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Could Potential Postoperative Chylous Fistula Be Prevented in Patients Undergoing Neck Dissection by Using Fibrin Glue?

Boyun Diseksiyonu Yapılan Hastalarda Postoperatif Gelişebilecek Şilöz Fistüller FibrinYapıştırıcı ile Önlenebilir mi?

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This study was presented at the 41st Turkish National Otorhinolaryngology Head and Neck Surgery Congress. (13-17 Nov 2019, Antalya,Turkey).

ABSTRACT Objective: The purpose of this study was to determine the effectiveness of fibrin glue in the treatment of chylous fistula caused by neck dissection in the light of our experience and the literature. **Material and Methods:** We collected demographic data regarding age, gender, diagnosis, smoking habit and alcohol consumption, preoperative radiotherapy and previous surgery from nine patients with chylous fistula following neck dissection. We also retrospectively reviewed type of neck dissection, intraoperative chylous drainage, time of onset of postoperative drainage, time of withdrawal of chylous drainage, treatment protocols employed, need for re-exploration and length of hospital stay. **Results:** The study included nine patients (5 male, 4 female) with mean age of 54.7 years ranging from 34 to 70 years. It was found that postoperative fistula developed in six patients with intraoperative chylous fistula which were closed with ligation. Of these, re-exploration and fibrin glue were employed in two patients as conservative methods and octreotide failed to decrease drainage. In three patients, the fibrin glue was applied to defect site after ligation during primary surgery. Of these patients, postoperative low-output chylous fistula was detected in only one patient. The short-term (3 days) octreotide therapy was used in only one of three patients in whom fibrin glue was used during primary surgery. The mean duration of octreotide therapy was five days in patients in whom fibrin glue was used by re-exploration. Mean length of hospital stay ranged from 4 to 62 days. One patient died due to infection caused by chylous fistula, flap necrosis, fluid-electrolyte disorder and pulmonary embolism. **Conclusion:** We think that fibrin glue use during primary surgery may prevent development of postoperative fistula, particularly in selected patients such as those with metastatic lymph node or mass at level 4, those undergoing wide dissection or those with no clear identification of defective structures.

Keywords: Chylous ascites; fistula; neck dissection; somatostatin; octreotide; fibrin tissue adhesive

ÖZET Amaç: Fibrin yapıştırıcının boyun diseksiyonuna bağlı şilöz fistül tedavisindeki etkinliğinin, klinik tecrübemiz ve literatür eşliğinde değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Boyun diseksiyonu sonrasında şilöz fistül gelişen 9 hastanın yaş, cinsiyet, tanı, sigara ve alkol kullanımı, preoperatif radyoterapi ve geçirilmiş cerrahi öykülerini içeren demografik veriler toplandı. Ayrıca boyun diseksiyonunun tipi, intraoperatif şilöz drenaj durumu, postoperatif drenajın başlangıç günü, şilöz drenajın kesildiği süre, uygulanan tedavi protokolleri, re-eksplorasyon ihtiyacı ve hastanede yatış süreleri retrospektif olarak değerlendirildi. **Bulgular:** Çalışmaya, yaşları 34-70 arasında değişen ve ortalaması 54,7 olan 9 (5 erkek, 4 kadın) hasta dâhil edildi. İntraoperatif şilöz fistül görülen ve ligasyon ile kapatılan 6 hastada postoperatif şilöz fistül geliştiği görüldü. Bu hastaların 2'sinde konservatif tedavi ve oktreotid ile drenaj azalmadığı için re-eksplorasyon yapıldı ve fibrin yapıştırıcısı uygulandı. Üç hastada, primer cerrahi sırasında ligasyondan sonra defekt bölgesine fibrin yapıştırıcısı uygulandı. Bu hastaların ise yalnızca birinde düşük debili şilöz fistül gelişti. Primer cerrahi sırasında fibrin yapıştırıcı kullanılan 3 hastadan sadece birinde kısa süreli (3 gün) oktreotid tedavisi kullanıldı. Fibrin yapıştırıcısının, re-eksplorasyon sırasında kullanıldığı hastalarda ortalama oktreotid tedavisi süresi ise 5 gündü. Ortalama hastanede kalış süresi 4-62 gün arasında idi. Bir hasta şilöz fistül, flep nekrozu, sıvı-elektrolit bozukluğu ve pulmoner emboli nedeniyle oluşan enfeksiyon nedeniyle öldü. **Sonuç:** Fibrin yapıştırıcının primer cerrahi esnasında; özellikle düzey 4'te metastatik lenf nodu veya kitlesi olan, geniş diseksiyon yapılan, hasarlı yapıların net tespit edilemediği olgular başta olmak üzere, seçilmiş olgularda kullanılması ile postoperatif fistül gelişiminin engellenebileceği kanaatindeyiz.

