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Original Article

The primary prevention of pancreatic fistula using a vascularised rectus abdominis muscle flap – A porcine model ☆,☆☆

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ABSTRACT

Background: A pancreatic fistula is one of the most devastating complications following a Whipple's procedure. Fistula rates remain high despite various modifications to surgical techniques. We propose the use of a vascularised muscle flap in the primary prevention of pancreatic fistulas.

Method: A distal pancreatectomy was performed on 5 pigs in our porcine model. A pancreaticojejunal (PJ) anastomotic leak was simulated. The pigs were divided into treatment (4 pigs) and control groups (1 pig). A left pedicled rectus abdominis flap was wrapped around the PJ anastomosis for the treatment group and omitted for the control group. Serum and drain amylase levels were recorded. The PJ-rectus abdominis flap complex was evaluated histologically.

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Results: There was no biochemical evidence of anastomotic leak in the treatment group. The drain-serum amylase ratio was less than 1.5 in the treatment group (p=0.006). Microscopically, the muscle adjacent to the anastomotic leak showed mild necrotic changes with an affected muscle depth of less than 10%.
Conclusion: The vascularised rectus abdominis muscle is a durable flap to withstand proteolytic pancreatic enzymes. It is able to provide a water-tight seal around the PJ anastomosis and mitigate intraperitoneal haemorrhage and infection caused by erosion from the pancreatic fistula.

Introduction

A pancreatic fistula or pancreaticojejunal (PJ) anastomotic leak is one of the most feared complications following a Whipple's procedure. The incidence of pancreatic fistula ranges between 6% and 24%[1,2] and is associated with a mortality rate of 20%-80%.[3] Autodigestion and destruction of surrounding tissues and vessels by pancreatic proteases can result in devastating intra-abdominal sepsis and haemorrhage.[3,4]

Various modifications to surgical techniques have been developed to mitigate an anastomotic leak. These range from changes to anastomotic techniques (e.g., the Blumgart,[5] invagination[6] or binding techniques[7]), pancreatic duct stenting[8] and the usage of somatostatin or octreotide. In spite of these efforts, the rate of pancreatic fistulas has not seen a marked decrease. The omentum flap has been described in the primary prevention of pancreatic fistulas with varying degrees of success.[9–11] This serves as the basis of our proposal for the use of a vascularised muscle flap in an attempt to prevent pancreatic fistulas.

The rectus abdominis flap is a workhorse flap for perineal reconstruction. It has been described in the repair of gastrojejunostomy leaks and duodenal perforations.[12,13] The rectus abdominis flap has a robust muscular component, making it more likely to be able to withstand the proteolytic effects of the pancreatic enzymes, and thus prevent the formation of pancreatic fistula.

By the use of a porcine model, we aim to evaluate the reliability of the rectus abdominis flap in the primary prevention of pancreatic fistulas.

Methods

Five Yorkshire Landrace Pigs weighing 44 to 80 kg were obtained from a single commercial source (Sembawang Animal Husbandry and Hospital/National Large Animal Research Facility, Singapore). Approval of the study was obtained from the Institutional Animal Care and Use Committee (Protocol:2021/SHS/1679). Experimentation was performed in compliance with the ARRIVE guidelines and carried out in accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals.

Surgical Technique

The pigs were divided into a control group (Pig 1) and treatment group (Pigs 2 to 5). A distal pancreatectomy was performed via a midline laparotomy incision in both groups. A limb of transected jejunum was then brought up in a roux-en-Y fashion to the remnant proximal pancreas to create a PJ

