Autologous platelet rich fibrin glue for sealing of low-output enterocutaneous fistulas: An observational cohort study

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Background. *Glue sealing has become an alternative option for occlusion of enterocutaneous fistula (ECF) because of it minimal invasiveness and simplicity. This study aimed to determine efficacy and safety of autologous, platelet-rich fibrin glue (PRFG) in promoting closure of ECFs.*

Methods. *This was a nonrandomized cohort study, recruiting patients who had low-output ECFs (<200 mL/24 h). Beside standard of care, patients were assigned to either the PRFG or control group. Clinical efficacy and safety were determined prospectively. Moreover, a well-balanced subcohort was generated by propensity score (PS) matching. Unadjusted and adjusted Cox proportional hazard models were employed to determine hazard ratios (HRs) of ECF closure in both cohorts.*

Results. *From January 2008 to January 2012, 145 patients were enrolled initially, with 70 in the control group and 75 in the PRFG-treated group. Compared with the control group, patients in the PRFG group had lesser median time of fistula closure (7 vs 23 days; P = .0010). In addition, PRFG healed more fistulas within the first 28 days (77% vs 57%; P = .0127). For all fistulas included, PRFG-treated fistulas were 3.13 (95% confidence interval [CI], 1.82–5.36) times more likely to achieve closure than those with the non-PRFG approach in the adjusted Cox model. In a PS-matched cohort with 28 paired fistulas, HRs were 3.41 (95% CI, 1.91–6.07) for all fistulas regardless of location. No adverse events related to glue applications were observed.*

Conclusion. *Autologous PRFG seems to be safe and effective in the treatment of low-output ECFs, and can lessen closure times and promote closure rates. (Surgery 2014;155:434-41.)*

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Management of enterocutaneous fistula (ECF) has remained a persistent challenge and carries mortality rate of up to 5–37%.[1-3] ECFs are most often seen in the postoperative period owing to anastomotic leakage, which can occur after operations for intestinal obstruction, trauma, cancer, or inflammatory bowel disease.[4] Thus, 75–85% of ECFs are iatrogenic.[5] Regardless of the pathogenesis, management of ECFs, for example, control of sepsis, fluid and electrolyte balance, maintenance of nutrition, and wound care, often requires costly hospital stay and multidisciplinary care.[6] Therefore, an ECF is a devastating complication for patients, families, and physicians, and leads to anxiety, depression, and considerable financial hardship.[7] The incidence of spontaneous closure of ECFs varies from 15% to 71% after conservative treatment.[7]

Use of fibrin glue in the fistula tract has been shown to promote closure of low-output ECFs.[8] Autologous, platelet-rich fibrin glue (PRFG), a novel fibrin gel containing high concentrations of human fibrinogen and thrombin, has been used in operative procedures as a biologic adhesive for tissue adhesion or hemostasis.[9,10] The lack of risk of transmission of infections,[11] allergic reactions,[12] and high cost, however, make autologous PRFG favorable over other fibrin sealants. Another advantage of autologous PRFG is the presence of high concentration of thrombocytes, from which a group of growth factors are released

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on activation of thrombin.[13-15] Additionally, compared with other adhesives, autologous PRFG presents better biocompatibility and biodegradation.[16] Therefore, as a matrix, autologous PRFG is able to enhance dermal and epidermal regeneration in chronic wounds even without keratinocytes; despite these potential advantages of PRFG, there have been no reports of autologous PRFG on closure of ECFs. The aim of this study was to investigate the efficacy and safety of autologous PRFG in the treatment of single, low-output ECFs compared with patients treated with standard of care (SOC).

MATERIALS AND METHODS

Study design. This prospective, nonrandomized cohort study initiated in January 2008 and completed in January 2012 in Department of Surgery, Jinling Hospital, was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board Ethics Committee at Jinling Hospital. This study was registered at ClincialTrials.gov (number NCT01561066). Each subject was properly consented before enrollment.

Subjects were assigned to one of two senior investigators (G.G. or G.W.) according to patient choice. One team offered SOC along with PRFG treatment and another offered SOC only within 28 days after the day of enrollment. After the treatment period, patients who failed to achieve medical closure were further evaluated whether the fistulas were complicated with infection, foreign body, distant bowel obstruction, and so on. These unhealed fistulas would either be treated by definitive surgery or continue to be treated conservatively based on patient's best interest and physicians' discretion. Then patients were followed for ≤180 days after enrollment.

Sample size calculation. The hypothesis of the study is that PRFG treatment could accelerate the fistula closure during the 28-day treatment period. Calculation of a sample size based on the hypothesized difference between treatment arms was not possible owing to unavailability of standard deviation of 2 groups. We, therefore, decided to base this calculation on detecting the minimal, clinically relevant difference of success rates of 2 arms. From our preliminary study, it was determined that the closure rates in treatment and control group were 80% and 55%, respectively. Based on these assumptions, it was determined that 60 patients per group were needed based on alpha of 0.05 with a power of 90%. Taking into account a dropout rate of 10%, a total sample size of 140 patients would be included.

Patients. As a national referral center for gastrointestinal (GI) disorder, we served approximately 400 patients annually with various fistulas and bowel diseases transferred from community hospitals through nationwide network. The inclusion criteria of this study were patients who were present with a single tubular (tract length, >2 cm) and low-output volume ECF (<200 m1/24 h). Patients with cancer-infiltrated fistula, associated abscess, inflammatory bowel disease, foreign bodies, and distal bowel obstruction were excluded.

SOC. Medical SOC is composed of supportive measures to support the patient, including provision of adequate drainage, cutaneous protection, fluid/electrolyte balance, nutritional replacement, and bowel rest via enteral or parenteral nutrition, wound care, and antibacterial therapy in patients with signs of systemic sepsis or inflammation with pain. Nasogastric or nasointestinal feeding was provided whenever possible; otherwise, parenteral nutrition along with 0.9 g/24 h somatostatin (Stilamin, Serono, Switzerland) was infused intravenously; enteral feeding was restarted gradually when closure was achieved. To assist in remission of infection, normal saline was dripped continuously to rinse the fistula tracts; at the same time, percutaneous suction drainage of these tracts was conducted. Nursing staff monitored the daily external output by collecting output volumes.

Preparation and application of PRFG. As described previously,[17] platelet-rich cryoprecipitate and thrombin were obtained from 300 to 400 mL of whole blood of each patient enrolled in the study group. To apply the glue, the full length of the fistula tract was determined by image examination, or with assistance of endoscopy via the fistula tract (Fig 1).[18] This procedure was repeated in patients up to 3 times within 28-day PRFG treatment period. A repeat glue sealing was conducted if the fistula persisted for 5 days after the former procedure.

Clinical efficacy and safety outcome. The primary efficacy endpoint of this study was time to fistula closure, which was defined as the interval between the day of enrollment and day of closure. Closure[19] was defined as complete closure of fistula tract and internal and external openings later confirmed by contrast-enhanced computed tomography at each follow-up visit without drainage or any sign of inflammation. Secondary efficacy included closure rate up to 28 days (PRFG treatment period) and fistula recurrence.

The incidence of adverse events and serious adverse events (defined as an event that was fatal