Intravenous proton-pump inhibitor for acute peptic ulcer bleeding – is profound acid suppression beneficial to reduce the risk of rebleeding?

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ABSTRACT

Objective: to compare two regimens of pantoprazole administered intravenously in patients with ulcerative gastrointestinal bleeding (UGB), and a high risk of presenting with persistent or recurrent hemorrhage.

Material and method: patients were randomized into two groups: group 0 - treatment with a 80 mg bolus of pantoprazole administered intravenously, followed by continuous infusion of 8 mg/h for 72 hours; group 1 - treatment with 40 mg of pantoprazole administered intravenously on a daily basis. The percentage of hemorrhagic persistence/recurrence in both groups was analyzed, as were transfusion requirements, need for surgery, and mortality resulting from the hemorrhagic episode.

Results: there were 20 patients in group 0 and 21 in group 1. No differences were found between groups in terms of gender, age, smoking habits, use of NSAIDs, presence of hemodynamic instability or stigmata in ulcer crater (Forrest Ia: 5 vs. 14.3%, p = 0.322; Forrest Ib: 30 vs. 33.3%, p = 0.819; Forrest Ila: 60 vs. 50.1%, p = 0.753). In group 0, 90% of patients received endoscopic treatment, versus 100% in group 1, p = 0.232. In group 0, 50% of patients had a transfusion, as compared to 52.4% in group 1, p = 0.879. In group 0, 2 patients (10.5%) presented with recurrent hemorrhage, versus 3 patients (14.3%) in group 1. Surgery was required by 1 person from each group, and 1 patient in group 0 died.

Conclusions: maximum acid inhibition with a bolus and a then a continuous infusion of pantoprazole does not yield better results than treatment with conventional doses in acute hemorrhagic episodes.

Key words: Digestive haemorrhage. Proton pump inhibitors. Pantoprazole. Peptic ulcer.

RESUMEN

Objetivo: comparar dos pautas de pantoprazol por vía intravenosa en pacientes con hemorragia digestiva alta (HDA) ulcerosa de alto riesgo para presentar persistencia o recidiva hemorrágica.

Material y método: se randomizaron los pacientes en dos grupos: grupo 0: tratamiento con bolo de 80 mg i.v. de pantoprazol y perfusión continua a 8 mg/h durante 72 horas; grupo 1: tratamiento con 40 mg i.v. de pantoprazol diarios. Se analizó el porcentaje de persistencia/recidiva hemorrágica entre ambos grupos, requerimientos transfusionales, necesidad de cirugía y mortalidad del episodio hemorrágico.

Resultados: se incluyeron 20 pacientes en el grupo 0 y 21 en el grupo 1. No se encontraron diferencias entre ambos grupos en cuanto al sexo, edad, hábito tabáquico, consumo de AINE, presencia de inestabilidad hemodinámica, estigma sobre el nicho ulceroso (Forrest Ia 5 vs. 14.3%, p = 0.322; Forrest Ib 30 vs. 33.3%, p = 0.819; Forrest Ila 60 vs. 50.1%, p = 0.753). El 90% de los pacientes del grupo 0 recibió tratamiento endoscópico vs. el 100% del grupo 1, p = 0.232. El 50% de los pacientes del grupo 0 recibió transfusión vs. el 52.4% del grupo 1, p = 0.879. Dos pacientes (10.5%) del grupo 0 presentaron recidiva hemorrágica vs. 3 pacientes (14.3%) del grupo 1, precisando cirugía 1 paciente de cada grupo y falleciendo 1 paciente del grupo 0.

Conclusiones: la inhibición ácida máxima de la secreción ácida gástrica mediante bolo e infusión continua de pantoprazol no ofrece resultados superiores al tratamiento con dosis convencionales en el episodio hemorrágico agudo.

Palabras clave: Hemorragia digestiva. Inhibidores de la bomba de protones. Pantoprazol. Úlcera péptica.

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INTRODUCTION

Gastrointestinal hemorrhage caused by peptic ulcer is still one of the most prevalent digestive episodes requir-
ing emergency treatment. The use of proton-pump inhibitors (PPIs) is the therapy of choice (1) as it reduces the risk of rebleeding as a result of the profound acid suppression this therapy achieves (2).

But whereas the efficacy of endoscopic therapy in the treatment of ulcerative gastrointestinal bleeding has been clearly and consistently proven by clinical trials (3), the clinical efficacy of PPIs remains controversial and the data so far available are not definite as regards the optimal regimen and dose for this type of patients (4). Moreover, different results have been reported for different geographical locations (5).

The objective of the present paper is to analyze whether profound acid suppression by means of bolus and continuous infusion of pantoprazole is more effective than conventional therapy for the treatment of ulcerative gastrointestinal hemorrhage in patients showing endoscopic evidence for rebleeding risk.

