Abstract: Fibrin glue is a topical biological adhesive, which mimics the end product of the coagulation pathway. The haemostatic and adhesive properties of fibrin glue can be employed in cases where conventional suture methods are difficult to apply. It is formed from concentrated fibrinogen and thrombin. It is completely absorbed during wound healing without foreign body reaction or extensive fibrosis. Here we share our experience with biological tissue glue (tisseel) in the closure of pharyngeal mucosa during total laryngectomy and its effectiveness in preventing pharyngocutaneous fistula. 

Keyword: fibrin glue, pharyngocutaneous fistula, tissue adhesive

Introduction: Total laryngectomy is the most common oncological intervention performed for carcinoma larynx. One of the most common complications of a total laryngectomy is a pharyngocutaneous fistula. It increases the patient’s morbidity and mortality, prolongs hospital stay, causes delay in adjuvant treatment and causes an increase in treatment cost. Various factors have been described that could be related to the appearance of this fistula - a poor diet, previous radiotherapy, preoperative tracheotomy, broad resection of the pharyngeal mucosa, the type of incision made in the neck, incorrect closure of the mucosa, surgical border affected by neoplastic infiltration, failure of the wound drainage system, obstruction of the nasogastric tube, post-operative infection, a low level of postoperative hemoglobin and oral feeding being started too early. Most of the fistulas that develop in the immediate postoperative period are usually due to a failure of the hemetic closure of the suture. Here we share our experience with biological tissue glue (tisseel) in the closure of pharyngeal mucosa during total laryngectomy to prevent such complications. Tissue glue hastens wound healing, reduces post-operative complications, and decreases the need for a drain following surgery.

Fibrin glue is a topical biological adhesive which mimics the end product of coagulation cascade. It serves as a primary hemostatic plug as well as a matrix to enhance wound healing. Both the extrinsic and the intrinsic mechanisms of blood coagulation are bypassed. They are independent of the body’s clotting mechanism, they are also effective in patients with coagulopathies who are receiving heparin or anti-coagulants.

In the last step of the coagulation cascade fibrinogen is transformed to fibrin monomers which aggregate and form a gel. Concomitantly, thrombin transforms factor XIII to factor XIIIa in the presence of calcium ions. Factor XIIIa cross-links the aggregated fibrin monomers to a high molecular weight polymer.

Fibrin glue was developed in 1972 by Matras et al., who successfully used a fibrinogen cryoprecipitate in peripheral nerve anastomoses on animal models. The FDA approved Tisseel in June 1998.
Human Fibrin Glue (tisseel) is made of two components contained in separate vials (fig-1).
Freeze dried concentrate of clotting proteins, mainly fibrinogen, Factor XIII and fibronectin (the sealant)  
Freeze-dried thrombin (the catalyst)
The first component is reconstituted with an aprotinin solution that inhibits tissue fibrinolysis. The second component (thrombin), available in 500 I.U. concentration is dissolved with calcium chloride. These are loaded into two syringes (fig-2) with tips forming a common port. When injected the two components meet in equal volumes at the point of delivery. The thrombin converts the fibrinogen to fibrin by enzymatic action at a rate determined by the concentration of thrombin. The more concentrated thrombin solution produces a fibrin clot in about 10 seconds, and the more dilute thrombin solution forms the clot in about 60 seconds after the glue is applied to the surgical field. Here the concentration of the fibrinogen is 15 to 25 times higher than in circulating plasma. Therefore fibrin is formed much faster. The final fibrin sealant is subject to fibrinolytic degradation by both endogenous and exogenous plasmin. Antifibrinolytics such as aprotinin, tranexamic acid, and -aminocaproic acid can be added to the mixture to reduce the rate of fibrinolysis and creation of fibrin degradation products. Thus, the survival of fibrin sealant can be controlled through suitable dosages of aprotinin, after having evaluated the fibrinolytic activity of the relevant area. Fibrinogen can be obtained from pooled, single-donor, and autologous blood. The concentration of the fibrinogen is 15 to 25 times higher than in circulating plasma. Therefore fibrin is formed much faster. The final fibrin sealant is subject to fibrinolytic degradation by both endogenous and exogenous plasmin. Antifibrinolytics such as aprotinin, tranexamic acid, and -aminocaproic acid can be added to the mixture to reduce the rate of fibrinolysis and creation of fibrin degradation products. Thus, the survival of fibrin sealant can be controlled through suitable dosages of aprotinin, after having evaluated the fibrinolytic activity of the relevant area. Fibrinogen can be obtained from pooled, single-donor, and autologous blood donors and is usually isolated by the process of cryoprecipitation. The thrombin component is generally derived from commercial bovine source. The time of resorption depends on the applied quantity and on the location. A fast resorption can be found in tissues with good blood supply.

