Use of Indocyanine green (ICG) angiography to minimize anastomotic leak in the neck after esophagectomy.

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Abstract

Introduction: Anastomotic leak after esophagectomy for cancer of mid and lower esophagus and gastroesophageal junction (GEJ) still remains a major challenge. Poor perfusion of the gastric conduit remains the main factor for leak. Intra-operative assessment of the gastric conduit with indocyanine green (ICG) angiography helps to select a properly perfused site for anastomosis, thus minimizing the leak.

Methods: Patients undergoing surgery for cancer of esophagus and GEJ either through open or minimally approach were taken up for this study. Stomach was used for reconstruction and anastomosis was made in neck. A 0.1ml of test dose of ICG was given intra-dermally to look for any reaction. After that a dose of 5-10 milligrams was injected intravenously. Perfusion was assessed with infrared light using laparoscopic telescope. The timing of perfusion of the conduit was recorded. Well perfused segment was used for gastroesophageal anastomosis. Different parameters including leak were compared with non-ICG group.

Results: We studied 474 patients. Among these patients 67 were in ICG group and 407 were in non-ICG group. Mean age, mean weight loss and co-morbidities were similar in both groups. 72% of patients in ICG group and 50% of patient in non-ICG groups had multimodality treatment. 67% of patients in ICG group and 46% of patients in non-ICG group underwent minimally invasive surgery ($p<0.001$). Post-operative complications like pneumonia, recurrent laryngeal nerve palsy and surgical site infection were similar in both groups. Post-operative mortality was seen in 1.5% and 3.7% in ICG group and non-ICG group respectively ($p=0.4$). Overall leak in ICG group was 9% and 16.5% in non-ICG group ($p=0.06$). In ICG group with the perfusion time of more than 60 seconds, the leak rate was only 3.5% in comparison to 16.5% in non ICG group ($p=0.009$).

Conclusion: ICG angiography provides an objective assessment about the perfusion of gastric conduit during the time of anastomosis. Anastomosis at area of gastric conduit with perfusion time less than 60 seconds, minimizes leak rate in neck.

Key words: Indocyanine green; esophagectomy; anastomotic leak.

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Introduction

Despite various therapeutic modalities, surgery remains main stay of treatment for cancer of mid and lower esophagus and gastroesophageal junction. Surgery is usually performed following neoadjuvant therapy. For squamous cell carcinoma, chemoradiation is the preferred neoadjuvant therapy whereas for adenocarcinoma of gastroesophageal junction, chemotherapy is the preferred therapy in neoadjuvant setting.[1] Whatever be the surgical technique, stomach remains the organ for reconstruction as long as it is available. Esophago-gastric anastomosis is done either in neck or in chest depending on the tumor location and surgical expertise. Esophago-gastric anastomosis made in the neck are more prone to complications in the form of leaks, fistulas, strictures and bleeding. Anastomotic leak (AL) following esophago-gastric anastomosis remains one of the main causes of postoperative morbidity and mortality.[2] Optimal perfusion of gastric conduit and tension free anastomosis are two important predictors for anastomotic healing.[3] The right gastric and right gastroepiploic arteries are the only vessels supplying the gastric conduit. The vascular arcade does not reach the proximal stomach which is mainly supplied by submucosal plexus.[4,5,6] In the past several techniques like intra-operative oxygen saturation measurements, intraoperative doppler sonography, conventional and CT angiography and ischemic preconditioning of the stomach have been tested in order to evaluate the perfusion of anastomotic site. However, none of these methods were feasible for day-to-day surgical practice[7], hence emphasizing the clear need for a safe, reproducible and non-invasive method to assess graft perfusion. Lately, intraoperative indocyanine green (ICG) fluorescence angiography has been introduced as a method of assessment of perfusion intraoperatively. [8,9] After intravenous injection, with the use of near-infrared camera, ICG can be visualized. It offers the surgeon real-time information regarding the perfusion status of the conduit.

In this study, we assessed the use of ICG angiography to evaluate the perfusion of gastric conduit after esophagectomy and we also compared the anastomotic leak rates with non-ICG group.

Methods

This is an observational study conducted at B. P. Koirala Memorial Cancer Hospital, Department of Surgical Oncology, Thoracic Unit. The study period was from February 2018 to August 2021. Patients diagnosed as carcinoma of esophagus (squamous cell carcinoma and adenocarcinoma) and planned for surgery with esophago-gastric anastomosis in the neck were enrolled in this study. Evaluation of the patients was done with upper GI endoscopy and tissue biopsy, CECT of the chest and abdomen and other routine blood parameters. Patients were taken for surgery either directly or following neoadjuvant therapy. Patients with radiologically bulky disease with positive nodes with squamous histology were considered for neoadjuvant chemotherapy or neoadjuvant chemo-radiotherapy followed by surgery. Those with adeno histology were considered for perioperative chemotherapy and surgery for bulky disease. For resectable adenocarcinoma cases upfront surgery followed by chemotherapy was considered.

