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Triple-drug therapy to prevent pancreatic fistula after pancreatectomy in a rat model

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ABSTRACT

Background: Pancreatic fistula (PF) is one of post-operative complications in pancreatic surgery, but there is no consensus about the optimal treatment for PF. Our group has established a rat model of PF, and we conducted the present investigation to determine the efficacy of the triple-drug therapy (somatostatin analogue, gabexate mesilate, and imipenem/cilastatin) against PF using our rat model.

Methods: In the PF rat model, the triple-drug therapy was administered to the treated (T) group (n = 4), and we compared the results with those of a control (C) group (n = 4). The rats were sacrificed on postoperative day 3 (POD 3) and the levels of amylase and lipase in serum and ascites were measured. The intra-abdominal adhesion was scored. Each pancreas was evaluated pathologically, and inflammation was scored.

Results: The ascitic amylase levels on POD 3 were 1982 (1738–2249) IU/L in the C group and significantly lower at 136 (101–198) IU/L in the T group (p = 0.02). The ascitic lipase levels on POD 3 were 406 (265–478) U/L in the C group and significantly lower at 13 (7–17) U/L in the T group (p = 0.02). The intra-abdominal adhesion score on POD 3 was 2 (1–2) in the C group and significantly lower at 0 (0–1) in the T group (p = 0.02). The histological evaluation showed that the average of pancreatic inflammatory score was 8.5 (8–9) in the C group and significantly milder at 5 (5–7) in the T group (p = 0.01).

Conclusion: Our findings suggest that the triple-drug therapy could be useful as a treatment for PF in clinical settings.

1. Introduction

Pancreatic surgery has become safer due to improvements in surgical techniques and devices in recent years [1–5], but the frequency of complications after pancreatic surgery remains high at 30%–50% [6]. Pancreatic fistula (PF) is one of the most serious postoperative complications in pancreatic surgery because of its character. A PF can melt adipose tissues and induce abscess formations and a pseudoaneurysm that could be life-threatening when it ruptures [7–10]. Controlling a PF would thus be the most important aspect of peri-operative care for patients who undergo a pancreatic resection. However, there is no guideline or consensus about the treatment of PF, and there are many types of treatments for this complication.

Somatostatin analogue is a drug that binds to the somatostatin receptor and suppress the release of hormones by organ [11]. Some studies have shown that somatostatin analogue suppresses pancreas secretions, and the studies' authors suggested that these medications are effective against PF [12–14], but other studies obtained negative results about the efficacy of these drugs for PF [15–17]. The efficacy of somatostatin analogues for PF thus remains controversial.

Gabexate mesilate is a protease inhibitor that controls trypsin activation, which suppresses pancreatic self-digestion and necrosis. It is widely used to treat acute pancreatitis in Japan. There are some descriptions about this drug in the Japan Guidelines for the Management of Acute Pancreatitis [18], but it concludes that the efficacy of this drug is not clear and more RCTs are needed.

Imipenem/cilastatin is known as an antibiotic that has a

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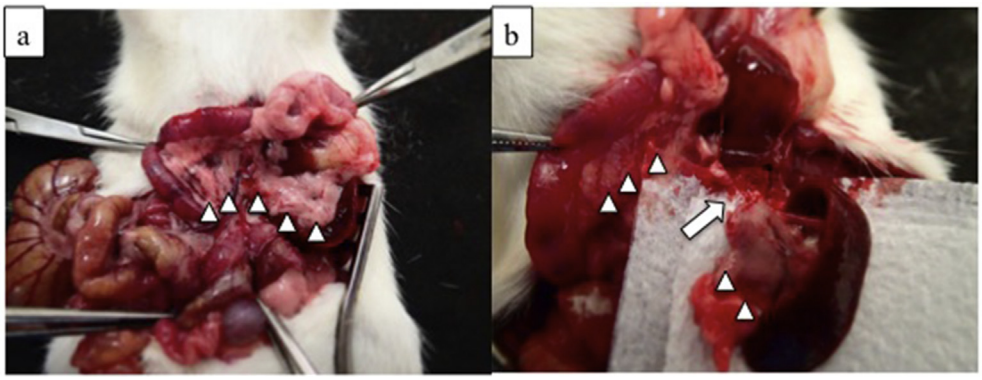

Fig. 1. The procedure for making PF rat model. a) The pancreas was unfolded (indicated by triangles). The splenic vein was identified, which ran with splenic duct. b) Pancreas was transected preserving the splenic vessels (indicated by arrow).

sufficient tissue penetration to pancreas. There are some descriptions of reference between use of prophylactic antibiotics and reduction of infectious pancreatic complications in above-cited guideline, but it also concludes that more RCTs are needed [18].