MATERIAL AND METHODS

We carried out a prospective, randomized study of consecutive patients with ulcerative gastrointestinal hemorrhage admitted to the Bleeding Unit of University Hospital Virgen del Rocío in Seville. The following information was collected: age, sex, smoking habits, use of NSAIDs, baseline disease (6) (diseases that may increase the morbidity of hemorrhagic episodes), presence of hemodynamic instability (whenever two or more of the following criteria were met: systolic arterial pressure < 100 mm Hg, cardiac output > 100 bpm, signs of peripheral hypoperfusion, alterations in arterial pressure or cardiac output following orthostatism), stigmata in ulcer craters according to Forrest’s classification, and endoscopic therapy employed in cases of active hemorrhage, visible vessel with unstable clot. Patients were randomly assigned to two groups: Group 0 who received an 80 mg intravenous bolus of pantoprazole and continuous infusion of 8 mg/h for 72 h, thus achieving a profound acid suppression, and Group 1, who were administered 40 mg of intravenous pantoprazole for 72 h. Within 24-48 h after admission a new endoscopy was performed, and therapy was repeated if the stigmata of rebleeding risk persisted. The percentage of hemorrhagic persistence/recurrence was analyzed in both groups, as were transfusion requirements, need for surgery, and mortality resulting from the hemorrhagic episode. Patients gave their informed consent before their inclusion in the study.

Statistical analysis

We analyzed both quantitative and qualitative variables, which were expressed as mean or percentage, respectively. Student’s t-test was used to compare quantitative variables and the Chi-squared test to analyze qualitative ones. A multivariate logistic regression analysis was employed to study factors associated to persistence/recurrence of the hemorrhagic episode. A p value < 0.05 was considered statistically significant.

RESULTS

Table I shows the baseline characteristics of patients. As we can observe, both groups coincide regarding age, sex, baseline disease, smoking habits, use of NSAIDs, presence of hemodynamic instability, and Forrest’s classification of initial endoscopy performed on admission. Endoscopic therapy was used in 90% of patients in Group 0 compared to 100% of patients in Group 1 (p = 0.232). This therapy consisted of an injection of diluted adrenaline (1:10000) and 2% polydocanol. An early follow-up endoscopy revealed ulcers with a clean fibrinous base or flat hematine stains in all patients; as a result none of them required a new treatment. Table II shows the evolution of patients where we can see no differences between both groups as regards transfusion requirements, rebleeding, necessity for surgery, or mortality.

A multivariate logistic regression analysis did not reveal risk factors associated with hemorrhagic recurrence, including the two different pantoprazole regimens administered to patients.

| Table I. Characteristics of the patients included in this study (n = 41) |
|-------------------------|-------------------------|----------|
| Group 0 (n = 20) | Group 1 (n = 21) | p       |
| Age (years) | 60.05 ± 16.75 | 60.67 ± 13.34 | 0.892* |
| Sex (% males) | 80 | 85 | 0.471** |
| Smoking habits (% ) | 55 | 45 | 0.654** |
| Smoking habits (% ) | 35 | 65 | 0.085** |
| Use of NSAIDs (% ) | 50 | 76.2 | 0.082** |
| Baseline disease (% ) | 42.1 | 47.6 | 0.726** |
| Forrest Ia ( % ) | 5 | 14.3 | 0.322** |
| Forrest Ib ( % ) | 30 | 33.3 | 0.819** |
| Forrest IIa ( % ) | 60 | 50.1 | 0.753** |

*Student’s T test. **Chi-squared test.

| Table II. Evolution of patients included in the sample (n = 41) |
|-------------------------|-------------------------|----------|
| Group 0 (n = 20) | Group 1 (n = 21) | p       |
| Transfusion requirements (%) | 50 | 52.4 | 0.879* |
| Rebleeding (n) | 2 | 3 | 0.549* |
| Need for surgery (n) | 1 | 1 | 0.731* |
| Mortality (n) | 1 | 0 | 0.475* |

*Chi-squared test.
DISCUSSION

The use of PPI therapy without endoscopic hemostasis has not proved effective to stop bleeding or prevent recurrence in patients with upper gastrointestinal hemorrhage caused by peptic ulcer (7). Yet, the introduction of endoscopic therapy for the treatment of ulcerative upper gastrointestinal bleeding is considered the most significant advance in the management of these patients, highly superior to drug therapy. Nevertheless, in vitro studies have shown that a sustained intragastric pH > 6 should be accompanied by an improvement in the hemostatic mechanisms of bleeding ulcers (8). Thus, continuous intravenous infusion of omeprazole and pantoprazole achieves a pH > 6 for more than 90% of the administration period (9), which is also true for the oral administration of these drugs, according to a recent report (10).

However, although PPIs have proved more effective than other drugs in the management of these patients due to the profound acid suppression they achieve, the most important meta-analyses and systematic reviews have revealed some results which do not agree on the optimal therapeutic regimen of PPIs. For instance, in one study, patients with ulcerative upper gastrointestinal hemorrhage who had undergone endoscopic therapy were randomized to receive a placebo substance or an 80 mg intravenous bolus of omeprazole followed by the intravenous infusion of 8 mg/h for three days. The group of patients receiving omeprazole showed a rebleeding recurrence rate of 4.2 vs. 20% in the placebo group (11). Nevertheless, a recent systematic review of 24 randomized controlled trials including 4,373 patients, carried out to evaluate the efficacy of PPIs in the management of ulcerative hemorrhage, concludes that no differences are observed as regards mortality between the control group and the group of patients receiving PPIs, but when PPI patients were compared with placebo patients, hemorrhage recurrence rates and necessity for surgery did diminish significantly. Yet, the need for surgery was similar in the PPI group and in the group of patients treated with histamine type-2 receptor antagonists. Also, it has been proved that the results obtained are independent of both the administration mode and the different PPI regimens used (12). