Effectiveness of Autologous Platelet-Rich Plasma for the Healing of Ulcers after Endoscopic Submucosal Dissection

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Background/Aims: Platelet-rich plasma (PRP) has been used for wound healing in various medical fields. The aim of this study was to evaluate the clinical efficacy and safety of local PRP injections after endoscopic submucosal dissection (ESD).

Methods: Patients were non-randomly divided into the following two groups: (1) control group in which patients were administered only an intravenous proton pump inhibitor (PPI), and (2) a study group in which patients were administered an intravenous PPI and a topical PRP injection. We assessed the reduction in the ulcer area and stage of the ulcer after the procedure (24 hours, 48 hours, and 28 days after endoscopic surgery).

Results: We enrolled 7 study and 7 control patients. In the study group, the rate of ulcer reduction was 59% compared to 52% in the control group ($p=0.372$), 28 days after ESD. There were 5 patients in the S stage and 2 patients in the H stage in the study group compared to no patient in the S stage and 7 patients in the H stage in the control group ($p=0.05$), 28 days after ESD. There were no serious complications in either group.

Conclusions: The local injection of PRP is a safe and effective procedure for ulcer healing after ESD.

Key Words: Endoscopic submucosal dissection; Platelet-rich plasma; Ulcer healing

INTRODUCTION

Endoscopic submucosal dissections (ESDs) are commonly performed for early gastric cancers (EGCs) and dysplasia, and various complications, such as hemorrhage, perforation, and stenosis, have been reported after ulcer healing.1,3 ESD causes an iatrogenic ulcer in the resection area, resulting in bleeding and abdominal pain, similar to peptic ulcers. The optimum regimen and duration of treatment for ESD-induced ulcers remain poorly researched. However, recently, a proton pump inhibitor (PPI) (or H2 receptor blocker) has been administered empirically for 4–8 weeks.5,7 Several studies have been conducted using polyglycolic acid adhesives, fibrin glue, and local steroid injection to prevent post-ESD complications and stenosis after ulcer healing. However, a large-scale prospective study has not been conducted to date.8,10

Interestingly, platelets are known to be involved in gastric ulcer healing, and results from animal studies show that oral administration of platelet-rich plasma (PRP) resulted in a faster recovery of gastric ulcer wounds.11 Platelets were originally only thought to play a role in the process of blood clotting, but it has been shown that they also aid tissue regeneration and healing through the action of abundant growth factors and cytokines, such as platelet-derived growth factor-AB (PDGF-AB) or transforming growth factor beta-1.12 For instance, angiogenesis is an important process in gastric ulcer healing. Various pro-angiogenic factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor and...
PDGF, are stored in platelets. During the hemostasis phase of ulcer healing, these growth factors are produced and secreted in the new blood vessels,\textsuperscript{13-15} suggesting that they also play a role in wound healing. PRP is obtained by centrifugation of the autologous blood and contains a higher concentration of platelets than in the entire blood volume. Specifically, PRP contains more than four times the platelet concentration of normal peripheral blood.\textsuperscript{11} Currently, PRP is used in various fields such as plastic surgery, orthopedics, dermatology, and dentistry,\textsuperscript{16-25} but not in the field of gastroenterology. Thus, the aim of this study was to evaluate the clinical efficacy and safety of local PRP injections after ESD.

**MATERIALS AND METHODS**

**Study design**

This study was a non-randomized pilot study conducted from May 2017 to November 2017. Patients were divided into a control group and a study group: (1) patients in the control group only received an intravenous PPI after ESD, and (2) patients in the study group received intravenous PPI and a local PRP injection after ESD. All participants were administered a PPI intravenously for the first 3 days, followed by oral PPI administration for up to 4 weeks after the procedure.

We assessed healing of the ulcer after ESD by evaluating the ulcer size and stage. The initial ulcer size was measured by the size of the specimen after ESD. At follow-up, the ulcer size was measured by an upper gastrointestinal endoscopic probe. The Sakita and Fukutomi classification system was used to assess the ulcer stage,\textsuperscript{26} and an endoscopist scored the ulcer stage from 1 to 6 (1, 2: active ulcer [A1, 2]; 3, 4: healing ulcer [H1, 2]; 5, 6: scarring ulcer [S1, 2]).