Based on the studies described above, in our department we usually use these three drugs (somatostatin analogue Octreotide, gabexate mesilate, and imipenem/cilastatin) simultaneously for patients who are at high risk of the development of a PF. We have reported the efficacy of this triple-drug therapy in a clinical setting [19]. Although this pharmacological treatment for PF has been effective in our experience, exactly how these drugs affect PF is unclear.

Our group has established a PF model in rats [20]. The aim of the present study was to determine the efficacy of the triple-drug therapy against PF using the rat model.

2. Methods

2.1. Animals

Eight-week-old male Fisher 344 rats weighing 250–300 g (CLEA Japan, Tokyo) were used. All rats were housed in plastic cages with standard feed and water at the Laboratory Animal Center for Biochemical Research at the Nagasaki University Graduate School of Biomedical Sciences. All animal protocols were approved by the Animal Experimentation Committee of Nagasaki University.

2.2. Making the PF rat model

The PF rat model was created as described [20]. In brief, after a laparotomy was performed, pancreas was unfolded (Fig. 1a). The rat pancreatic duct consists of four smaller duct; common duct, gastric duct, duodenal duct, and splenic duct. To transect splenic duct induce PF model in rats without removing any pancreas lobe [20]. Pancreas which included splenic duct was transected along the portal vein to preserve the splenic vessels (Fig. 1b). After the pancreas transection, the abdomen and skin were closed by suturing with 3–0 silk. We divided the rats into two groups: the triple-drug therapy (T) group (n = 4) and the control (C) group (n = 4). All rats of both groups were sacrificed on postoperative day (POD) 3.

2.3. The triple-drug therapy

We medicated rats with using Osmotic Pumps (model 2ML1, Alzet, Cupertino, CA, USA). It is a small pump that can be used for the continuous dosing of unrestrained laboratory animals. The pump filled with a solution of drugs can release drugs continuously in a subcutaneous site for one week. The dosage of somatostatin analogue (Octreotide), gabexate mesilate, and antibiotics (Imipenem/cilastatin) used in clinical settings are 300 μg/day, 600 mg/day, and 1000 mg/day respectively. In this study we medicated each rat with 5 μg/kg/day of somatostatin analogue, 10 mg/kg/day of gabexate mesilate, and 16.6 mg/kg/day of antibiotics respectively. These three drugs were dissolved in saline and injected into the pump. T-group rats underwent the above-described PF operation first, and then we made an incision on the rats' back and implanted the pumps into the subcutaneous space (Fig. 2). The incision was sutured and closed with 3–0 silk. For the C group, we performed the PF operation first, and then simply made the incision and closed

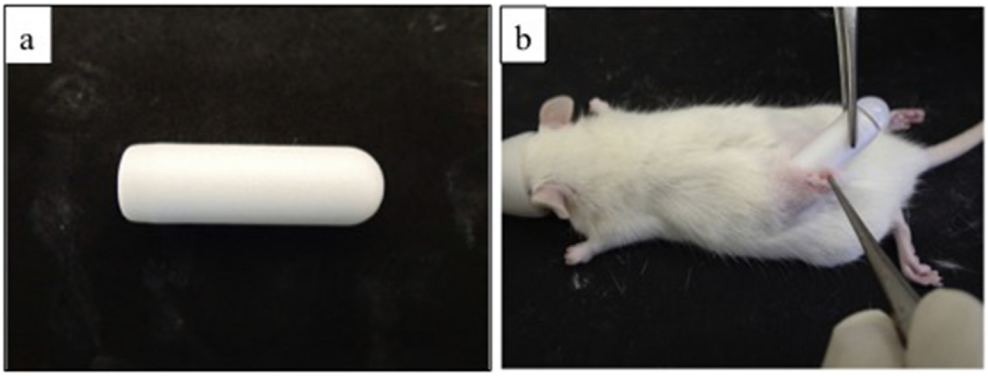

Fig. 2. The procedure for implanting pumps. a) Osmotic Pumps (model 2ML1, Alzet, Cupertino, CA, USA) filled with three drugs. b) Implanting pumps in the subcutaneous site.