The surgical approach was planned according to the location of tumor. If the tumor was located in mid and lower esophagus/ GEJ Siewert I, three incision esophagectomy was considered. If the tumor was located in GEJ

Siewert II, transhiatal esophagectomy was performed. Gastric conduit was used for reconstruction in every patient. Gastric tube 4-6 cm in diameter was created on right gastroepiploic and right gastric vascular pedicles. Rest of the vessels to stomach were divided. A small vascularized pedicle of omentum was left at the level of proposed anastomosis to wrap the anastomosis at the end of the procedure.

ICG, available as a 25mg vial was diluted in 10ml of sterile saline. A test dose of 0.1ml was given intradermally half an hour prior to check for hypersensitivity. If no reaction was observed, then a dose of 5-10mg was given intravenously. Stryker laparoscopic set (model 1588) was used to delineate the vascular course using near infrared light mode. The perfusion of the gastric conduit along with the perfusion of the omental pedicle was checked. The timing of perfusion up to the tip of the conduit was noted. If the perfusion of the proposed anastomotic site was not satisfactory, then that segment was discarded and a well perfused segment was selected for anastomosis. The stomach was then pulled to the neck and a hand-sewn esophago-gastric anastomosis was made in the neck. The omental pedicle was wrapped around the anastomosis. Each patient underwent feeding jejunostomy for early enteral feeding. If there was no leak, then oral feeding was started on 5th to 7th POD. The AL was confirmed clinically as discharge from the neck wound other than seroma and pus. If leak was observed, then jejunostomy feeding was continued till the leak healed. AL was managed conservatively with regular neck dressings.

Comparison was made using different variables between the ICG and non-ICG groups and the primary aim was to compare the incidence of AL. The non -ICG group had the patients who were operated before 2018. Statistical analysis was done using SPSS 18.0.

Results

We analyzed a total of 474 patients. There were 67 patients in ICG groups and 407 patients in non-ICG groups. Basic parameters of the patients are shown in table 1.

Table 1: Basic parameters of patients

Parameters	ICG group (n=67)	Non-ICG group (n-407)	p
Mean age	59	58	0.45
Weight loss (kg)	8	9	0.4
Hemoglobin (gm/dl)	12.2	11.9	0.2
Operation time (minutes)	213	238	0.01
Post-operative stay (days)	14.7	13.8	0.3
MIS	45 (67%)	185 (46%)	0.001
Radical node dissection	63 (94%)	346 (85%)	0.047

Treatment groups were divided into surgery alone and multimodality treatment (MMT) group (table 2). Post-operative complications are listed in table 3.

Table 2: Treatment Groups

	ICG group	Non-ICG group	p
Surgery alone	18 (27%)	205 (50%)	<0.001
MMT group	48 (72%)	202 (50%)	

Table 3: Post-operative complications

Complications	ICG group	Non-ICG group	p
Surgical site infection (SSI)	2 (3%)	21 (5%)	0.15

RLN injury	5 (7%)	32 (8%)	0.4
PO pneumonia	13 (19.4%)	100 (25%)	0.2
Leak	6 (9%)	67 (16.5%)	0.06
PO mortality	1 (1.5%)	15 (3.7%)	0.4%

Healing of leak took 22 days in ICG group and 23 days in non-ICG group (p =0.7).

In ICG group, perfusion time was less than 60 seconds in 57 (85%) patients and more than 60 seconds in 10 (15%) patients. Leak rate vs perfusion time is shown in table 4.

Table 4: Leak rate vs perfusion time

Perfusion time	Leak rate	p
<60 seconds	2 (3%)	<0.001
>60 seconds	4 (6%)	

Comparison of leak rates after excluding perfusion time of more than 60 seconds is shown in Table 5.

