

The effect of fibrin glue on the postoperative lymphatic drainage after gastrectomy and D2 dissection: a randomized clinical trial

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Abstract

Introduction: Disturbance in the lymphatic drainage during D2 dissection is associated with significant morbidity. We aimed to assess the effect of fibrin glue on reduction of postoperative seroma formation.

Methods: Prospective double-blinded randomized clinical trial with forty patients in each study arm was conducted. All patients diagnosed, staged and became candidate for D2 dissection based on NCCN 2019 guideline for gastric cancer. Intervention group received 1 cc of IFABOND® applied to the surgical bed.

Results: The difference between study groups regarding age, gender, tumor stage was insignificant. (All p values > 0.05). The median of daily drainage volume was 120 milliliter with the first and the third interquartile being 75 and 210 milliliter, respectively for intervention group. The control group had median, the first and the third interquartile of 350, 290 and 420 milliliter. The difference between daily drainage volumes was statistically significant (p value < 0.001). The length of hospital stay was significantly different between two groups and intervention group were discharged sooner (median of 7 Vs 9 days, p value: 0.001).

Conclusion: This study showed possible role of fibrin glue on reducing postoperative seroma formation after gastrectomy and D2 dissection.(IRCT20200710048071N1, 2020.08.16)

Introduction

Gastric cancer is one of the leading causes of cancer-related mortality worldwide[1]. Historically, there was a difference between Eastern and Western countries regarding the management of gastric cancer[2]. However, both Eastern and Western guidelines emphasized on the role of lymphadenectomy on the local control of the disease and reported superior survival results especially in long term follow ups[3]. So lymphadenectomy should be performed as a part of standard procedure for resectable gastric cancers[4]. Today, National Comprehensive Cancer Network (NCCN) advice to perform regional lymphatic resection along with gastrectomy which includes perigastric lymph nodes, named as D1 dissection, and those along the named vessels of celiac axis, named as D2[5].

However D2 dissection has been associated with significant morbidity in terms of anastomotic leakage, pancreatic leakage, reoperation rates, wound infection seroma formation, lymphocele, chylous ascites and even systemic complications such as pulmonary complications[6]. Thus the classic D2 dissection which included pancreateosplenectomy has evolved and now involves the removal of both the greater and lesser omenta plus all the lymph nodes along the left gastric artery, common hepatic artery, celiac artery and splenic artery[7, 8].

Oncological surgery usually involves lymph node dissection in order to accurately stage the tumor or to reach to local control of the tumor. Lymph node dissection is now considered a part of surgical approach in gynecologic cancer, breast cancer, head and neck carcinomas and melanoma[9– 11]. The one common complication after lymphatic drainage disturbance in all these anatomical sites is seroma formation[12].

There has been a growing interest toward the use of fibrin containing products in these anatomical sites to prevent postoperative complications related to lymphatic drainage. Fibrin glue contains fibrinogen, factor XIII, thrombin, calcium chloride, and aprotinin. They have been utilized to secure the anastomosis of nerves, repair of dura rupture, hemostasis in cardiovascular operations, and orthopedic surgery [8]. Given the complex anatomy of perigastric lymphatic drainage, there is a high chance of disturbing normal anatomy even for experienced surgeons. According to our knowledge, there has been no study to evaluate the effect of these materials in a randomized clinical trial on post-D2-dissection seroma formation. So this study aimed to investigate.

Materials And Methods

This prospective double-blinded randomized clinical trial was designed and constructed by Department of Surgical Oncology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran between August 2020 and December 2020. The ethic committee of Tehran University of Medical Sciences approved study protocol by reference number of IR.TUMS.IKHC.REC1399.106 and it was registered in Iranian registry of clinical trials by reference number of IRCT20200710048071N1 on August 16th 2020. Clinical trial registry was based on International Committee of Medical Journal Editors (ICMJE) guideline. All patients diagnosed with gastric cancer who were candidate to perform gastrectomy and D2 dissection based on NCCN 2019 guideline for gastric cancer has been invited to participate. Informed consent was obtained from all subjects.

Patients with following criteria were excluded; previous history of abdominal surgery, hematological disorders of coagulation defects, history of thromboembolic disease or lymphatic system disorder, allergy to aprotinin and refuse to participate in the study.

All patients underwent the same chemotherapy regimen prior to surgery. Also, thoraco-abdomino-pelvic computed tomography prior to surgery and complete blood count, serum level of urea, creatinine, potassium, sodium, prothrombin time, partial thromboplastin time, aspartate aminotransferase, alanine aminotransferase, albumin were evaluated.

Patients were randomly assigned to intervention group who received 1 cc of IFABOND® (Peters surgical worldwide, France) applied to the surgical bed of D2 dissection and control group. Block randomization was used to assign patients to study groups. The patient, the surgical attendings and the residents who performed the follow-up sessions were blinded to the randomization sequence. Only the attending surgeon who performed the surgery knew about the randomization sequence. All patients underwent midline laparotomy for gastrectomy and D2 dissection (including the removal of both the greater and lesser omenta plus all the lymph nodes along the left gastric artery, common hepatic artery, celiac artery and splenic artery). Two 18 Fr closed drain tubes were inserted prior to wound closure, one of them was inserted in the surgical bed of D2 dissection and the other one was inserted in Morrison's pouch.

All the patients received the same protocol for antithrombotic and antibiotic prophylaxis adjusted for weight and comorbidities. All the procedures being carried out using ultrasonic shears (Harmonic®,

Ethicon, Cincinnati, OH, USA). Data were collected on the following variables: age, gender, pathological stage based on the 8th edition of the American Joint Committee on Cancer tumor-node metastasis staging system for gastric cancer[13], drainage volume and length of hospital stay.

Drain output was charted until it was less than 10 cc daily and then it was discharged. Follow-up session conducted at three weeks after surgery and every three months thereafter. The sample size was calculated assuming an overall incidence of seroma formation of 34.7%, based on Segural et al[14], study. We estimated that a sample of at least 40 patients for each study arm was needed to declare an absolute 30% incidence reduction of seroma formation with the treatment as significant with an alpha of 0.05 and beta of 0.80% power. All the methods used to perform this study were carried out in accordance CONSORT 2010 guidelines[15]. Categorical variables are shown as frequency, and relative frequency and continuous variables are shown as median. Collected data for categorical variables were compared using the chi-squared test. An independent student t-test was used to compare between the two groups at each follow up visit and baseline. All analyses were performed by the two-sided method using Statistical Package of Social Science software (SPSS version 22; SPSS, Inc., Chicago, IL), and the p-value of < 0.05 was set as statistically significant.

Results

The median of age was 62 years old with the first and the third interquartile being 56 and 69.5 years old, respectively for intervention group. Also, control group had median age of 63 years old with the first and the third interquartile of 58 and 69 years old, respectively. Participants were mostly men in each group, 31 cases (77.5%) in intervention group and 28 cases (70%) in control group. Tumor stage distribution in intervention group was as follows: stage I (2 cases, 5%), stage II (10 cases, 25%) and stage III (28 cases, 70%). Control group included 3 cases (7.5%) of stage I, 9 cases (22.5%) of stage II and 28 cases (70%) of stage III. There was no statistically significant difference between two groups regarding age, gender and tumor stage (all p values > 0.05). Table 1 demonstrate baseline characteristics of study groups.

Table 1
– Baseline characteristics of study groups.

	Intervention (n = 40)	Control (n = 40)	P value
Age (year)	62 (56–69.5)	63 (58–69)	0.795
Gender (F/M)	9/31 (22.5%/77.5%)	12/28 (30%/70%)	0.446
Stage			0.768
I	2 (5%)	3 (7.5%)	
II	10 (25%)	9 (22.5%)	
III	28 (70%)	28 (70%)	
Data presented as median (Q1 – Q3) and count (%)			

The median of daily drainage volume was 120 milliliter with the first and the third interquartile being 75 and 210 milliliter, respectively for intervention group. Regarding daily drainage volume the control group had median, the first and the third interquartile of 350, 290 and 420 milliliter. The difference between daily drainage volumes was statistically significant (p value < 0.001). The length of hospital stay was significantly different between two groups and intervention group were discharged sooner (median of 7 Vs 9 days, p value: 0.001). Table 2 shows daily drainage volume and length of hospital stay of study groups

Table 2
Study endpoints

	Intervention (n = 40)	Control (n = 40)	P value
Daily Drainage Volume (mL)	120 (75–210)	350 (290–420)	< 0.001
Length Hospital Stay (day)	7 (7–8)	9 (7–10)	0.001
Data presented as median (Q1 – Q3)			

Discussion

In this study, we performed the first randomized clinical trial on the effect of fibrin glue on the postoperative lymphatic drainage after gastrectomy and D2 dissection. It was shown that fibrin glue could effectively reduce postoperative lymphatic drainage which leads to reduced length of hospital stay.

The exact incidence of postoperative seroma formation after gastrectomy is not clear, however it has been reported that by increasing the extent of lymph node dissection the incidence of seroma formation after gastrectomy increases [16]. It is reported to be about 0.4% for D2 dissection and reaches to 3.6% for D2 dissection plus pre-aortic lymphadenectomy[17]. Furthermore, dissection of lymph nodes along the common hepatic artery and the celiac artery increases the chance of seroma formation.

Considering the significant morbidity in patients who underwent radical lymphadenectomy in different anatomical sites, different strategies have been applied to reduce the amount of seroma formation which mainly can be divided in to three categories. First, surgical devices for sealing vessels such as argon diathermy[18], laser scalpel, ultrasonic scalpel, and ultrasonic scissor[19], second the methods of limiting the dead space[20, 21] and third, hemostatic agents applied directly to surgical site[9].

