Routine second look endoscopy: Ineffective, costly and potentially misleading

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Despite the best medical and endoscopic efforts, some patients with nonvariceal upper gastrointestinal bleeding suffer recurrences. Because high risk stigmata (visible vessels, active bleeders and adherent clots) often persist despite apparently successful initial hemostasis and have a variable natural history, it would seem reasonable to at least consider a routine second look endoscopy. However, a review of the literature revealed six randomized trials that, in aggregate, do not support such a strategy. In fact, a second look does not appear to be effective and is associated with an increased number of procedures, treatment sessions and possibly retreatment-related complications. In addition, the cointerventions in these trials are already out of date and the potential absolute risk reductions are low when a second look is used with intravenous proton pump inhibitors and/or the application of endoscopic hemoclips or combination endoscopic therapy. Finally, the Forrest classification may provide dangerously misleading estimates of prognosis because it is being used out of context. This review critically analyzes routine second look endoscopy.

Key Words: *Endoscopic therapy; Gastroscopy; Nonvariceal upper gastrointestinal bleeding; Peptic ulcer disease*

Une endoscopie de contrôle systématique : inefficace, coûteuse et peut-être trompeuse

Malgré les plus grands efforts médicaux et endoscopiques, certains patients souffrant d'hémorragie gastro-intestinale non variqueuse présentent des récurrences. Parce que des stigmates à haut risque (vaisseaux visibles, saignées actives et caillots d'adhérence) subsistent souvent malgré une hémostase initiale en apparence réussie et qu'ils ont des antécédents naturels variables, il semblerait raisonnable d'au moins envisager une endoscopie de contrôle systématique. Cependant, une analyse bibliographique révèle que six essais aléatoires n'appuient pas, dans l'ensemble, une telle stratégie. En fait, un contrôle ne semble pas être efficace et s'associe à un plus grand nombre d'interventions, de séances de traitement et, peut-être, de complications reliées au deuxième traitement. En outre, les co-interventions utilisées dans ces essais sont déjà dépassées, et les réductions absolues et potentielles du risque sont faibles lorsque ces interventions sont les inhibiteurs de la pompe à proton par voie intraveineuse ou l'application de pinces hémostatiques endoscopiques. Enfin, la classification de Forrest comporte peut-être des évaluations dangereusement trompeuses du pronostic parce qu'elle est utilisée hors contexte. La présente analyse évalue l'endoscopie de contrôle d'un œil critique.

Despite advances in the endoscopic treatment of bleeding peptic ulcer disease, there remains a significant rebleeding rate of 10% to 20% (1,2). Adjuvant intravenous proton pump inhibitor therapy has been proven to reduce the rebleeding rate when used with successful endoscopic hemostasis (3). Endoscopic hemoclip application also appears to be effective in selected cases (4). Certainly more controversial, however, is the question of whether a routine second look endoscopy in those patients with high risk lesions, with or without additional endoscopic therapy, would further reduce that rebleeding rate.

Routine second look endoscopy is defined as an endoscopy that is performed 24 h to 48 h after the initial procedure in patients with bleeding peptic ulcer disease and initially high risk stigmata but without evidence of rebleeding, with the intention of either retreating persistent high risk stigmata or, in their absence, of considering early discharge. This does not include repeat endoscopy for other specific reasons such as: clinical signs of rebleeding; inadequate visualization at the first endoscopy (eg, a fundic blood pool); re-evaluation of a gastric ulcer to rule out malignancy or confirm healing; or to take biopsies for *Helicobacter pylori*.

Why consider a routine second look?

The rationale for second endoscopy for patients with bleeding peptic ulcer disease includes several issues:

- There is a residual rebleeding rate after medical and endoscopic therapy (1,2);
- The natural history of high risk stigmata is variable in that some disappear very quickly whereas others persist for days (5);
- Several clinical trials have used this procedure as part of their protocol for assessing effectiveness of the initial endoscopic treatment (6-11); and
- A second trial of endoscopic therapy is worthwhile in cases of clinical rebleeding (12).

Yang et al (5) studied the natural history of high risk stigmata in 34 patients with or without injection therapy. They found that, within three or four days, more than one-half of the visible vessels had converted to flat spots or clean-based ulcers, and 90% of all high risk lesions were gone by six days. The only

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type of lesion that appeared to respond to endoscopic injection therapy was the visible vessel, for which progression to a lower risk lesion was accelerated by approximately half a day. Similarly, almost all adherent clots were gone by three or four days. Because this study found that a small percentage of patients still harboured high risk stigmata at the time of planned discharge (72 h), it appears reasonable to at least consider a predischarge endoscopy.