Discussion

Incidence of anastomotic leaks in patients undergoing esophagectomy with anastomosis in the neck ranges from 5-20% even in high volume centers.[10] These leaks are associated with significant morbidity and mortality.[11]. Various risk factors that contribute to anastomotic leak have been identified.[12]

Table 5: Leak rates excluding perfusion time of more than 60 seconds

Groups	Leak rate	p
ICG group (n=57)	2 (3.5%)	<0.009
Non-ICG group (n=407)	67 (16.5%)	

These risk factors are usually associated with decreased perfusion of the gastric conduit that leads to high incidence of conduit ischemia and anastomotic leak. Proper assessment of the conduit perfusion and selecting a well perfused site for anastomosis therefore helps in reducing the anastomotic leak. In the past subjective assessment along with several other techniques like intraoperative oxygen saturation measurements, intraoperative doppler sonography, conventional and CT angiography and ischemic preconditioning of the stomach have been attempted but with unsatisfactory results.[4]

Risk factors
Age
Male gender
Nutritional status and obesity
Comorbid conditions (Diabetes, renal failure, cardiovascular disease)
Smoking/ alcohol abuse
Neoadjuvant therapy
Prolonged operative time
Intraoperative blood loss

ICG was approved for clinical use by Food and Drug Administration in 1956.[13] ICG has been used in various aspects of medical fields like to determine cardiac output, to assess hepatic function and delineate biliary anatomy and to assess ophthalmic vascular anatomy. Shimada first introduced ICG angiography in esophageal surgery to assess vascularity of anastomosis.[14] The use of ICG to assess the perfusion of gastric conduit has gained popularity since then.

Various studies have shown decrease in AL rates after adopting ICG angiography to assess gastric conduit perfusion. Campbell et al published his results showing a reduction in AL rates after implementing ICG angiography.[15] Ishiguro et al reported a case of a patient who had macroscopically well perfused gastric conduit which was detected as malperfused by ICG angiography.[16] Kumagai et al found that malperfusion of the gastric tip is associated with a higher rate of anastomotic problems or graft necrosis.[3] In a series of 144 patients with neck anastomosis, Zehetner et al used the SPY imaging system and found significantly lower leakage rates in those cases where the gastric conduit could be shortened to the transition point (2%) versus anastomosis beyond this point (45%).[5] Furthermore, no major leakage was found in patients where the anastomosis was placed distally to the transition point.

Kumagai Y et al established a '90-second rule' to confirm good blood perfusion at the anastomosis site. They evaluated the rate of anastomotic leakage of 70 consecutive patients who underwent esophagectomy with gastric tube reconstruction using ICG fluorescence angiography. Esophago-gastric anastomoses were made in the area where enhancement was noticed less than 90 seconds on ICG fluorescence angiography. In 18 patients the time for enhancement of the gastric tube tip exceeded 60 seconds (60-204). The hypoperfused area was excised. After excision, the median time for enhancement of the gastric tube tip shortened from 95.5 (60.0-204.0) seconds to 41.0 (9.0-77.0) seconds ($P < 0.001$). 1 patient who had enhancement time of 77 seconds after revision of conduit leaked (1.4%). They concluded that the 90-second rule is a safe and effective method for deciding the site of anastomosis.[17]

Van Daele E et al reviewed 1186 patients with primary esophagogastric anastomosis in the neck. Overall leak rate was 13.8%. Leak rate in ICG group and non-ICG group was 9.9% and 20.5% respectively ($p<0.001$)[18]. In ICG group, 6.3% of patients had leak despite good ICG perfusion. 93 patients who had low perfusion at the tip underwent different types of correction and the leak rate was 6.5% comparable to AL of well perfused patients. Nakashima et al used pedicled omental flap and evaluated the blood flow at the omental flap and anastomosis by ICG angiography with good results.[19]

We had reported our initial results in 28 patients with satisfactory results.[20] In our center in recent days, we assess the gastric conduit perfusion with ICG angiography in each patient. The non-ICG group is the group of patients that were operated before ICG angiography came into practice. In both groups, the basic parameters like age, These risk factors are usually associated with decreased perfusion of the gastric conduit that leads to high incidence of conduit ischemia and anastomotic leak. Proper assessment of the conduit perfusion and selecting a well perfused site for anastomosis therefore helps in reducing the anastomotic leak. In the past subjective assessment along with several other techniques like intraoperative oxygen saturation measurements, intraoperative doppler sonography, conventional and CT angiography and ischemic preconditioning of the stomach have been attempted but with unsatisfactory results.[4]

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ICG fluorescence angiography is basically meant to provide the real time imaging of the micro perfusion of gastric conduit during esophagectomy. It can be easily used in both open and minimally invasive surgery. Furthermore, ICG is cheap and is readily available. It is non-toxic and shows minimal antigenic effect. None of our patient had any immediate or long-term toxic reaction related to its use.

Conclusion

In our study, we found that the use of ICG angiography to assess gastric conduit perfusion during esophagectomy resulted in lower anastomotic leak rates. Hence ICG angiography seems to safe and relatively inexpensive tool in accessing the perfusion of gastric conduit during esophagectomy. Using the cut off time of 60 seconds, patients with perfusion time of less than 60 seconds have lesser chances of anastomotic leak.

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