EDITORIAL

Gut and Liver, Vol. 8, No. 5, September 2014, pp. 459-461

The Myth and Truth about the Usefulness of Second-Look Endoscopy Following Endoscopic Submucosal Resection

Hye Kang Kim and Dae Young Cheung

Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Korea

See "The Need for Second-Look Endoscopy to Prevent Delayed Bleeding after Endoscopic Submucosal Dissection for Gastric Neoplasms: A Prospective Randomized Trial" by Jong Sun Kim, et al, on page 480, Vol. 8. No. 5, 2014

We read with great interest the article "The need for second-look endoscopy to prevent delayed bleeding after endoscopic submucosal dissection for gastric neoplasms: a prospective randomized trial" by Kim *et al*.[1] The study was designed to evaluate whether the second-look endoscopy (SLE) strategy can reduce the delayed bleeding complication in patients who underwent endoscopic submucosal dissection (ESD) for gastric neoplasms. The study was well designed in prospective cohort and powered to answer the main question with a sample size of 441 patients. Study resulted in the delayed bleeding in 4.1%. The frequency of the delayed bleeding were not different between the SLE and non-SLE groups. Authors concluded that the SLE has no role in prevention of the delayed bleeding in ESD ulcers.

Endoscopic hemostasis and neutralization of intragastric acidity are the two major tactics to heal the ulcer and prevent bleeding in both peptic and ESD ulcers. However, differences exist between the ESD and peptic ulcers. In the ESD ulcers, inflammatory infiltrates on ulcer base is minimal and fibrotic scarring is scarce. Underlying vascular network and mucosal integrity around the ESD ulcers are healthy and intact. The advance of endoscopic knives, hemostatic devices, electrosurgical units and technical skills further reduce the tissue injury the area of ESD. With these factors, we can reasonably consider ESD ulcer less risky for bleeding and better for healing than peptic ulcer. The question about SLE begins here.

The intraprocedural or immediate bleeding are recognized easily and controlled promptly in in-hospital setting, but the delayed bleeding may occur in out-patients setting and need more attention. The incidence of the delayed bleeding is about 2.1% to 7.0% (Table 1).[2-7] Factors including large mucosal defect,[2] longer procedure,[3] old age,[3] high grade histology[4], low platelet count, and use of antithrombotic drugs[2] are proposed risk factors for the delayed bleeding following ESD, but the significance of these factors varies among investigators.

What can we do to reduce the delayed bleeding following ESD? The visible vessels are apt to be injured. Takizawa *et al*.[5] proved the usefulness of the post-ESD coagulation (PEC) of visible vessels on the ESD ulcer base. The delayed bleeding was more frequent in non-PEC group than PEC group, the odds ratio 2.47 (95% confidence interval, 1.27 to 4.80). Second consideration is about the SLE. The SLE can evaluate the healing condition of the ulcers and do additional hemostasis if necessary. However, there are argues about the cost and benefit of the SLE on peptic ulcers as well as the ESD ulcers.

With introduction of proton pump inhibitor (PPI), the morbidity and mortality of peptic ulcer disease has markedly decreased. Consequently, the role of routine SLE for peptic ulcer has also been on the table of debate. A meta-analysis by El Ouali *et al*.[8] reported the value of the SLE following bleeding peptic ulcer. The rebleeding rate and the need of surgery decreased to a half, but mortality was not influenced by SLE. Among the analyzed literatures, a trial using high-dose PPI did not show a benefit of SLE. When removing the two trials including patients at highest risk of rebleeding, no significant benefit attributable to SLE was noted. Another report by Imperiale and Kong[9] suggested that, if rebleeding risk is not 31% or greater, routine SLE cost highly over the benefit for bleeding peptic ulcer.