Evidence from six randomized trials

Nonrandomized trials in this area are difficult to interpret for a few reasons. First, the residual rebleeding rate varies with the baseline clinical and endoscopic factors and the type of medical and endoscopic therapy applied. Therefore, it is difficult to confirm a reduction in this rate compared with a nonrandom or historical control group. Second, patients who undergo repeat endoscopic therapy are often those whom one is most worried about at the initial endoscopy, and have a higher residual rebleeding rate. Third, endoscopic high risk stigmata are frequently discovered at the second endoscopy and this observation is often used to justify repeat endoscopic therapy; however, the natural history of these lesions after therapy has already been applied is unknown. A randomized trial addresses the above problems, allowing known and unknown confounders to be balanced, and allows the natural history of residual high risk stigmata to be documented. Therefore, the remainder of the discussion focuses on randomized trials.

There have been six randomized trials of second look endoscopy (13-18), including two that were published in abstract form only. Of these studies, four (Table 1) showed that a routine second look endoscopy is not effective for reducing rebleeding rates or other adverse outcomes (13,15,16,18). One of the two positive studies was published only in abstract form several years ago (17). The other had a sample size of only 20 patients in each treatment arm (14).

The earliest randomized trial was published by Villanueva et al (13). A total of 104 patients was randomized, after initial injection therapy with epinephrine, to either a second procedure at 18 h to 24 h with retreatment if persistent high risk stigmata were found, or a repeat endoscopy only if there were signs of clinical rebleeding. Rebleeding rates were 21% with second look endoscopy compared with 29% in the conservative group. There was also a trend toward a higher rate of surgery in the conservative group (8% versus 15%). At the second look endoscopy, potentially treatable lesions were seen in 59% of patients, a small proportion of which were actively bleeding. Of the 11 patients who had recurrent bleeding in this group, two (18%) rebled before the date of their second endoscopy and, therefore, would not have been helped by this strategy. Another five (45%) rebled despite retreatment of their lesions and four (36%) did so despite having no high risk stigmata at the second endoscopy. In fact, the rebleeding rates in patients who underwent a second course of therapy and in those who were felt to be low risk at their second endoscopy were almost the same. One should note that the Forrest classification (19) of the appearance of bleeding peptic ulcers was neither designed nor validated for patients who had already undergone endoscopic therapy. More than 40 excess endoscopies were performed in the 52 patients randomized to the second look group, and 24 patients underwent arguably unnecessary repeat endoscopic therapy when the conservative approach appeared to be equally effective.

In a study published in abstract form in 1996, Lin et al (17) randomly assigned 115 patients to either second look endoscopy or standard care after hemostasis was achieved with epinephrine and fibrin glue. High risk stigmata were present in 42% of the second look patients at the time of the second procedure. The rebleeding rate was lower in the group receiving the routine second look (7% versus 22%). This paper has never been published as a full manuscript after nearly a decade, which should affect how much weight its results are given.

The third randomized trial by Saeed et al (14) was restricted to extremely high risk patients, in that they had high risk stigmata as well as a high Baylor bleeding score (pre-endoscopy score greater than five or postendoscopy score greater than 10). Many patients were excluded because they failed to meet the latter criteria, despite having high risk stigmata. Heater probe was the main method of hemostasis, but epinephrine was used in 50% of patients (eg, combination therapy). Forty patients were randomized to either routine second look endoscopy or conservative treatment, which were associated with rebleeding rates of 0% and 24%, respectively.

There were several concerns with the Saeed study (14). First, an extremely high proportion of active bleeders (70%) were enrolled, which makes it difficult to generalize the results to the average patient with bleeding peptic ulcer disease. Persistent high risk stigmata led to retreatment in 84% of the patients, which is a much higher proportion than in most other studies (19% to 59%) (13,16,17). Third, there was no case of early (within 24 h) rebleeding. In most other studies, approximately 20% of patients had already experienced rebleeding before the second endoscopy at 24 h (13,16). Fourth, 40% of rebleeding episodes occurred extremely late (more than 72 h after initial endoscopy), at six and 10 days, respectively. This finding is unexplained but illustrates the extremes that can occur by chance in small studies.

Rutgeerts et al (15) published the fourth study, a very large (854-patient) multicentre randomized trial that included three groups: polidocanol; fibrin glue; and daily fibrin glue injections until high risk stigmata disappeared. Recurrent bleeding occurred in 19% of the 266 patients in the fibrin glue arm and 15% of the 270 patients randomized to repeated fibrin glue injections. There were no significant differences in rates of rebleeding, surgery or death.