Primarily, fibrin glue was used in cardiovascular, liver, lung, gynecological and urological surgery as hemostatic agent. Moreover, upcoming studies showed their role in tissue recovery, regeneration and faster healing[22]. Thus, it became useful in microneurosurgery[23], and gastrointestinal anastomoses[24]. Generally, the mechanism of action of different types of fibrin-containing-products is to trigger the coagulation process by activating the reaction of fibrinogen and thrombin. Upon contact with a

bleeding surface, the fibrinogen-thrombin reaction transforms the active fibrinogen to fibrin and promotes the formation of the fibrin clot. Various types of fibrin-containing-products have been used worldwide and most popular ones are Floseal®, Tachosil® and Tissucol®. These products are different regarding the source of fibrinogen, thrombin and aprotinin which could be of the human or bovine origin. Newer products contain human based compound, in order to lessen potential immunogenic reaction[25, 26] or anaphylaxis caused by bovine aprotinin[27].

The efficacy of fibrin-containing-products have been assessed through different studies. It has been used in various types of malignancy and various anatomical sites. This divergence has led to different results about the effectiveness of these products. One of the studies in the field of evaluating efficacy of fibrin sealant patches on the incidence of lymphatic morbidity after radial lymphadenectomy has been performed by Gasparri et al[9]. They gathered data on 720 patients from 10 different clinical trials which used fibrin-thrombin sealant in patients whom underwent axillary dissection for breast cancer, extraperitoneal dissection for prostate cancer, inguinal dissection for vulvular cancer or melanoma and pelvic dissection for endometrial cancer. The final conclusion of this study was that application of fibrin-thrombin sealant was effective in reducing postoperative lymphocele formation and reduced the need to percutaneously drain the seroma, the median total volume of lymph drained, and the duration of drainage. The underlying rationale behind the use of these products is the fact that endothelial cells of blood and lymphatic vessels produce coagulation and fibrinolytic factors in natural hemostatic cascades and cause sealing of lymphatic capillaries, thus the use of such products may have a role in augmentation of the final stage of coagulation when fibrinogen is converted into stable fibrinogen clot[25, 28].

Gerken et al[29] ran a systematic review and meta-analysis to investigate the preventive effect of fibrin-containing tissue sealants on lymphocele formation after radical inguinal lymph node dissection in patients with melanoma. They used six clinical trials including 194 patients. This study failed to show the effect of tissue sealants on the duration of drain placement, total drainage volume, the incidence of postoperative seroma formation, wound infection and skin necrosis. This result might be explained as every study used different setting regarding the surgical radicality, the size of the wound surface, the definition of drain removal criteria, and the route of application of fibrin-containing product (glue or patch). Thus, this heterogeneity in the study designs had finally caused indefinite results [30–32].

Another systematic review and meta-analysis of randomized controlled trials on application of fibrin sealant for the prevention of lymphocele after lymphadenectomy in patients with gynecological malignancies was performed by Prodromidou et al[27]. Four hundred eighty one patients from six randomized clinical trials were included and it was found that fibrin sealant could significantly decrease total amount of drained fluid and mean duration of drainage. Also, there was no difference in overall incidence of lymphocele[33, 34].

The English literature about the effect of fibrin-containing products on seroma formation after lymphadenectomy is now inconclusive because there are several serious limitations in each study even

systematic reviews and meta-analysis ones[35]. The lack of precise definition of seroma formation, diagnostic tools to evaluate and appropriate prophylactic and therapeutic approaches to treat this condition resulted in significant amount of studies without solid statement[36]. Thus to reach safe conclusion studies with high number of included patients, unified planning and design are warranted.

Finally, this study showed possible role of fibrin glue on reducing postoperative seroma formation after gastrectomy and D2 dissection, a result which should be taken cautiously because of limited number of participants.

Declarations

Acknowledgment: None

Conflict of interest: All authors declare that there is no conflict of interest to disclose.

Declaration:

Ethical approval and consent to participate:

Ethic committee of Tehran University of Medical Sciences approved study protocol by reference number of IR.TUMS.IKHC.REC1399.106 and all patients gave informed consent under the [Creative Commons Attribution License 4.0](#)

Consent to publish:

Not applicable.

Availability of data and materials:

All the data regarding study variables is available. The corresponding author will provide supplementary files up one request.

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Authors' contributions:

Habib Allah Mahmoudzadeh. M. D.: Analysis and/or interpretation, Supervision

Ehsanollah Rahimi Movaghar. M. D.: Data collection and/or processing, Writing the paper

Ramesh Omranipour. M. D.: Critical review, writing the paper, Supervision

Mohammad Shirkhoda. M. D.: Data collection and/or processing

Amirmohsen Jalaeefar. M. D.: Critical review, Conception and Design of the study

Seyed Rouhollah Miri M. D.: Conception and Design of the study

Amirsina Sharifi. M. D.: Analysis and/or interpretation, writing the paper

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