ORIGINAL ARTICLE

Gastric cancer surgery: clinical outcomes and prognosis are influenced by perioperative blood transfusions

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Abstract

Gastric cancer in patients is often associated with bleeding; when it occurs, especially in the presence of an anemia, a transfusion is necessary to avoid further deterioration of the patient's clinical state. The aim of this study was to evaluate the relationship between the administration of peri-operative transfusions due to the anemia or the clinical status and the postoperative clinical outcomes. 188 patients diagnosed with of gastric cancer were recruited at Surgery 2 of the Department of General and Specialist Surgery of the Tertiary Care Hospital "A. Cardarelli" of Naples. All patients had a total or a subtotal gastrectomy accompanied by D2 lymphectomy for gastric cancer. The clinical data most frequently associated with blood transfusion is the appearance of a post-operative infection (OR 2.26, 95% CI 0.87–5.79, $P = 0.061$). If the administration time of transfusion is considered, the clinical outcomes are different: preoperative transfusions showed a higher incidence of infections (OR 2.26, 95% CI 0.87–5.79, $P = 0.061$) and acute renal failure (OR 2.82, 95% CI 0.70–10.78, $P = 0.078$); patients who received intra or post-operative transfusions showed a prolonged hospitalization (OR 8.66, 95% CI 1.73–83.00, $P = 0.002$). The administration of blood products in the perioperative period is correlated in a statistically significant manner to the incidence of infections, acute renal failure and prolonged hospitalization; therefore, transfusions should be avoided unless clinically necessary and in particular intraoperative transfusions should be avoided because the immunomodulation effect linked to surgical stress may be enhanced hence worsening the prognosis.

Keywords Gastric cancer · Blood transfusion · Post-operative infection · Perioperative transfusion

Introduction

The prognosis of gastric cancer is mainly associated with cancer depth and lymph node status [1, 2].

Despite the improvements in diagnostic techniques and the increasingly numerous screening campaigns, the early diagnosis of gastric cancer is not always possible, so very often, at the time of diagnosis, the lesions are already in an advanced stage of disease. Gastric neoplasms are the fourth most frequent by incidence and the second by mortality due to the neoplastic disease. Elective treatment, compatible with the stage in which the disease is found at the time of diagnosis, is surgical therapy that involves a total or a subtotal gastrectomy, accompanied by D2 lymphectomy [3–5].

The most frequent symptoms gastric neoplasms present are dysphagia, epigastric pain and anemia.

Anemia in patients with gastric cancer may be due to poorly sustained bleeding over time or visible digestive bleeding occurring in the form of hematemesis and/or melena.

When bleeding occurs, especially in the presence of anemia, it is necessary to transfuse the patient to avoid further deterioration of the patient's clinical status and it is clear that a total or a subtotal gastrectomy and the D2 lymphectomy,

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which are performed to obtain radical surgery, themselves represent a further depletion of blood volume to the detriment of the patient's homeostasis.

While transfusions represent a clinical benefit to the patient, more and more data highlight their negative prognostic role on postoperative outcomes, suggesting that there is a correlation between peri-operative transfusions and a worsening of the prognosis of these patients [6].

Among the main factors contributing to these effects could be the immunomodulation induced by transfusions and the activation of the inflammatory system. [7].

The aim of this study was to evaluate the relationship between the diagnosis of anemia that induces the administration of peri-operative transfusions and the post-operative clinical outcomes of patients undergoing a total or a subtotal gastrectomy accompanied by D2 lymphectomy for gastric cancer.

Since other variables such as the patient's age, the disease stage and comorbidity may play a fundamental role in the prognosis of gastric cancer, each of these variables have been evaluated separately.

Materials and methods

For the present study, all patients admitted at Surgery 2 of the Department of General and Specialist Surgery of the Tertiary Care Hospital "A. Cardarelli" of Naples from 2009 to 2015 to undergo a total or a subtotal gastrectomy with D2 lymphectomy for gastric cancer were recruited.

The "A. Cardarelli" Hospital ethics committee approved a retrospective analysis of anonymous data. A signed patient informed consent allowed for the committee's approval, because it was a retrospective analysis.

All patients undergoing a total or a subtotal gastrectomy for non-neoplastic pathologies (sleeve gastrectomy or gastric bypass for obesity), emergency patients, patients with synchronous neoplasms, patients presenting septicemia at the time of diagnosis and patients who underwent long-term therapy with corticosteroids were excluded from the study.

Each patient at the time of admission to the hospital was subjected to blood tests and instrumental diagnostic tests such a chest X-ray, an abdominal ultrasound and a total body scan (TAC) for staging the disease according to the tumor-lymph node-metastasis (TNM) system. A staging system of gastric cancer and an anesthesiological examination were always performed before the surgery was scheduled.

A total or a subtotal gastrectomy surgery was always accompanied by D2 lymphectomy; they were performed by surgeons trained to perform stomach surgery for neoplasm.

After the resection, the continuity of the digestive tract was obtained with the creation of termino-lateral esophagus-jejunostomy with Roux loop in the case of total gastrectomy, while in the case of subtotal gastro-resection it was obtained by the creation of termino-lateral gastro-jejunostomy.

