Prospective Study

Submucosal injection of platelet-rich plasma in endoscopic resection of large sessile lesions

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AIM

To prospectively evaluate the efficacy of submucosal injection of platelet-rich plasma (PRP) on endoscopic resection of large sessile lesions.

METHODS

Eleven patients were submitted to endoscopic mucosal resection (EMR) with prior injection of PRP obtained at the time of endoscopy. Patients were followed during 1 mo. The incidence of adverse events (delayed bleeding or perforation) and the percentage of mucosal healing (MHR) after 4 wk were registered.

RESULTS

EMR was performed in 11 lesions (46.4 mm ± 4 mm, range 40-70 mm). Delayed bleeding or perforation was not observed in any patient. Mean ulcerated area at the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
baseline was 22.7 cm$^2$ ± 11.7 cm$^2$ whereas at week 4 were 2.9 cm$^2$ ± 1.5 cm$^2$. Patients treated with PRP showed a very high MHR after 4 wk (87.5%).

**CONCLUSION**
PRP is an easy-to-obtain solution with proven and favourable biological activities that could be used in advanced endoscopic resection.

**Key words:** Platelet-rich plasma; Endoscopic mucosal resection; Submucosal injection; Large lesions

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Core tip: This was a prospective single-center study to evaluate the efficacy of submucosal injection of platelet-rich plasma (PRP) on 11 patients submitted to endoscopic resection of large lesions. PRP as lifting solution proved absence of delayed bleeding or perforation and strong healing activity.

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**INTRODUCTION**
Submucosal injection of fluid solutions is crucial to prevent of delayed perforation (DP) in advanced resection techniques, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), by avoiding deep thermal injury. The perforation rate is traditionally considered as a quality of standard practice. It has a rate of 0.03%-0.8% during diagnostic procedures and 0.15%-3% during therapeutic procedures[1]. Otherwise, delayed bleeding (DB) is a well-known and the most frequent adverse event after these resections, with an incidence of 2.6%-9.7%, not prevented by adding adrenaline to the submucosal fluid cushion or applying argon plasma coagulation, because these methods only decrease the incidence of early bleeding[2-4].

There is no scientific evidence to recommend the systematic closure of the eschars with hemostatic clips to prevent DB because they are ineffective in large mucosal defects and increase procedure costs[5].

The ideal submucosal solution should provide a sustained lift, facilitate en-bloc or oligopiecemeal resection, be inexpensive, widely available and have few adverse effects[1]. The optimal fluid to lift the lesion is still a matter of debate. Platelet-rich plasma (PRP), as autologous concentrated in plasma, has demonstrated strong healing properties as a shield over the eschars after

EMR in preclinical models[6,7], PRP solution has showed the best electrical and rheological properties to perform safety endoscopic resections[8]. Therefore, we aim to evaluate the efficacy of submucosal injection of PRP on EMR of large sessile lesions.

**MATERIALS AND METHODS**

**Subjects**
This study was registered at ClinicalTrials.gov under the identifier NCT02931149 (EndoPRP study), was conducted from August 2016 to March 2017. Subjects eligible for the study were men and women aged 18 and older who were submitted for EMR of sessile lesions larger than 35 mm. We obtained a written informed consent in all participants. The Healthcare Ethics Committee of our institution (University Hospital Germans Trias i Pujol) approved the study protocol (IRB approval PT-16-002 on July 8, 2016), and was performed in accordance with the Declaration of Helsinki.

**Study design**
This was a non-randomized prospective single-center study. We performed an expanded access study (compassionate use) of PRP outside of a clinical trial because we wanted to generate information with a small number of individual patients. Patients were allocated to receive PRP as submucosal injection of PRP prior to EMR (Figure 1). After the procedure, all patients were followed during 4 wk. EMR was performed with blended current controlled by a microprocessor (ME 402 maximum KLS martin, Tuttlingen. Germany). The device used in all patients was a circular polyfilament snare 25 mm in diameter (SnareMaster, Olympus. Tokyo). After the procedure coagulation of the base with APC was performed in all cases.