**PRP preparation**

On the day of the procedure, 15 mL of the patient’s peripheral blood was collected and mixed with 2 mL sodium citrate. The blood was then centrifuged at 3,500 rpm for 6 minutes. Two milliliters of PRP containing a buffy were obtained and stored in a separate bottle after centrifugation (Fig. 1). After this, 1 mL of PRP without additional dilution was injected into the submucosal layer in all 4 directions around the resection site (total 4 mL) (Fig. 2).

**Patients**

Patients aged 20 to 65 years who underwent ESD for EGC and dysplasia were included in this study.

Exclusion criteria were as follows:

1. Patients who refused to provide consent for the study;
2. Severe or uncontrolled heart, lung, or mental ailments, and acute severe infections;
3. History of esophageal and stomach surgery;
4. Patients with an Eastern Cooperative Oncology Group performance status of 2 or greater;
5. Patients without adequate bone marrow function, i.e., those with an absolute neutrophil count of 1,500/mm\textsuperscript{3} and platelets <100,000/mm\textsuperscript{3};
6. Creatinine levels 1.5-times above the upper limit, in patients with inadequate renal function;
7. Aspartate transaminase and alanine aminotransferase levels 2.5 times above the normal upper limit and total bilirubin 1.5 times above the normal upper limit;
8. Clinically-proven thrombocytopenia, or platelet dysfunction;
9. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) within 48 hours prior to the procedure;
10. Use of systemic steroids within 2 weeks prior to the procedure;
Hemoglobin count <10 g/dL; and Platelet count <100,000/μL

All patients provided informed consent for the procedure. All procedures were conducted in accordance with the ethical standards of the Hospital Ethics Committee and Institutional Review Board of CHA University (approval number: CHAMC 2017-05-033).

**ESD procedure**

ESD was performed using an insulation-tipped diathermic knife (IT Knife, KD-610L; Olympus, Tokyo, Japan) and a dual knife. A VIO 300D device (ERBE, Tübingen, Germany) was used as an electrosurgical unit. A circumferential incision was made using the Endocut Q mode (effect 3, cutting duration 3, cutting interval 2). Hemostasis was performed using the SoftCoag mode (effect 6, 60 watts). Complete removal of the lesion was achieved with submucosal dissection using the swift coagulation mode (effect 3, 30 watts). The procedure duration and the number of preventive hemostasis application events, bleeding events, and perforations were recorded. After the procedure, coagulation was performed using Coagrasper forceps (FD-410LR; Olympus) or hemostatic clips (EZ-CLIP, HX-110QR; Olympus). All ESD procedures were performed by a single experienced endoscopist (JYC), who has conducted more than 400 endoscopic resections annually. JYC also performed all follow-up endoscopies.

**Study measurements**

The primary endpoint of this study was the assessment of the ulcer size and stage (Sakita classification) after endoscopic resection (28 days after endoscopic surgery), which was reported by the endoscopist who performed the ESD. We conducted a follow-up endoscopy to compare the ulcer stage and ulcer reduction rate or ratio (calculated by dividing the ulcer dimensions at 28 days after ESD by the ulcer dimensions at 24 hours after ESD) between the two groups.

Secondary endpoints included assessment of the rate of acute complications by evaluating the pain score, bleeding, perforation, and stricture after the procedure. The pain score was evaluated using the Numeric Pain Rating Scale (NRS), with a level >3 qualifying as pain. Post-ESD bleeding was defined as hemorrhage that persisted for more than 1 minute after ESD with symptoms, including included dizziness, black stool, blood loss, decrease in hemoglobin levels (by 2 g/dL or more), or a decrease in blood pressure. Post-ESD perforation was diagnosed endoscopically and/or by the presence of free air on plain radiography and/or computed tomography immediately after ESD. The presence of strictures was evaluated by symptoms (dysphagia, nausea, and vomiting) and endoscopic findings.

**Statistical analysis**

The ulcer size and stage were compared between the study and control groups using an independent t-test, Fisher's exact test, and the Mann-Whitney U test. The frequency of post-operative complications, such as bleeding, perforation, and delayed stenosis, was analyzed. Differences were considered statistically significant when \( p < 0.05 \).