For some patients multiple resections were required depending on local invasion to organs or structures.

For all patients, 6 mm silicone drains were placed in the sub-hepatic space, in the area of the anastomosis and in the pelvic area.

All patients were given a prophylactic antibiotic therapy with third-generation cephalosporins and the therapy was extended from 3 to 5 days post-operatively as needed.

For each patient, their age, sex, familiarity with neoplastic pathology and comorbidity at the time of diagnosis were taken into account.

Follow-up at 6 months, 1 year and 3 years after discharge was performed.

The decision to transfuse the patient was made on a clinical basis for all patients with anemia (with hemoglobin values below 80 g/L) or for patients with hemoglobin values between 80 and 100 g/L in relation to the clinical conditions.

For the purposes of the study, all transfusions that the patients received from the time they were admitted to hospital up to the time of discharge were characterized from transfusion in pre-operative (from admission to surgery), intra-operative (performed during surgery) and post-operative (from the time returning to the ward until the patient's discharge). In the case of multiple transfusions, the time in which the first transfusion was performed was taken into consideration for evaluation.

Statistical analyses were performed with IBM SPSS Statistics for Windows (Ver. 24, NY: IBM Corporation). All data were expressed as mean ± standard deviation (SD) or median (interquartile range; IQR). The unconditional logistic regression model was used for calculating the odds ratio (OR) in assessing the relationship of preoperative anemia, pre-, intra-, and post-operative transfusion to the clinical outcome with the estimation of 95% confidence interval (CI). The Kaplan–Meier survival analysis was also performed with a log-rank test.

A P value < 0.05 was considered to represent statistical significance.

Results

From 2009 to 2015, according to established exclusion criteria, 188 consecutive patients with a diagnosis of gastric cancer who underwent a curative gastrectomy from Surgical Division 2 of Tertiary Care Hospital "A. Cardarelli" of Naples were enrolled in this retrospective study.

Clinical and pathologic variables were prospectively collected.

The demographic characteristics of these patients are listed in Table 1.

Table 1 Demographic characteristics in patients with gastric cancer receiving gastrectomy

Age (year)	58 (60–78)
Gender (male/female)	116/72
Gastric cancer (n)	
Adenocarcinoma	180
Malignant GIST	4
Other malignancies	4
Stage (n)	
I/II	46
III/IV	134
Hb level (g/dL)	
Admission	11.3 ± 2.9
4 days post-op	10.7 ± 1.9
Discharge	10.6 ± 2.7
Transfused patients (n) RBC product used (unit)	
Pre-OP	23 (1 unit)
Intra-OP	48 (1–4 unit)
Post-OP	60 (1 unit)
LHS (day)	
From admission to discharge	16 (12–25)
From OP to discharge	13 (9–19)
Complication events (n)	
Infectious	63
Respiratory	21
Renal	17
Bleeding	3
Mortality rate (%)	
6-month	1.06
1-year	3.39
6-year	7.98

Hb hemoglobin, *OP* operation, *LHS* length of hospital stay

Among these diagnoses of gastric cancer, 180 were adenocarcinoma, 4 were malignant GIST and 4 belonged to other types of gastric malignancies (including 2 cases of gastric lymphoma and 2 cases of neuroendocrine gastric carcinoma).

Also, 46 were in early stage (stage I/II) and 134 were in late stage (stage III/IV).

The Hb level upon admission, the 4 days post-operative Hb level and the final Hb level before discharge were 11.3 ± 2.9, 10.7 ± 1.9 and 10.6 ± 2.7 g/dL, respectively.

Preoperatively, 23 subjects received transfusions with an average of 1 unit per patient, and 48 patients with an average of 2 units per patient (minimum 1 and maximum 4) were transfused during surgery. In the postoperative period 60 patients received blood transfusions with an average of 1 unit per patient.

The hospitalization rate from admission to discharge and from operation to discharge was 16 and 13 days with IQR of 12–25 and 9–19 days, respectively. Additionally, the most common post-operative complication was an infection ($n = 63$, 33.5%), followed by respiratory symptoms ($n = 21$, 11.17%), renal acute failure ($n = 17$, 9.04%) and bleeding ($n = 3$, 1.59%), respectively. The overall 6-month, 1-year and 3-year mortality rates of all patients with gastric cancer subjected to gastrectomy were 1.06, 3.39 and 7.98%, respectively. Univariate analysis for pre-operative anemia states and RBC transfusion in assessing the outcomes of patients with gastric cancer receiving gastrectomy are shown in Table 2.

