CLINICAL UPDATE

Updates on study findings in essential therapeutic areas of gastroenterology and hepatology

Is Combined Endoscopic Therapy Superior to Thermal Monotherapy in Patients With Actively Bleeding Peptic Ulcers?

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In high-risk peptic ulcer bleeds, combined endoscopic treatment is increasingly considered the gold standard. In the initial study, outcomes of combination therapy versus bipolar coagulation alone in these patients were compared.[1] Patients who had endoscopically confirmed bleeding peptic ulcers with active bleeds or visible vessels were randomized into two groups. The study group (n=58) received epinephrine injection followed by bipolar coagulation. The control group (n=56) was treated with bipolar coagulation alone. Outcome measures included initial hemostasis, ulcer rebleeding, surgery, transfusion, duration of stay, and mortality.

Initial hemostasis was significantly higher in the study group (P=.02; absolute risk reduction [ARR], 31.6%; 95% confidence interval [CI] 5.4–57.7). Recurrent bleeding was similar in the two groups, although slightly more common with gold probe alone in the subgroup of active bleeders. Transfusion requirements were greater in the control group (P=.006). There was no difference in duration of hospital stay, rate of need for surgical intervention, or rate of mortality between the two groups.

In cases of severe peptic ulcer hemorrhage, treatment with combined injection and bipolar coagulation achieved significantly higher rates of initial hemostasis in patients with active bleeding, whereas all other outcome measures were similar with either treatment in patients with nonbleeding stigmata.

Study Update

Since the publication of the original article, an algorithm of treatment has been developed within our institution, according to which all patients presenting with an actively bleeding peptic ulcer

at emergency endoscopy are treated with a combination of epinephrine injection followed by bipolar coaptation using the Injector-Gold Probe (Microvasive). Conversely, all patients with a nonbleeding stigmata (ie, a nonbleeding visible vessel or adherent clot) are treated with either thermal or mechanical monotherapy. Thermal monotherapy is delivered by means of heater probe, gold probe, or argon plasma coagulator, at the discretion of the operator.

In a 6-month period, 13 additional patients with active arterial bleeding were treated with combination therapy and prospectively evaluated for major endpoints. In accordance with the trial findings, initial hemostasis was achieved in all patients (100%) and recurrent bleeding was recorded in one patient (7.7%) with a deep ulcer on the lesser curve of the stomach who was successfully treated with surgery. In the same period, 35 patients were admitted for upper gastrointestinal bleeding due to peptic ulcer disease and were endoscopically shown to have a nonbleeding visible vessel or an adherent clot at the ulcer base. Of these, 21 were treated with thermal monotherapy and 14 with the application of hemoclips. In the subgroup of patients treated with thermal therapy, the recurrent bleeding rate was 9.5% (2 of 21). Endoscopic re-treatment was successful in both rebleeders, avoiding the need for surgical exploration, though one patient with chronic obstructive pulmonary disease ultimately died of respiratory failure.

Comment

Endoscopic treatment reduces morbidity and mortality in patients with severe peptic ulcer bleeding and is significantly better than conservative management for the control of active bleeding and prevention of recurrent hemorrhage.[2-4]

Accurate prediction of those patients likely to respond negatively to endoscopic hemostasis would aid suitable placement and subsequent management of patients after endoscopy, possibly including early semi-elective surgery. The presence of active spurting activity at the time of endoscopy is an independent risk factor for recurrent bleeding (odds ratio [OR], 4.81).[5] This holds true after injection monotherapy, which incurs a 6-fold increase in the risk of rebleeding after treatment (OR, 6.48),[6] as well as after combinaton therapy with epinephrine injection plus heater probe, although with this combination the increased risk of therapeutic failure is somewhat lessened (OR, 1.65).[7]

Research in endoscopic therapy over nearly two decades has allowed for the evolution of techniques, to the point where primary hemostasis in over 95% of patients with actively bleeding peptic ulcers is expected. In the most experienced centers, recurrent bleeding occurs in 4–10% of these patients and 5–10% die.[5] Many treatment methods have been investigated, both alone and in combination, but statistically significant differences are difficult to demonstrate due to low event rates and inadequate study sizes. Moreover, few studies report outcomes of endotherapy as subgroup analyses, thus preventing the possibility of assessing whether there is a markedly more efficacious method of endoscopic treatment in extreme–high-risk patients.

According to current evidence, injection monotherapy is no longer considered sufficient, regardless of the injected drug. Injection monotherapy should only be used as a preliminary step prior to definitive thermal treatment in a sequential protocol.[8] Thermal monotherapy has been reported to be more effective than injection therapy alone for the prevention of further hemorrhage in patients with actively bleeding ulcers,[9] with no differences between contact and noncontact devices.[10]

The rationale for combination therapies is to further improve the results obtained with individual treatments. A recent meta-analysis provided evidence that, compared to injection therapy alone, combination therapy is more effective. The addition of a second endoscopic treatment following epinephrine injection improved outcomes in high-risk bleeding ulcers, reducing recurrent bleeding (OR, 0.53), need for emergency surgery (OR, 0.64), and mortality (OR, 0.51).[11] In this combined endoscopic approach, contact and noncontact probes,[12] as well as smaller (7 French) and larger (10 French) probes,[13] seem to be absolutely equivalent.

Given the higher initial efficacy of thermal methods, the therapeutic gain of combined therapy over thermal monotherapy may be less relevant. Data from the Center for Ulcer Research and Hemostasis (CURE) at the University of California Los Angeles yielded significantly higher rates of initial hemostasis with combination therapy as compared to bipolar coagulation alone only in patients with active arterial bleeding. However, for high-risk patients and nonbleeding stigmata, outcomes were similar with either treatment.[14,15]

In a randomized trial from Scotland, the combination of coaptive coagulation plus injection of thrombin did not confer any additional benefit over coaptation alone, independent of the presence of a bleeding or nonbleeding stigmata.[16] Thermal coagulation was so effective that the presence of an active bleed made no difference, suggesting that an actively bleeding stigmata plays a role in predicting the ultimate outcome mainly in the use of endoscopic approaches other than coaptive coagulation.

The presently discussed study[1] was specifically designed to test the hypothesis of a difference in outcome between thermal contact monotherapy and combined treatment. Results show a beneficial effect of combined

therapy in achieving primary hemostasis in the subgroup of active bleeders (ARR, 31.6%; 3 treated patients needed to achieve therapeutic effect). As for recurrent bleeding, both treatments showed equal efficacy. There was a trend toward a lower rebleeding rate in the dual-therapy arm in the subgroup of patients who initially had an actively bleeding ulcer. Actual values were small but an 18% difference is clinically relevant and did not reach statistical significance likely due to a beta error (ie, the study may have been underpowered for such a subanalysis). No significant difference was found between the two treatment groups in terms of the need for surgery or rate of mortality.

Cost analysis of the various therapeutic methods would be of interest, but data are scant. The incremental cost of epinephrine injection is not high because the drug is relatively inexpensive. However, cost analyses must include recurrent bleeding, further endoscopic or surgical treatments, and related prolonged hospital stay. If combination therapy provides greater efficacy in active bleeds, and the addition of injection therapy is inexpensive, it could be argued that combination therapy is the best course in nonbleeding patients with any stigmata beyond a clean ulcer base as well.

We strongly advise against such overtreatment because the safety of any procedure (and costs of related negative outcomes) should be taken into account. Injection therapy is safe as long as diluted epinephrine (even at high doses) is used, but other agents (ie, ethanol or sclerosants), present a higher risk. Therefore, if there is no evidence of any clinical advantage and complications may arise from such a choice, a widespread policy of combined injection and thermal endoscopic hemostasis therapies in nonbleeders is not necessarily a sensible choice. In these patients, thermal monotherapy is the best treatment option and every endoscopist should become proficient in at least one method of thermal coagulation.

In conclusion, active arterial spurting in endoscopy is an independent predictor of poor outcomes. Spurting bleeds may therefore represent a subgroup of patients most likely to benefit from the application of combined endoscopic therapies. In such patients, combination of epinephrine injection with a thermal method is superior to thermal therapy alone in achieving initial hemostasis. No significant difference was found for other relevant outcome measures (recurrent bleeding, need for surgery, mortality) but further adequately powered studies are necessary to clarify this issue.

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