Anahtar Kelimeler: Şilöz asitler; fistül; boyun diseksiyonu; somatostatin; oktreotid; fibrin doku yapıştırıcı

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Chylous fistula is a serious complication which may develop after neck dissection with incidence of 1-2.5%.[1,2] It may result in wound site infection, flap necrosis, sepsis and death by impaired wound healing via protein loss and fluid-electrolyte disorder. Thus, it does not only increase morbidity but also results in fatal consequences. In the treatment, conservative approach includes medium-chain fatty acid-richened diet with low fat content, compression dressings and drainage. In addition, use of octreotide, a somatostatin analogue, has been reported in the literature.[2,3] Surgical approach is preferred in patients with failure in conservative or medical treatment or in those with high-output fistula. Although primary goal is surgical repair of defective area and ligation of chylous vessels, several methods including closure of thoracic duct, anastomosis between lymphatic and venous systems and muscular flaps have been discussed in the literature.[3] However, it has been observed that fistulas developed in the postoperative period in the presence of extensive intraoperative interventions.

Fibrin glue (sealant) is a natural hemostatic agent that contains thrombin, fibrinogen, calcium, aprotinin and fibrin stabilizing factor.[4] In this study, it was aimed to discuss effectiveness of fibrin glue in the treatment of chylous fistula in the shed of our experience and the literature.

MATERIAL AND METHODS

The study included nine patients who underwent neck dissection due to head-neck cancer and developed chylous fistula after dissection. We retrospectively collected demographic data including age, gender, diagnosis, smoking habit and alcohol consumption, history of preoperative radiotherapy and previous surgery. In addition, we also reviewed parameters related with treatment employed such as type of neck dissection, intraoperative chylous drainage, time of onset of postoperative drainage, time of withdrawal of chylous drainage, treatment protocols employed, need for re-exploration and length of hospital stay.

This study was approved by local ethics committee and conforms to the principles of the Declaration of Helsinki. (52332816/14/10.4.2018)

Written informed consent was obtained from all participants.

STATISTICAL ANALYSIS

All statistical analyses were performed using the SPSS for Windows 15.0 (SPSS Inc, Chicago, IL, USA) statistics software. Continuous variables were expressed as mean values ± standard deviation. Categorical variables were expressed as numbers and percentage.

RESULTS

The study included nine patients (5 male, 4 female) with mean age of 54.7 years ranging from 34 to 70 years. The neck dissection was performed due to metastatic squamous larynx carcinoma in four patients; papillary thyroid carcinoma in two patients; medullary thyroid carcinoma in one patient; and squamous cell carcinoma of tongue in two patients. There was history of smoking in seven patients, alcohol consumption in five patients and preoperative radiotherapy in one patient. Table 1 presents demographic data and outcomes.

TREATMENT MODALITIES AND OUTCOMES

In all patients in whom chylous fistula was observed during neck dissection, disrupted lymphatic vasculature was simultaneously ligated by nonabsorbable sutures with atraumatic smooth needle. The patients were placed in Trendelenburg position via positive-pressure ventilation and cessation of leakage was confirmed. However, chylous fistula was observed after oral nutrition at postoperative period in six patients. Of these, re-exploration was required in two patients and fibrin glue (Tisseel, Baxter International Inc., Westlake Village, CA, USA) was used in the secondary surgery. In these two patients, the fibrin glue was applied to defect site after disrupted lymphatic vasculature that could be detected was ligated by nonabsorbable sutures with atraumatic smooth needle. Fibrin glue was used similarly in three patients during primary surgery. In all patients, conservative treatment (drainage, compressive dressing, bed rest and nutritional modifications) was employed at postoperative period until withdrawal of chylous fistula. Medium-chain fatty acid-richened diet with low

TABLE 1: Summary of demographic data and treatment parameters of the patients.