Apart from a negative trial published in abstract form by Ell (18), the latest randomized study was published by Messmann et al (16) in 1998. After initial treatment with epinephrine and fibrin or thrombin, 105 patients were randomized to either programmed endoscopic monitoring (second look) at 16 h to 24 h or conservative therapy, where a second endoscopy was performed only if there were clinical signs of rebleeding. Only 19% of the programmed endoscopy subjects had persistent high risk stigmata that were worth treating. There were no differences in clinical outcomes such as transfusion requirements or rates of rebleeding (21% versus 17%), surgery or mortality. Fourteen patients in the second look group rebled and, similar to the Villanueva et al study (13), 29% did so before the second endoscopy. One-half of the rebleeding episodes occurred despite a second course of endoscopic therapy and 21% of them were actually in patients considered to be at low risk at their second endoscopy. This finding again illustrates the potential danger of using the Forrest classification outside the context of the initial (pretreatment) endoscopic assessment. Early discharge or early discontinuation of intravenous proton

TABLE 1
Summary of the four full-manuscript randomized trials

		Rebleeding		Surgery		Mortality		
Study	n	Control (%)	Second look (%)	Control (%)	Second look (%)	Control (%)	Second look (%)	Comments
Villanueva et al (13)	104	29	21	15	8	4	2	18% rebled early* 59% had high risk stigmata on second scope 45% versus 36% rebleeding in high and low risk stratification on second endoscopy
Saeed et al (14)	40	24	0†	NA	NA	10	5	70% active bleeders 0% rebled early* 84% had high risk stigmata on second scope High proportion of late rebleeders (40%)
Rutgeerts et al (15)	536	19‡	15	5‡	3	5‡	4	Three-arm study of polidocanol versus fibrin glue versus repeated fibrin glue
Messmann et al (16)	105	17	21	4	6	4	6	29% rebled early* 19% had high risk stigmata on second scope 21% of bleeds were in patients with low risk at second endoscopy

**Early' implies that bleeding occurred before second look endoscopy was arranged; †P <0.05; ‡Fibrin glue arm. NA Not available*

pump inhibitors would have been detrimental to these patients.

A recent meta-analysis

Marmo et al (20) recently published a meta-analysis on this topic. Unfortunately, it is plagued by several problems. First, in the plot of odds ratios for rebleeding, the CIs for Messmann et al's study (16) are shown as not crossing 1.0, in spite of the fact that the differences in rebleeding rates in that study were clearly not significant. Second, there was significant clinical heterogeneity in patient characteristics and initial and subsequent treatment. Although statistical heterogeneity appeared to be absent, no attempt was made to correct for clinical heterogeneity (eg, no variables were assigned to each study to try to adjust for these differences). It is well known that the power of conventional tests of statistical heterogeneity is poor. Even overlooking these flaws, only a minimal difference in rebleeding was found (6.2%), with a CI of 1.3% to 11%. The upper range for the number needed to treat CI, to prevent one rebleeding episode, was 75. The meta-analysis found no differences in surgery or mortality rates.

DISCUSSION AND SUMMARY

Although it is theoretically reasonable to entertain a second look endoscopy in patients with bleeding peptic ulcers and high risk stigmata, it appears to be ineffective in randomized trials. Approximately 20% of all rebleeding episodes occur before the planned second procedure at 24 h to 48 h. In addition, persistent, high risk lesions are seen in only approximately one-half of patients who undergo repeat endoscopy; this proportion strongly depends on the timing of the second look. It is important to emphasize that 20% to 50% of rebleeding episodes occur in patients who are considered 'low risk', as determined by findings at the second endoscopy. Therefore, it may be dangerous to discharge a patient early, based on a favourable (according to the Forrest classification) endoscopic appearance. The rebleeding rate for a low risk lesion that is found one or two days after endoscopic therapy is likely to be much higher than that for the same lesion if found before therapy at the initial endoscopy (13,16).

A policy of routine second look endoscopy would lead to many unnecessary procedures that would be associated with significant excess costs and possibly additional complications, and the absence of any significant improvement in outcome. In addition, because many advances have been made since the most recent study was published in 1998, it is very difficult to apply the results to the current situation. For example, all of the studies were undertaken before intravenous proton pump inhibitors, combination endoscopic therapy or endoscopic hemoclipping were well studied (4). Because these adjuvant therapies reduce the residual rebleeding rate, the absolute benefit of a second look is likely now to be even smaller.

Only two of the six randomized studies were positive: 1) a seven-year-old abstract, still not published in full and 2) a study of 40 extremely high risk patients, mostly active bleeders with a high unexplained delayed bleeding rate. The Marmo meta-analysis (20) may have been flawed, was heavily influenced by the one small positive study in highly selected patients (14) and yet still showed only a very small benefit. It is unclear if patients presenting with active bleeding, or having other comorbid conditions that are associated with higher than usual rebleeding or mortality rates, might benefit from a second look. It is certainly difficult to widely apply the results of this small positive study (14) when Saeed himself wrote an editorial accompanying Messmanns et al's study (16) entitled "Second thoughts about second look endoscopy for ulcer bleeding?" (21).

