentration were not re-tested at a fixed interval, the time of the recovery of hemoglobin concentration during the use of iron sucrose injection cannot be accurately assessed. Third, the duration of iron sucrose injection was not fixed. Finally, serum ferritin level was not regularly measured.

In conclusion, for patients with gastrointestinal diseases, especially those with liver cirrhosis or gastrointestinal bleeding, intravenous iron sucrose injection may improve the hemoglobin concentration in the case of anemia with serum iron concentration of <11 mmol/L.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command [No. k (2019) 41]. Because of the retrospective nature of the research, the requirement for informed consent was waived.

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