No	Age/sex	Neck procedure	Preoperative RT	Intraoperative chylous leak	Start of Leak (POD)	High/low output	Chylous leak controlled (POD)	Re-exploration	Treatment (CT, O, FG)	Duration of hospitalization (days)
1	70/M	Bilateral 1-5 ND	No	Yes	3	Low	8	No	CT+O	11
2	65/M	Bilateral 2-4 ND	No	Yes	3	High	14	No	CT+O	19
3	34/F	Left 2-4 ND	No	No	2	High	11	No	CT+O	14
4	43/F	Left 2-4 ND	No	Yes	3	Low	9	No	CT+O	16
5*	68/M	Right 1-5 Sol MRND	Yes	Yes	2	High	12	Yes	CT+O+FG	26
6*	64/F	Bilateral 1-5 ND	No	Yes	3	High	21	Yes	CT+O+FG	62
7**	38/F	Left 1-5+ central ND	No	Yes	-	-	-	No	CT++FG	6
8**	53/M	Bilateral 2-4+ central ND	No	Yes	-	-	-	No	CT++FG	4
9**	58/M	Left MRND	No	Yes	2	Low	4	No	CT+O+FG	9

M: Male; F: Female; MRND: Modified radical neck dissection; POD: Postoperative day; ND: Neck dissection; RT: Radiotherapy; CT: Conservative treatment; O: Octreotide; FG: Fibrin glue.

*Patients underwent re-exploration and received fibrin glue, **Patients received intraoperative fibrin glue during primary surgery.

fat content was prescribed to all patients. In all patients with no improvement in drainage, 100 mg octreotide (Sandostatin 0,1 mg ampule, Novartis Pharma AG, Switzerland) via subcutaneous route by 8-hours intervals was given (maximum duration: 10 days).

FOLLOW-UP AND COMPLICATIONS

The fistula was defined as low-output in patients with drainage <500 mL/24 hours while it was defined as high-output in those with drainage >500 mL/24 hours.[5] It was found that postoperative fistula developed in six patients with intraoperative chylous fistula which were closed with ligation. Of these, re-exploration and fibrin glue were employed in two patients as conservative methods and octreotide failed to decrease drainage (case 5 and 6). In these two patients, it was observed that the leakage was widespread in the left level 4 and there was no lymphatic vessel to be ligated. Fibrin glue was applied to the region and the operation was terminated. Postoperative fistula rate decreased to less than 500 mL/24 hours in both patients and chylous fistula ended within a mean of two weeks. In three patients, the fibrin glue was applied to defect site after ligation during primary surgery. Of these patients, postoperative low-output chylous fistula was detected in only one patient, which was closed by short-term (3 days) octreotide therapy and conservative approach. Mean duration of octreotide therapy was nine days in cases followed with conservative treatment (case 1-4). The patient who underwent glossectomy due to squamous cell carcinoma of tongue and treated with deltopectoral flap died due to infection caused by chylous fistula, flap necrosis, fluid-electrolyte disorder and pulmonary embolism. In remaining patients, no complication other than mild electrolyte disturbance and low albumin level was observed. Mean length of hospital stay ranged 4 to 62 days (Table 1).

DISCUSSION

Lymphatic drainage generally occurs in two ways. Left lymphatic system is directly drained to left subclavian vein via thoracic duct while right lymphatic system is drained to right innominate vein at the conjunction of right subclavian vein and right internal jugular vein.[6] However, anatomic studies have reported many variations in the lymphatic system.[7] The lymphatic flow contains fatty acids, cholesterol, protein, glucose and electrolytes. Thus, loss of lymph can result in metabolic problems including hyponatremia, hypokalemia, hypoalbuminemia and hypovolemia. In addition, due to collection at wound site, it may lead to delayed wound healing, flap necrosis, sepsis, prolonged hospital stay and death.

Although it can be seen intraoperatively, chylous fistula is diagnosed by white, milky drainage after enteral nutrition in postoperative period. In addition, diagnosis can be made by biochemical analysis of draining fluid. The triglyceride level >100 mg/dL or higher than the level found in sera favor chylous fis-

tula.[8] The increased amount of drainage or prolonged drainage should arise suspicion for chylous fistula.