It is clear that further research is needed, including a priori stratified blocking by rebleeding risk, the coadministration of combination endoscopic therapy and high dose intravenous proton pump inhibitor therapy. Such a study might never be undertaken because of the very small reduction of absolute risk, resulting in the requirement for a very large sample size. In the meantime, the currently available evidence does not support the routine use of second look endoscopy for nonvariceal upper gastrointestinal bleeding.

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REFERENCES

1. Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. Gastroenterology 1992;102:139-48.
2. Sacks HS, Chalmers TC, Blum AL, Berrier J, Pagano D. Endoscopic hemostasis. An effective therapy for bleeding peptic ulcers. JAMA 1990;264:494-9.
3. Lau JY, Sung JJ, Lee KK, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000;343:310-6.
4. Cipolletta L, Bianco MA, Marmo R, et al. Endoclips versus heater probe in preventing early recurrent bleeding from peptic ulcer: A prospective and randomized trial. Gastrointest Endosc 2001;53:147-51.
5. Yang CC, Shin JS, Lin XZ, Hsu PI, Chen KW, Lin CY. The natural history (fading time) of stigmata of recent hemorrhage in peptic ulcer disease. Gastrointest Endosc 1994;40:562-6.
6. Chung SC, Leung JW, Steele RJ, Crofts TJ, Li AK. Endoscopic injection of adrenaline for actively bleeding ulcers: A randomised trial. Br Med J (Clin Res Ed) 1988;296:1631-3.
7. Chung RS, Schertzer M. Pathogenesis of complications of percutaneous endoscopic gastrostomy. A lesson in surgical principles. Am Surg 1990;56:134-7.
8. Hirao M, Kobayashi T, Masuda K, et al. Endoscopic local injection of hypertonic saline-epinephrine solution to arrest hemorrhage from the upper gastrointestinal tract. Gastrointest Endosc 1985;31:313-7.
9. Chen PC, Wu CS, Liaw YF. Hemostatic effect of endoscopic local injection with hypertonic saline-epinephrine solution and pure ethanol for digestive tract bleeding. Gastrointest Endosc 1986;32:319-23.
10. Campbell K, Steele RJ. Non-steroidal anti-inflammatory drugs and complicated diverticular disease: A case-control study. Br J Surg 1991;78:190-1.
11. Steele RJ, Park KG, Crofts TJ. Adrenaline injection for endoscopic haemostasis in non-variceal upper gastrointestinal haemorrhage. Br J Surg 1991;78:477-9.
12. Lau JY, Sung JJ, Lam YH, et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. N Engl J Med 1999;340:751-6.
13. Villanueva C, Balanzo J, Torras X, Soriano G, Sainz S, Vilardell F. Value of second-look endoscopy after injection therapy for bleeding peptic ulcer: A prospective and randomized trial. Gastrointest Endosc 1994;40:34-9.
14. Saeed ZA, Cole RA, Ramirez FC, Schneider FE, Hepps KS, Graham DY. Endoscopic retreatment after successful initial hemostasis prevents ulcer rebleeding: A prospective randomized trial. Endoscopy 1996;28:288-94.
15. Rutgeerts P, Rauws E, Wara P, et al. Randomised trial of single and repeated fibrin glue compared with injection of polidocanol in treatment of bleeding peptic ulcer. Lancet 1997;350:692-6.
16. Messmann H, Schaller P, Andus T, et al. Effect of programmed endoscopic follow-up examinations on the rebleeding rate of gastric or duodenal peptic ulcers treated by injection therapy: A prospective, randomized controlled trial. Endoscopy 1998;30:583-9.
17. Lin CK, Lai KH, Lo GH, et al. The value of second-look endoscopy after endoscopic injection for bleeding peptic ulcer. Gastroenterology 1996;110:A177. (Abst)
18. Ell C, and the German Study Group. Scheduled endoscopic retreatment vs. single injection therapy in bleeding gastroduodenal ulcers: Results of a multicenter study. Gastrointest Endosc 1998;47:A883. (Abst)
19. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717-27.
20. Marmo R, Rotondano G, Bianco MA, Piscopo R, Prisco A, Cipolletta L. Outcome of endoscopic treatment for peptic ulcer bleeding: Is a second look necessary? A meta-analysis. Gastrointest Endosc 2003;57:62-7.
21. Saeed ZA. Second thoughts about second-look endoscopy for ulcer bleeding? Endoscopy 1998;30:650-2.