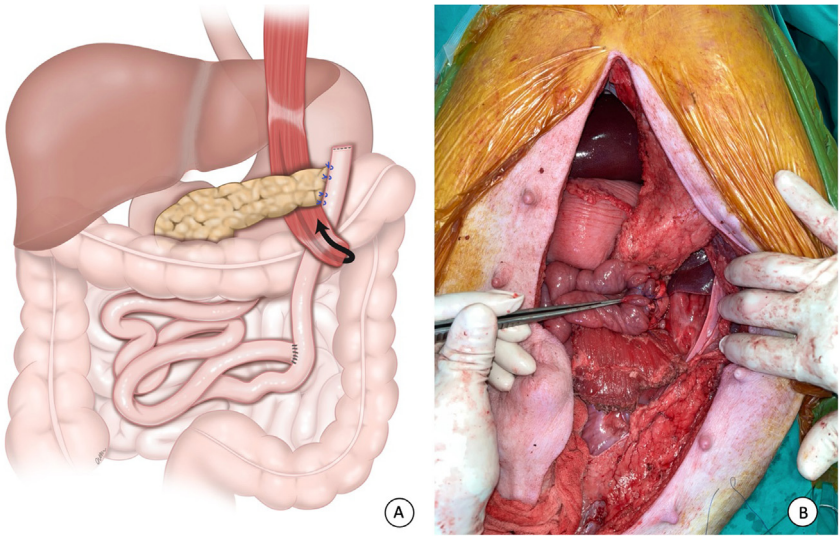

Figure 1. A) An illustration depicting our porcine model. A distal pancreatectomy was performed. A PJ anastomosis was created with a limb of transected jejunum in a roux-en-Y fashion to the remnant pancreas. A controlled PJ leak was simulated by intentional omission of the 12 o'clock duct-to-mucosa suture in the Blumgart technique. A left pedicled rectus abdominis flap was raised based on the superior epigastric system and wrapped around the PJ anastomosis. B) A clinical picture demonstrating the left pedicled rectus abdominis flap delivered in a posterior to anterior fashion to wrap around the PJ anastomosis.

anastomosis; this served to simulate the PJ anastomosis found in Whipple's procedure. The PJ anastomosis was created using the modified Blumgart technique (3 double trans-pancreatic sutures and interrupted duct-to-mucosa anastomotic sutures). A controlled PJ leak was simulated by intentional omission of the 12 o'clock duct-to-mucosa suture. A pedicled rectus abdominis flap was used to wrap around the PJ anastomosis for pigs in the treatment group (Figure 1A-B). A rectus abdominis flap wrap was not performed in the control group.

The left rectus abdominis flap was chosen for its proximity to the PJ anastomosis. The rectus abdominis flap was pedicled on the superior epigastric artery and wrapped around the PJ anastomosis in a tension-free manner. To anchor it in position, the distal portion of the muscle flap was stitched back onto itself with polydioxanone sutures after it had completely encircled the PJ anastomosis. To further secure this wrap, the muscle flap was anchored onto the jejunum with circumferential interrupted sutures (polydioxanone) to the serosal layer of the jejunum (Figure 2A-C). A surgical drain was placed adjacent to the flap for Pigs 1 to 4 and adjacent to the PJ anastomosis for the control pig. Oral feeding was started on post-operative day 1. Drain outputs were recorded daily.

Serum and drain amylase levels were recorded pre-operatively and on post-operative days 1, 3, 5 and 7. The presence of an anastomotic leak was diagnosed according to the International Study Group of Pancreatic Fistula (ISGPF) definition: A drain output of any measurable volume of fluid on or after post-operative day 3 with an amylase content greater than 3 times the serum amylase activity.[14] Statistical analysis was performed using STATA Version 17.0 (Statacorp LLC, College Station, TX, USA). A p value of <0.05 was considered statistically significant.

All pigs were euthanised on post-operative day 7. Post-mortem laparotomy and a thorough inspection of the abdominal cavity were performed. The PJ-rectus abdominis flap complex was retrieved in the treatment group for histological sampling.