**RESULTS**

In total, 14 patients were included in the study, after 4 patients were excluded for their history of esophageal and stomach surgery and taking NSAIDs within 48 hours before the procedure. We enrolled 7 patients in the study group and 7 patients in the control group. Both groups were similar in terms of sex, age, past medical histories, indications for ESD, and location of the target lesion (Table 1).

In the study group, precancerous lesions such as carcinoma or adenoma in the stomach were included. Final histopathologic findings varied from dysplasia to carcinoma in both groups. There were 3 cases of low-grade dysplasia (LGD), 1 case of high-grade dysplasia, and 3 cases with EGC in the study group. Most of the patients in the control group had LGD (6 patients) and 1 had EGC.

In the study group, the reduction in mean ulcer size 28 days after ESD was 59.71%, compared to 52.57% in the control group \( (p=0.372) \). Mean ulcer size reduction was higher in the study group, but the difference was not statistically significant (Table 2) (Fig. 3).

However, 28 days after ESD, there were 5 patients in the S stage and 2 patients in the H stage in the study group compared to no patient in the S stage and 7 patients in H stage in the control group \( (p=0.05) \) (Table 3). Scar formation after ESD was more rapid in the study group.

There were no life-threatening serious complications in either group. Two patients in the study group developed bleeding that required blood transfusions, but no one in the control group required a transfusion. Two patients were treated locally with argon plasma coagulation, due to minimal oozing at the resection site, although there was no definitive bleeding after ESD. Three patients in both groups complained of pain after ESD, ranging from 4–5 points on the NRS. There were no cases of perforation or stricture in either group.

**DISCUSSION**

Recently, ESD, which enables the *en-bloc* resection of lesions in the gastrointestinal tract with minimal invasion,\(^{27,28}\)
has gained popularity. However, iatrogenic ulcers and complications, such as significant bleeding, abdominal pain, and delayed wound-healing, are occasionally observed after resection.\(^7\) Although the mechanism for ESD-induced ulcer healing is unclear, many studies have been conducted to prevent and treat these complications, but no definitive treatment has been established to date. Antiplatelet drugs, such as aspirin and NSAIDs, which inhibit platelet function, interfere with gastric ulcer healing and hemostasis. Since angiogenesis is involved in wound healing, we were interested in the role of platelets in modulating gastric ulcer healing.\(^2\) During tissue damage, platelets aggregate to induce vascular repair. Pro-angiogenic factors, such as VEGF, fibroblast growth factor, epidermal growth factor, and PDGF, stored in the platelets, are then released and regulate wound healing by interacting with anti-angiogenic factors, such as endostatin.\(^3\)\(^-\)\(^8\) Based on this mechanism, PRP containing large amounts of platelets was used in this study for patients who underwent ESD. Additionally, PRP has already been used in various medical disciplines, such as dermatology (for acute and chronic ulcers, such as chronic refractory diabetic ulcer and venous leg ulcers), orthopedics (for muscle injury, ligament injury, tendinopathy, and other such conditions),\(^9\)\(^-\)\(^25\) neurology,\(^24\) ophthalmology,\(^35\) and dentistry.\(^36\) A meta-analysis on the use of PRP in experimentally-induced skin wounds with an animal model\(^37\) and some animal studies on the efficacy and safety of PRPs in

| Table 1. Baseline Characteristics of Patients |
|---------------------------------------------|
| Control group (n=7) | Study group (n=7) | p-value |
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| Sex, M:F | 5:2 | 7:0 | 0.462\(^a\) |
| Age, yr | 72.57±7.74 | 71.57±5.41 | 0.784\(^b\) |
| Procedure time, min | 37.14±24.47 | 42.14±25.97 | 0.717\(^b\) |
| Location of target lesion, n | 3 | 4 | 0.842\(^c\) |
| Antrum | 3 | 4 | 0.842\(^c\) |
| Angle | 1 | 1 | 0.842\(^c\) |
| Body | 3 | 2 | 0.842\(^c\) |
| Final diagnosis, n | 0.223\(^d\) |
| LGD | 6 | 3 | 0.223\(^d\) |
| HGD | 0 | 1 | 0.223\(^d\) |
| EGC | 1 | 3 | 0.223\(^d\) |
| Complication, n | 0.306\(^e\) |
| None | 5 | 2 | 0.306\(^e\) |
| Abdominal pain | 1 | 2 | 0.306\(^e\) |
| Major bleeding (required transfusion) | 0 | 2 | 0.306\(^e\) |
| Perforation | 0 | 0 | 0.306\(^e\) |
| Stenosis | 0 | 0 | 0.306\(^e\) |
| Minor bleeding | 1 | 1 | 0.306\(^e\) |