Chylous fistula, although rare, is a well-described complication of neck dissection. The risk for chylous fistula and lymphatic injury is particularly higher during level 4 dissection since lymphatic vessels are located at around conjunction of left internal jugular vein and subclavian vein.[7] The risk is further increased in the presence of metastatic lymph node or primary tumor.[9]

Although description is unclear, chylous fistulas are classified as low-output and high-output in the literature.[5] In this study, the fistula was considered as low-output in patients with drainage <500 mL/24 hours while it was defined as high-output in those with drainage >500 mL/24 hours. In the treatment of chylous fistula, the initial step is conservative treatment including stopping oral intake or establishing medium chain fatty acid-richened diet with low fat content, compressive dressing and drainage. However, conservative approach fails particularly in high-output fistula.[2,10] In our study, octreotide, a somatostatin analogue, was initiated in all patients with no improvement in their amount of drainage during three days of conservative treatment. This result may be due to shorter duration of conservative treatment in our study.

Total parenteral nutrition (TPN) may be an option in patients in whom conservative treatment has failed. However, one should be careful due to the need for central catheterization, higher costs and risk for pneumothorax, hematoma and electrolyte imbalance.[11] In our study, no patient received TPN.

Octreotide, a somatostatin analogue, inhibits pancreatic and gastrointestinal secretion via both endocrine and paracrine route. It also reduces hepatic venous pressure and splanchnic blood flow.[12] Octreotide is used in the treatment of chylous fistula as it minimizes lymph fluid secretion by directly acting on vascular somatostatin receptors.[1,2,9] In all patients with no improvement in drainage within three days by conservative treatment, 100 mg octreotide via subcutaneous route by 8-hours intervals was given (maximum duration: 10 days). There was high-output fistula in two and low-output fistula in two of four patients who received conservative treatment plus octreotide (CT plus O) with a successful outcome. However, re-exploration was required in two patients who received CT plus O treatment without improvement in their amount of drainage and fibrin glue was used in both of these patients.

In surgical treatment, several methods have been recommended including ligation of injured vessels, cauterization and muscular flaps (anterior scalene, sternocleidomastoid, pectoralis major muscles etc.).[5,13] In addition, inflammatory and sclerosing agents such as cyanoacrylate, tetracycline and OK-432 were applied locally in order to encase bed of lymphatic ductus; however, neural injury was reported following tetracycline use.[14,15] The fibrin glue is a biocompatible, water-resistant hemostatic agent that contains thrombin, fibrinogen, calcium, aprotinin and fibrin stabilizing factor. In a few case reports, it was used in the treatment of chylous fistula together with muscle flaps.[16,17] In our study, fibrin glue was applied to injured vessel and adjacent tissues in two patients refractory to CT plus O treatment after ligation of injured lymphatics during revision surgery. In the follow-up, it was observed that amount of drainage rapidly decreased. After this experience, we preferred to use fibrin glue after ligation during primary surgery in patients with metastatic lymph node or mass lesion at level 4 or undergoing wide dissection or those without clear identification of damaged structures. Of these patients, low-output, short-term fistula was observed in only one patient during postoperative period. In this patient, short-term octreotide treatment was employed while remaining patients receiving no octreotide therapy. Flow volume and duration of fistula, duration and amount of octreotide therapy and length of stay were lower in patients receiving fibrin glue therapy (Table 1).

The most important limitation of our study is the small number of patients. Although fibrin glue treatment seems to be effective in two patients presented, multicentre studies including more patients are needed.

CONCLUSION

The development of chylous fistula is a serious complication that delays recovery, prolongs length of stay, leads to additional metabolic and respiratory problems and even death. The fibrin glue use during

primary surgery can prevent development of postoperative fistula, particularly in selected patients such as those with metastatic lymph node or mass at level 4, those undergoing wide dissection or those with no clear identification of defective structures. In conclusion, it may decrease fistula-related morbidity and mortality, length of stay and costs.

Ethical approval

This study was approved by local ethics committee. (52332816/14/10.4.2018). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** İbrahim Hira, Ali Bayram, Altan Kaya; **Design:** İbrahim Hira, Ali Bayram; **Control/Supervision:** İbrahim Hira, Ali Bayram, Cemil Mutlu; **Data Collection and/or Processing:** İbrahim Hira, Altan Kaya, Ali Bayram; **Analysis and/or Interpretation:** İbrahim Hira, Ali Bayram; **Literature Review:** Ali Bayram, Cemil Mutlu; **Writing the Article:** İbrahim Hira, Ali Bayram; **Critical Review:** Ali Bayram, İbrahim Özcan, İbrahim Hira.*

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