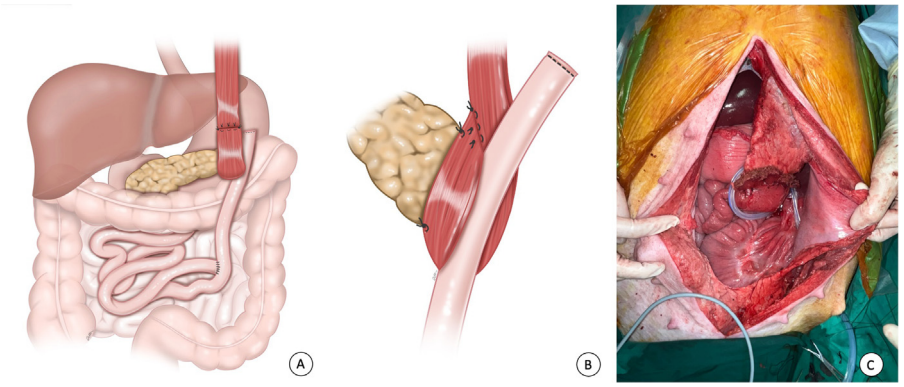

Figure 2. A) An illustration showing the rectus abdominis flap wrapped around the PJ anastomosis, with the distal muscle stitched back onto the main body of the flap to complete the encirclement. B) An illustration depicting the lateral view of the rectus abdominis flap encircling the PJ. C) The rectus abdominis flap was able to wrap around the PJ anastomosis in a tension-free manner within the intraperitoneal cavity, allowing easy closure of the abdominal wall.

Table 1
Serum and drain amylase levels of both control and intervention groups.

Pig	Amylase (U/L)	D0	D1	D3	D5	D7
1 (Control)	**Serum**	2830	4156	3450	3034	2971
	Drain	-	7941	10415	2961	2585
2	**Serum**	>4500	>4500	4384	3918	3591
	Drain	-	4049	4025	3569	4064
3	**Serum**	4287	2572	3364	677	3542
	Drain	-	0	0	0	3892
4	**Serum**	2822	2659	2956	2824	2774
	Drain	-	0	0	0	2354
5	**Serum**	3372	3930	2571	2120	2357
	Drain	-	0	3214	3295	2778

Results

Clinical Assessment

The pig in the control group (Pig 1) developed an anastomotic leak on post-operative day 3 in keeping with the ISGPF criteria. (The drain amylase content was 3 times the serum amylase activity.) Clinically, the pig was noted to be less active on post-operative day 4 with loss of appetite requiring intravenous dextrose fluid supplementation for the next 2 days. The pigs in the treatment group (Pigs 2 to 5) recovered uneventfully. The drain amylase levels for the treatment group did not fulfil the criteria for pancreatic fistula, returning less than 3 times the serum amylase levels (Table 1).

We performed further regression analysis on the serum and drain amylase results in both groups. The drain-serum amylase ratio in the treatment group remains consistently less than 1.5 and lower than in the control group. The ratio is noted to peak on post-operative day 3 in the control group, with a difference in ratios of -2.5 between treatment and control groups ($p=0.006$) (Figure 3).

Histological Assessment

At the time of the post-mortem evaluation, there was demonstrable seal macroscopically. The rectus abdominis flap remained well vascularised and there was no evidence of an anastomotic leak in the abdominal cavity.

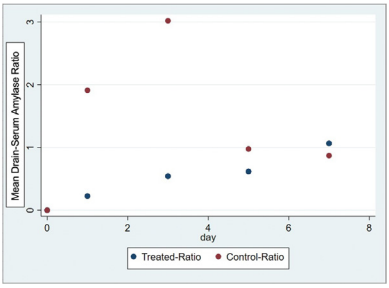

Figure 3. Graph showing the difference in mean drain-serum amylase ratio between the pigs.

Figure 4. PJ-rectus abdominis complex under high-pressure methylene blue dye instillation and demonstrating water-tight seal macroscopically. (P) denotes the pancreatic segment, (RA) denotes the rectus abdominis muscle wrap and (J) denotes the jejunal segment. Dotted green lines define the border of the rectus abdominis muscle wrap.

The PJ-rectus abdominis complex was retrieved. Fistulography was performed using retrograde high-pressure instillation of methylene blue dye from efferent jejunal outlet into the PJ anastomosis was performed with the proximal afferent jejunal inlet clamped. The rectus abdominis muscle demonstrated a water-tight seal around the anastomosis (Figure 4).

The PJ-rectus abdominis specimen was sectioned for visual analysis of the leak contained within the rectus abdominis muscle. An area of necrosis was noted at the point of the omitted duct-to-mucosa suture (area of controlled leak) (Figure 5A). This was contained and walled off within the rectus abdominis muscle. Most of the rectus abdominis muscle remained healthy with minimal necrosis. The rectus muscle not only achieved a water-tight seal of the leak, but it was able to withstand the proteolytic pancreatic enzymes.

Microscopically (haematoxylin and eosin staining at $\times$ 7 magnification), the rectus abdominis muscle adjacent to the anastomotic leak showed mild degenerative changes. There is marked presence of fibrotic reaction and granulation tissue formation. The affected muscle depth is less than 10% (Figure 5B).