Values expressed as median±standard deviation.
EGC, early gastric cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.
\(^a\)Fisher’s exact test. \(^b\)Independent t-test (normality test : Shapiro-wilks). \(^c\)Chi-square test.

| Table 2. Ulcer Size after Endoscopic Submucosal Dissection |
|---------------------------------------------|
| Control group (n=7) | Study group (n=7) | p-value |
| Control group (n=7) | Study group (n=7) | p-value |
| Ulcer size immediately after ESD, mm | 40.57±7.41 | 32.43±7.39 | 0.062\(^a\) |
| Ulcer size after 1 mo after ESD, mm | 16.00±8.16 | 12.71±3.86 | 0.209\(^b\) |
| Reduction rate of ulcer after 1 mo of ESD, mm | 52.57±15.91 | 59.71±12.71 | 0.372\(^a\) |

Values expressed as median±standard deviation.
ESD, endoscopic submucosal dissection.
\(^a\)Independent t-test. \(^b\)Mann-Whitney test.
ESD-induced ulcer healing have been published, but PRPs have rarely been used in human studies. PRP is a minimally-processed autologous blood product obtained from one’s own body. A major advantage of PRP is that it can be prepared by centrifugation of the patient’s own blood; thus, it is safe, cost-effective, and simple. PRP can be prepared at the patient’s bedside and administered immediately. The application of PRP can vary depending on the disease condition (such as in the liquid or gel form for wounds, shielding with spray for colon ESD in animal models, submucosal injection for orthodontic purposes, submucosal injection or topical application for non-healing ulcers); however, there is no report which identifies the best method for PRP administration. We used submucosal injections of PRP as we believed this might prolong the beneficial effects and accelerate ulcer healing. However, additional studies using alternative methods are needed, and further research on the differences of each method is also required.

In our study, local PRP injection at the resection site after ESD was easy and safe, without any serious complications. There was some slight submucosal bleeding during the local injection of PRPs, but this did not require any intervention. Although the difference in the mean reduction of ulcer size was not statistically significant between the two groups, scar formation was significantly faster in the study group. Thus, the local injection of PRP could be a safe and effective method for ulcer healing after endoscopic resection. This is the first human study to show the effect of PRP on ulcer healing post-ESD.

There are some limitations in our study: (1) the ulcer size was indirectly measured using an endoscopic probe. In the control group, the size of the ulcer after resection of the lesion was approximately 1 cm, which probably influenced the healing rate. Although patients with ulcer size >2 cm were not enrolled in this study, the PRP effect was more pronounced in the study group than in the control group. Larger lesion sizes will be studied in a follow-up study; (2) intravenous and oral PPI therapy were administered in all cases; hence, it was difficult to clearly identify, the independent effect of PRP. Therefore, a study showing the effect of a local injection of PRP without intravenous PPI therapy is necessary; (3) our study had a small patient population (n=7 in each group); (4) a continuous long-term follow-up is necessary, since our study only had a 28-day follow-up period; and (5) although PRP has the advantage of being an autologous product extracted from the patient’s own blood, the preparation protocol after analyzing the PRP components and practical methods for clinical use are still unclear. The various factors associated with PRP should be analyzed and the components should be sampled to develop practical methods for PRP preparation and administration for clinical use.

In conclusion, local injection of PRP is safe and easy, and this is a promising technique for preventing post-ESD wound complications. A larger sample size and additional long-term follow-up studies are needed to establish the efficacy and safety of local PRP injection for post-ESD wound healing.

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**Table 3. Ulcer Stage at 28 Days after Endoscopic Submucosal Dissection**

|                | Control group (n=7) | Study group (n=8) | p-value |
|----------------|---------------------|-------------------|---------|
| H1, n          | 3                   | 1                 | 0.05 (*)|
| H2, n          | 4                   | 1                 |         |
| S1, n          | 0                   | 3                 |         |
| S2, n          | 0                   | 2                 |         |

*Fisher’s exact test.*
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