Studies of SLE on the ESD ulcer look more unfavorable (Table 2).[1,10-12] Goto *et al*.[10] reported an interesting observation that a half of patients who experienced the delayed bleeding presented

Correspondence to: Dae Young Cheung
Department of Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea College of Medicine, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea
Tel: +82-2-3779-1519, Fax: +82-2-3779-1331, E-mail: adagio@catholic.ac.kr
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl14265

Table 1. Studies and Factors Related to Delayed Bleeding Following Endoscopic Submucosal Dissection in Literatures

Author (Year)	Study design	Bleeding rate	Risk factors	Results
Takizawa *et al*. (2008)[5]	Retrospective review (n=968)	3.3% in PEC 8.5% in non-PEC	Routine coagulation of visible vessel after ESD	Non-PEC increases OR 2.47 (95% CI, 1.27–4.80)
Jang *et al*. (2009)[4]	Retrospective review (n=144)	2.1%	Histology of gastric neoplasm	OR 6.77 (95% CI, 1.83–25.04)
Okada *et al*. (2011)[6]	Retrospective review (n=582)	4.81%	Large resected specimen size	36.5±18.8 mm for bleeding group (n=28) vs 29.9±10.8 mm for nonbleeding group (n=554) (p=0.0088)
Toyokawa *et al*. (2012)[3]	Retrospective review (n=1,123)	5.0%	Older age (≥ 80 yr) and longer procedure time	Old age, OR 2.15 (95% CI, 1.18–3.90) Long procedure time, OR 1.01 (95% CI, 1.001–1.007)
Koh *et al*. (2013)[2]	Retrospective review (n=1,032)	2.7%	Large resected specimen (>40 mm) and the use of antithrombotic drugs	Large specimen, OR 3.31 (95% CI, 1.60–6.86) Oral antithrombotic drug therapy, OR 2.67 (95% CI, 1.23–5.78)
Kim *et al*. (2013)[7]	Retrospective review (n=388)	3.1%	Large resected specimen (>40 mm)	Large specimen , OR 6.20 (95% CI, 1.91–20.11)

PEC, post-endoscopic submucosal dissection coagulation; OR, odds ratio; CI, confidence interval.

Table 2. Studies about the Usefulness of Second-Look Endoscopy Following Endoscopic Submucosal Dissection

Author (Year)	Study design	Delayed bleeding rate	Risk factors	Results and remarks
Choi *et al*. (2014)[12]	Prospective observation (n=616)	8.6% in patients with high risk stigma on SLE 0.8% in patients with low risk stigma on SLE	Nausea and submucosal fibrosis predict high risk stigma in SLE	Nausea increases the OR of high risk stigma to 4.76 (95% CI, 2.39–9.43) Submucosal fibrosis to 3.91 (95% CI, 1.92–7.94)
Ryu *et al*. (2013)[11]	Prospective RCT (n=182)	11.1% in non-SLE group vs 16.2% in the SLE group (p=0.66)	No risk factor related to bleeding after ESD	No benefit of SLE
Goto *et al*. (2010)[10]	Retrospective (n=454)	5.7% in total (2.8% before SLE vs 2.5% after SLE)	The morphology of tumors (flat and depressed type)	Delayed bleeding after SLE has no predictive lesion on the time of SLE examination
Kim *et al*. (2014)[1]	Prospective RCT (n=441)	4.1% in total (2.8% in non-SLE group vs 3.6% in SLE group [p=0.787])	The proportion of large tumors (>2.0 cm) in bleeding group	No benefit of SLE

SLE, second-look endoscopy; OR, odds ratio; CI, confidence interval: RCT, randomized controlled trial; ESD, endoscopic submucosal dissection.

after SLE and bleeding risk stigmata were not recognized on SLE. Two randomized controlled studies failed to prove beneficial effect of SLE in terms of the delayed bleeding prevention.[11] Ryu *et al*.[11] reported 16.2% of the delayed bleeding in the SLE group and 11.1% in non-SLE group (p=0.66). None of the supposed factors was found to be related to the delayed bleeding. This article by Kim *et al*.[1] also concluded no benefit of SLE.