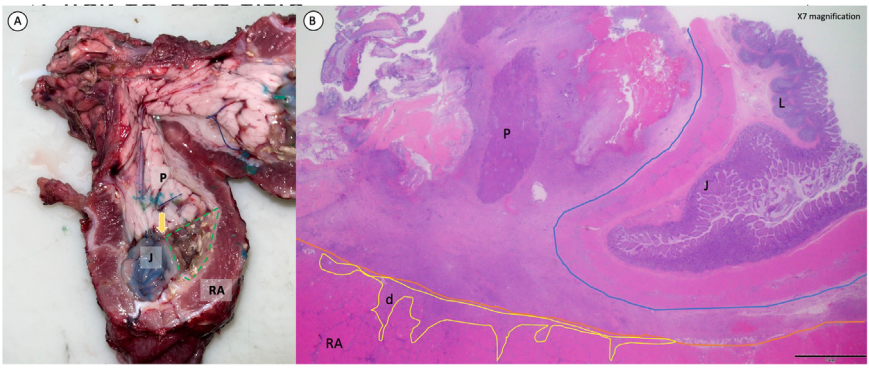

Figure 5. A) Coronal section of the PJ-rectus muscle complex. Methylene blue dye was instilled in a retrograde manner via the efferent jejunal outlet. Blue dye staining is noted within the jejunum (J) and lining the pancreatic duct within the pancreas (P). This demonstrates patency of the PJ anastomosis. A yellow arrow denotes the point of omission of the 12 o'clock Blumgart suture (i.e., area of controlled leak). The green dotted lines mark out an area of PJ leak with walled-off necrosis. The rectus abdominis muscle (RA) in contact with the necrosis shows some areas of scarring and fibrosis, indicating healing. Most of the muscle remains healthy. B) Haematoxylin and eosin staining of the pancreaticojejunal-rectus muscle complex (× 7 magnification). Along the PJ anastomosis-muscle border (orange line), there is presence of fibrosis and granulation. The RA in contact with the PJ anastomosis shows necrosis (marked out by yellow line, labelled d). The depth of muscle affected is less than 10%.

Discussion

In 1935, Dr Allen Oldfather Whipple performed the first reported total duodenectomy as part of his original 2-stage procedure.[15] After many years of evolution, it has now evolved to the commonly known single-stage Whipple procedure. In these modern times, the Whipple procedure remained one of the most technically challenging pancreatic surgery, often associated with significant morbidity and mortality. Advancements in surgical techniques and post-operative management of complications have led to improved clinical outcomes, reducing post-operative mortality rates. However, pancreatic anastomotic leaks remain as one of the frequent causes of morbidity and mortality, challenging even the surgeon on his best days. Prevention is better than cure, and primary prevention of pancreatic anastomotic leak would make the Whipple procedure less dangerous and daunting.

Historically, multiple attempts have been made to reduce this complication ranging from anastomotic techniques to the usage of pancreatic duct stenting. To date, the use of the omental flap was the most promising. When used as a roll-up flap around the PJ anastomosis, it can serve as a biological plug to prevent leakage and a source of neovascularisation for wound healing.[9,16] Though there is reduced overall morbidity, the rates of pancreatic fistulas remain high (up to 20.7%[11]). More recent meta-analyses showed that the use of an omental wrap could not prevent the occurrence of pancreatic fistulas. The risks of post-pancreatectomy haemorrhage were also similar for patients with or without omental wrapping.[17,18] This could be attributed to the non-uniformity of the vascular pattern in the greater omentum[19]. The omentum flap is also highly variable in size, and not of sufficient tissue density to resist proteolysis by pancreatic enzymes.