Materials and methods Case-1
55 year male patient, chronic smoker and diabetic was diagnosed with carcinoma larynx -stage 4. Total laryngectomy was planned and tracheostomy was performed 15 days prior to the surgery. Gluck- Sorensen incision was made with the stoma incorporated into the incision line. Superiorly, the hyoid bone incorporated into the incision line. Suturing incorporated into the incision line. Superiorly, the hyoid bone was identified in the midline. Suprahyoid musculature was released. The pharynx was entered and the larynx removed from above downwards. There is no subglottic extension of the tumor. The trachea was entered transversely between the second and third tracheal cartilages.
Pharyngeal mucosa was repaired with Connell’s stitch with a T-type closure with 3-0 vicryl. Pharyngeal closure is reinforced by suturing the second fascial layer and third reinforcing layer of pharyngeal constrictors. Fibrin glue was prepared and applied over the suture line(fig -3). Suction drain was kept for 3 days. Sutures were first removed alternatively, and completely removed at 10th post-operative day. Case was followed up once in a month for 3 months. There was neither fistula formation nor inflammatory reaction.
Case-2
65 years male patient, chronic smoker, hypertensive and ischemic heart disease on antihypertensives and antifibrinolytics was diagnosed with stage - 4 laryngeal carcinoma. Total laryngectomy was planned. Antifibrinolytics were stopped 1 week prior to surgery. Total laryngectomy was performed as mentioned above. Pharyngeal closure was performed in 3 layers and fibrin glue applied over the suture line. Sutures were removed on the 15th post-operative day. The case was followed up once in a month for 3 months. There was neither fistula formation nor inflammatory reaction.

Discussion
Total laryngectomy is a type of surgery that is characterized by the fact that the mucosa of the aerodigestive tract comes into contact with the surgical wound and is therefore exposed to secretions and bacteria from the oropharynx. Furthermore, wound infections and fistulas usually appear between the first and fifth day. Surgical technique and postoperative care play a major role in preventing fistula formation.

Advantages of fibrin glue:
- The adherent fibrin system could cause the margins of the wound of the pharyngeal mucosa to stick to each other and to the muscle and the flap. In the same way, it would have a hemostatic action on applying the adhesive a fine layer over the zone, occluding the small vessels and leaving the surface free from hematic leakages.
- Another possible mechanism would be to assist the impermeabilization and prevention of dehiscence of the pharyngeal suture.
- The application of fibrin glue to the surface of the pharyngeal mucosa causes reduction in dead space formation and at the same time stimulates tissue growth and repair.
- They are not associated with inflammation , foreign body reactions, tissue necrosis, or extensive fibrosis.
- Biocompatible and biodegradable.

Major drawback to its use is
- The risk of transmitting serological disease (prion disease, HIV)
- Immunogenic reactions caused by fibrinolysis inhibitor (bovine aprotinin) used in tisseel. It is highly immunogenic in humans. Patient related factors are also important in determining the immune response to bovine aprotinin. The most important of these is previous exposure to the antigen.

Conclusion
Although there have been studies analyzing the usefulness and effectiveness of tissue glue in managing a pharyngo-cutaneous fistula once it has formed, there were none discussing its role in the prevention of the same. No other studies have analyzed the use of an adhesive fibrin system in relation to the reduction in the frequency of postoperative pharyngeal fistulas. Although the results we obtained have been encouraging, no definitive conclusion can be arrived at this juncture, as the sample size in our study is too small. More studies are warranted in the future to prove its efficacy.

FIG - 3 APPLICATION OF TISSUE GLUE
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