Now can we safely conclude that the SLE is not needed any more in ESD ulcer? The facts lies on that the delayed bleeding is not zero and we still have to use SLE in other way of a better cost-benefit aspect. Factors including large ulcer and old age are obscure in significance. It is unclear that SLE has benefit in patients with these factors. Kim *et al*.[1] suggested that the large tumor (>2.0 cm) is a risk factor with odds ratio of 4.47. But it is weird that they did not compare the actual size of tumor with t-test rather than to compare the proportion of the over 2.0 cm tumors with chi-square test. It is highly suspicious that authors failed to prove the significance with tumor size as delayed bleeding risk factor and they may devise a new parameter. If this suspicion is correct, we have no evidence that any factor exerts effect on the delayed bleeding in SLE study.[1,11] The Forrest classification is the most powerful predictor for rebleeding

in ulcer disease.[13] On ESD ulcers, a prospective observational investigation reported that the rebleeding rate was 8.6% in patients with high risk stigma and 0.8% with low risk stigma on SLE.[12] Choi *et al*.[12] gave valuable cues suggesting high risk stigmata on SLE. Nausea and the presence of submucosal fibrosis during ESD increased the odds ratios of high risk stigmata to 4.76 and 3.91, respectively.

Evidences tell that the routine SLE has a limited role on the prevention of the delayed bleeding, especially for ESD ulcer. The question should be changed. Not "Do we need the SLE following ESD routinely?" but "Which patient should we do SLE following ESD?" We need to find the proper indication for SLE following ESD. New trials will compare the selective SLE and non-SLE strategies. Criteria for selection may consists of large mucosal defect, longer procedure, old aged patients, high grade histology, use of antithrombotic drugs, presence of submucosal fibrosis during ESD and nausea symptom.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Kim JS, Chung MW, Chung CY, et al. The need for second-look endoscopy to prevent delayed bleeding after endoscopic submucosal dissection for gastric neoplasms: a prospective randomized trial. Gut Liver 2014;8:480-486.
2. Koh R, Hirasawa K, Yahara S, et al. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. Gastrointest Endosc 2013;78:476-483.
3. Toyokawa T, Inaba T, Omote S, et al. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. J Gastroenterol Hepatol 2012;27:907-912.
4. Jang JS, Choi SR, Qureshi W, et al. Long-term outcomes of endoscopic submucosal dissection in gastric neoplastic lesions at a single institution in South Korea. Scand J Gastroenterol 2009;44:1315-1322.
5. Takizawa K, Oda I, Gotoda T, et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection: an analysis of risk factors. Endoscopy 2008;40:179-183.
6. Okada K, Yamamoto Y, Kasuga A, et al. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. Surg Endosc 2011;25:98-107.
7. Kim SE, Kim HH, Kim JH, et al. The role of second-look endoscopy in endoscopic submucosal dissection for early gastric cancer. Turk J Gastroenterol 2013;24:218-223.
8. El Ouali S, Barkun AN, Wyse J, et al. Is routine second-look endoscopy effective after endoscopic hemostasis in acute peptic ulcer bleeding? A meta-analysis. Gastrointest Endosc 2012;76:283-292.
9. Imperiale TF, Kong N. Second-look endoscopy for bleeding peptic ulcer disease: a decision-effectiveness and cost-effectiveness analysis. J Clin Gastroenterol 2012;46:e71-e75.
10. Goto O, Fujishiro M, Kodashima S, et al. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. Gastrointest Endosc 2010;71:241-248.
11. Ryu HY, Kim JW, Kim HS, et al. Second-look endoscopy is not associated with better clinical outcomes after gastric endoscopic submucosal dissection: a prospective, randomized, clinical trial analyzed on an as-treated basis. Gastrointest Endosc 2013;78:285-294.
12. Choi CW, Kim HW, Kang DH, et al. Clinical outcomes of second-look endoscopy after gastric endoscopic submucosal dissection: predictive factors with high risks of bleeding. Surg Endosc 2014;28:2213-2220.
13. de Groot NL, van Oijen MG, Kessels K, et al. Reassessment of the predictive value of the Forrest classification for peptic ulcer rebleeding and mortality: can classification be simplified? Endoscopy 2014;46:46-52.