The pathophysiology in an pancreatic anastomotic leak involves the activation of pancreatic proteases when it comes into contact with enteropeptidase found in the intestinal brush border. This results in autodigestion and destruction of surrounding tissue and vessels and can lead to intra-abdominal abscesses, peri-pancreatic collections and post-operative haemorrhage.[9] The use of a rectus abdominis muscle flap is ideal in this situation due to a few factors. Firstly, as a vascularised muscle flap, it imparts vascularity to the PJ anastomosis that is in relative ischaemia. Muscle has a dense capillary network of 2000 capillaries per square mm and a high resting blood flow.[20] Increased vascularity leads to improved antibiotic delivery and confers higher oxygen tension in local tissues, thereby promoting leucocytic action and bacterial elimination.[21] Secondly, this robust vascularity also allows the rectus abdominis flap to continuously heal while sustaining proteolytic damage from the

pancreatic enzymes. In addition, the healed rectus muscle wrap was able to withstand high-pressure instillation of methylene blue from the efferent jejunal outlet into the PJ anastomosis (Figure 4A), demonstrating its efficacy as a vascularised physical barrier. This is similar to the use of modern self-healing polymers in car coating, whereby the car coat will self-repair after a scratch. Thirdly, being a thick and wide muscle flap, the rectus abdominis flap would have enough tissue density to take on sustained proteolysis without perforation. In our study, this was evidenced histologically as only 10% of the rectus muscle thickness adjacent to the controlled anastomotic leak was affected, and there was also a marked presence of fibrotic reaction and granulation tissue, demonstrating signs of healing (Figure 5B). Wrapping the thick rectus abdominis muscle around the PJ anastomosis would also isolate it from the gastroduodenal artery stump and other major vessels. This mitigates intraperitoneal haemorrhage caused by the erosion from the pancreatic fistula. Fourthly, most Whipple procedures are still performed in the open midline fashion, and the rectus abdominis muscle flap is easily accessible and raised logistically. Moreover, sacrifice of the left rectus abdominis muscle does not result in significant functional deficit. When raised as a muscle-only flap (leaving the anterior rectus sheaths in situ), the strength of anterior abdominal wall can be preserved. This minimises the risk of abdominal wall hernias. By preventing a pancreatic leak, the advantages will outweigh that of the sacrifice of the muscle.

All 4 pigs in our treatment group did not exhibit any clinical or biochemical evidence of pancreatic fistula according to the ISGPF criteria. The drain-serum amylase ratio in the treatment group remains consistently less than 1.5, and lower than the control group ($p=0.006$). This clearly demonstrated the superiority of our technique in preventing the manifestation of a pancreatic fistula.

Larger sample sizes are required if the expected outcome is difficult to reproduce. In our animal model, we successfully simulated a pancreatic leak with full certainty through the omission of the 12 o'clock duct-to-mucosa suture. Hence, the sample size remains small, as we avoided the need for a larger sample group or unnecessary sacrifices to achieve the desired effect.

Our novel technique can be thought of as the use of a highly robust, self-healing autologous material to contain a leak in a water-tight fashion, until the efferent outflow can eventually stabilise and let the pancreatic leak seal.

Conclusion

Results from this porcine model demonstrate the promising utility of the rectus abdominis muscle as the ideal vascularised soft tissue in mitigating the devastating consequences of the formation of pancreatic fistula after Whipple's procedure.

Conflict of interest/Funding

The authors have no conflicts of interest to declare.

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References

1. Veillette G, Dominguez I, Ferrone C, Thayer SP, McGrath D, Warshaw AL, et al. Implications and management of pancreatic fistulas following pancreaticoduodenectomy: The Massachusetts General Hospital experience. *Arch Surg*. 2008 May;143(5):476–481.
2. Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman JA, Sohn TA, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo–controlled trial. *Ann Surg*. 2000 Sep; 232(3):419–429.
3. de Castro SMM, Busch ORC, van Gulik TM, Obertop H, Gouma DJ. Incidence and management of pancreatic leakage after pancreatoduodenectomy. *Br J Surg*. 2005 Sep;92(9):1117–1123.
4. Crippa S, Salvia R, Falconi M, Butturini G, Landoni L, Bassi C. Anastomotic leakage in pancreatic surgery. *HPB*. 2007;9(1):8–15.