The clinical data most frequently associated with blood transfusion, regardless of timing of administration, are the appearance of post-operative infection (OR 2.26, 95% CI 0.87–5.79, $P = 0.061$). If we analyze the transfusions in

Table 2 Correlation between pre-operative, intra-operative and post-operative transfusion and clinical outcome after gastric surgery

	LHS > 30	LHS < 30	OR (95% CI)	P value
Pre OP transfused	5	26	1.85 (0.43–7.07)	0.312
Pre OP not transfused	8	77		
Intra/post OP trasfused	11	40	8.66 (1.73–83.00)	0.002
Intra/post OP not transfused	2	63		
	Infection	No infection		
Pre OP transfused	17	14	3.70 (1.43–9.58)	0.002
Pre OP not transfused	21	64		
Intra/post OP trasfused	29	22	8.20 (3.11–22.62)	< 0.001
Intra/post OP not transfused	9	56		
	ARF	No ARF		
Pre OP transfused	3	28	0.80 (0.13–3.44)	0.754
Pre OP not transfused	10	75		
Intra/post OP trasfused	12	39	19.69 (2.66–854.56)	< 0.001
Intra/post OP not transfused	1	64		

OP operation, *LHS* length of hospital stay, *ARF* acute renal failure, *OR* odds ratio, *CI* confidence interval

relation to the time of administration, then these are related to different clinical outcomes. In particular, patients who received a transfusion in the preoperative period showed that postoperatively there was a higher incidence of infections (OR 2.26, 95% CI 0.87–5.79, $P = 0.061$) and acute renal failure (OR 2.82, 95% CI 0.70–10.78, $P = 0.078$); patients who received a transfusion during surgery or in the following days instead, showed a prolonged hospitalization (OR 8.66, 95% CI 1.73–83.00, $P = 0.002$).

In conclusion, therefore, the administration of blood products in the perioperative period is correlated in a statistically significant manner to the appearance of infections, acute renal failure and prolongation of hospitalization.

Discussion

Several studies have investigated the role of perioperative blood transfusions in patients undergoing gastric surgery for neoplastic pathology and the correlation between this event and the prognosis of these patients.

From the data emerged that Kaare Terp et al. demonstrated a strong correlation between receiving blood transfusions and the risk of anastomotic leakage after surgery in gastroesophageal-junction cancer patients [8]. Other studies also demonstrated that transfused gastric cancer patients had more postoperative complications [9, 10] and, more in general, Ojima et al. and Squires et al. have shown that allogeneic blood transfusion is an independent prognostic factor for long-term survival and recurrence-free in gastric cancer patients [11, 12].

In the literature, some studies look for a correlation between the number of transfusions performed and the appearance of adverse events or the worsening of the prognosis; however, this correlation was not statistically significant [11, 13, 14].

Regarding our results, according to Gui et al. and Elmi et al. our retrospective study showed that transfused patients had more postoperative complications than non-transfused ones [15, 16].

The contributing factor for which patients undergoing a blood transfusion have a reduction of disease-free time, of survival and an overall worsening of the prognosis is perhaps due to the fact that transfusion could disturb the immune system and cause a high morbidity correlated to an infection.

Gascon et al. and Blumberg et al. had demonstrated that a perioperative blood transfusion could result in immunological changes which might contribute to poor survival of patients [16, 17].

It could be possible that it was the transfusion itself which caused immunosuppression and poor prognosis rather than the amount of blood transfused. The possible reason might be that a blood transfusion could cause

immunomodulation, which decreases the activity of natural killer cells and increases the activity of regulatory T cells [18].

It was thought that the adverse outcome of a transfusion was related to the immune system because a transfusion could downregulate hematopoiesis and subsequently downregulate the immune response [19]. The remaining immunosuppressive impact on gastric cancer patients exacerbated the impaired immune response [20, 21] and remaining leukocytes and antibodies in transfused blood played an important role in immunosuppression and transfusion-related immunomodulation [22–25] which could be some factors that result in tumor recurrence.

Taylor et al. [26] reported 1717 trauma patients in the intensive care unit and showed that nosocomial infections were six times higher and mortality was two times higher than those in the non-transfusion group. So, the patients who received a transfusion developed a serious resistance to infection therapy and high incidence of cancer metastasis. We thought that the impaired immune system and the suppression of hematopoiesis were contributors to the adverse clinical outcomes for patients undergoing surgery; in fact, we found that clinical data showed that regardless of when the blood transfusion was administrated it was frequently associated with the appearance of a postoperative infection.

In addition, the study by Maeta et al. highlighted that patients with an intraoperative transfusion seem to have worse survival rates than preoperative and postoperative transfused patients [17]. This phenomenon is probably due to the effect that the surgery has itself on the immune system; in fact, it represents a stressful event and acts by inducing an immunosuppression [14].

So it follows that if we cannot avoid a perioperative transfusion, we may at least avoid an intraoperative transfusion.

Conclusion

The presented study, although limited by the number of recruited patients and by the intrinsic limits of observational studies, confirmed the negative prognostic role of blood transfusions on the post-operative outcomes in patients undergoing gastric surgery accompanied by D2 lymphectomy for neoplastic pathology.

The conclusion is that transfusions should be avoided when not strictly necessary and in particular the intraoperative ones should be avoided because the immunomodulation effect would enhance the one already linked to the surgical stress, hence worsening the patient's prognosis.

Compliance with ethical standards

Conflict of interest Authors disclose no conflicts of interest.

Ethical approval As observational study no ethical approval was requested by our institution.

Research involving human participants and/or animals As observational study, this article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent Informed consent has been signed by all the participants.

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