We obtained PRP with OLIN-1 kit (a single-use sterile product), that comes in both a 20 mL and 40 mL format, from a sample of patient’s blood (18-36 mL) drawn at our Endoscopy Unit prior to perform the EMR (Figure 2). Peripheral blood was centrifuged (2500 rpm/8 min at room temperature). Depending on the size of the lesions, smaller or larger than 40

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**Figure 1** Patient flow-chart. EMR: Endoscopic mucosal resection; PRP: Platelet-rich plasma.
mm, we used 18 or 36 mL of blood (1 or 2 kits). A 20-mL syringe prefilled with 2 mL acid citrate dextrose (15% vol./vol.) was used for the standardized blood draw. Syringes were centrifuged obtaining two different layers; erythrocytes (± 45% of volume) placed at the bottom, and PRP (55% vol., around 8 mL) on the top. PRP was activated with the addition of 20 mmol/L CaCl₂ just before the administration. A sample of 10 µL of blood and plasma were used to take a measurement of baseline blood platelet count and platelet count in PRP.

Assessments
The primary outcome was the assessment of the incidence of adverse events (DB or DP). Secondary objective was the evaluation of mucosal healing rate (MHR), calculated as a percentage of mucosal restoration after 1 mo. Measurement of mucosal lesion and mucosal defect was carried out as comparison with opened forceps (7 mm) or by direct measurement with the specimen before pinning the specimen. We calculated the mean ulcerated and mucosal healing rate by the use of ImageJ public software (Image Processing and Analysis in Java; https://imagej.nih.gov/ij/)(Figure 3).

Statistical analysis
Unless otherwise indicated, results are expressed as mean ± SE or proportions as required. Statistical analyses were carried out with SPSS for Windows version 14.0 (SPSS Inc., Chicago, IL, United States).

RESULTS
Patient characteristics
A total of 11 EMRs large colorectal or gastric lesions were performed in 11 patients (Table 1). There were 6 (54.5%) females and their mean age was 68.3 years (range 53 to 84 years). More than half were located in rectum or in left colon, mean basal platelet count was of 175 × 10⁹/L, whereas obtained PRP was 2 times the basal value. The mean lesion size was 46.4 mm (SD, 11.4 mm; range 40-70 mm). Oligopiecemeal technique with complete resection was reached in all cases. Histology showed absence of deep submucosal involvement in all patients.

Assessments
Patient outcomes are summarized in Table 2. DP or DB was not observed in any case. PRP does not prolong EMR time. No evidence of stricture was found during the follow-up. Mean ulcerated area at baseline was 22.7 cm² ± 11.7 cm² whereas after 4 wk was 2.9 cm² ± 1.5 cm². The percentage of mucosal healing at week 4 was of 87.5% (Figure 4).

DISCUSSION
In this prospective study, we found that submucosal injection of PRP has proven efficacy in EMR of lesions larger than 35 mm, showing strong healing activity. Otherwise, the use of a submucosal fluid cushion rich in platelets prevents the incidence of DB or DP.

EMR and ESD as resection techniques can produce adverse events, such as perforation or bleeding. Post-EMR bleeding occurs in 5%-7% lesions ≥ 20 mm, whereas perforation is an uncommon event with an
Research background
Submucosal injection of fluid solutions is crucial to prevent adverse events in endoscopic resections. Platelet-rich plasma (PRP) has demonstrated strong healing properties in preclinical models.

Research motivation
PRP solution proved excellent electrical and rheological properties to perform safety endoscopic resections. PRP could be an ideal lifting solution in therapeutic endoscopy.

Research objectives
The primary outcome was the assessment of the incidence of adverse events (delayed bleeding or delayed perforation). Secondary objective was the evaluation of mucosal healing rate (MHR), calculated as a percentage of mucosal restoration after 1 mo.

Research methods
This was a non-randomized prospective single-center study (ClinicalTrials.gov NCT02931149). Subjects eligible for the study were men and women aged 18 and older who were submitted for endoscopic resection (EMR) of sessile lesions larger than 35 mm. Patients were allocated to receive PRP as submucosal injection prior to endoscopic resection of large lesions. These data emphasize the need for continuing research in this topic.

Research results
EMR was performed in 11 lesions (46.4 mm± 4 mm, range 40-70 mm). Delayed bleeding or perforation was not observed in any patient. Mean ulcerated area at baseline was 22.7 cm^2 ± 11.7 cm^2 whereas at week 4 were 2.9 cm^2 ± 1.5 cm^2. Patients treated with PRP showed a very high MHR after 1 mo (87.5%).

Research conclusions
The new finding of this study is that PRP is lifting solution with proven and favourable biological activities that could be used as submucosal injection prior to endoscopic resection of large lesions. These findings and to perform a comparison study with other lifting solutions. PRP is an easy-to-obtain solution with proven favourable biological activities that could be applied as submucosal injection prior to endoscopic resection of large lesions. These data emphasize the need for continuing research in this topic.
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