5. Grobmyer SR, Kooby D, Blumgart LH, Hochwald SN. Novel pancreaticojejunostomy with a low rate of anastomotic failure-related complications. *J Am Coll Surg*. 2010 Jan;210(1):54–59.
6. Kennedy EP, Yeo CJ. Dunking pancreaticojejunostomy versus duct-to-mucosa anastomosis. *J Hepatobiliary Pancreat Sci*. 2011 Nov;18(6):769–774.
7. Peng S, Mou Y, Cai X, Peng C. Binding pancreaticojejunostomy is a new technique to minimize leakage. *Am J Surg*. 2002 Mar;183(3):283–285.
8. Kleespies A, Albertsmeier M, Obeidat F, Seeliger H, Jauch KW, Bruns CJ. The challenge of pancreatic anastomosis. *Langenbeck's Arch Surg*. 2008 Jul;393(4):459–471.
9. Shah OJ, Bangri SA, Singh M, Lattoo RA, Bhat MY. Omental flaps reduces complications after pancreaticoduodenectomy. *Hepatobiliary Pancreat Dis Int [Internet]*. 2015;14(3):313–319. [cited 2023 Feb 20] Available from:. https://pubmed.ncbi.nlm.nih.gov/26063034/.
10. Matsuda H, Sadamori H, Umeda Y, Shinoura S, Yoshida R, Satoh D, et al. Preventive effect of omental flap in pancreaticoduodenectomy against postoperative pseudoaneurysm formation. *Hepatogastroenterology*. 2012 Mar;59(114):578–583.
11. Choi SB, Lee JS, Kim WB, Song TJ, Suh SO, Choi SY. Efficacy of the omental roll-up technique in pancreaticojejunostomy as a strategy to prevent pancreatic fistula after pancreaticoduodenectomy. *Arch Surg [Internet]*. 2012 Feb 20;147(2):145–150. [cited 2022 Sep 19] Available from:. https://jamanetwork.com/journals/jamasurgery/fullarticle/1107782.
12. Somasekar RDR, Sankar AS, Krishna PS. Primary reinforcement with rectus abdominis muscle flap-a salvage technique for a tenuous post traumatic duodenal perforation- a case report. *Int J Surg Case Rep [Internet]*.. 2020 Jan 1;74:91 [cited 2023 Feb 20]; Available from: /pmc/articles/PMC7452464/.
13. Rectus abdominis muscle flap for repair of the gastrojejunal leakage after distal gastrectomy with Billroth II anastomosis for gastric cancer - PubMed [Internet]. [cited 2023 Feb 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/31333239/.
14. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery [Internet]*. 2005;138(1):8–13. [cited 2022 Sep 20] Available from:. https://pubmed.ncbi.nlm.nih.gov/16003309/.
15. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg [Internet]. 1935 Oct [cited 2023 Aug 9];102(4):763. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1391173/.
16. Adams W, Ctercteko G, Bilous M. Effect of an omental wrap on the healing and vascularity of compromised intestinal anastomoses. *Dis Colon Rectum [Internet]*. 1992 Aug;35(8):731–738. [cited 2023 Mar 4] Available from:. https://pubmed.ncbi.nlm.nih.gov/1379531/.
17. Preventive effect of omental flap in pancreaticoduodenectomy against postoperative complications: a meta-analysis - PubMed [Internet]. [cited 2023 Mar 4]. Available from: https://pubmed.ncbi.nlm.nih.gov/25911894/.
18. Andreasi V, Partelli S, Crippa S, Balzano G, Tamburrino D, Muffatti F, et al. A systematic review and meta-analysis on the role of omental or falciform ligament wrapping during pancreaticoduodenectomy. *HPB*. 2020 Sep 1;22(9):1227–1239. (Oxford) [Internet] [cited 2023 Mar 4] Available from:. https://pubmed.ncbi.nlm.nih.gov/32631806/.
19. Collins D, Hogan AM, O'Shea D, Winter DC. The omentum: anatomical, metabolic, and surgical aspects. *J Gastrointest Surg [Internet]*. 2009;13(6):1138–1146. Jun [cited 2023 Mar 5] Available from:. https://pubmed.ncbi.nlm.nih.gov/19291335/.
20. Tan BK, Fams E, Chen HC, He TM, Song IC. Flap prefabrication-the bridge between conventional flaps and tissue-engineered flaps.
21. SJ M, BS A, N C. Use of the muscle flap in chronic osteomyelitis: experimental and clinical correlation. *Plast Reconstr Surg [Internet]*. 1982;69(5):815–828. [cited 2021 Oct 7] Available from:. https://pubmed.ncbi.nlm.nih.gov/7071227/.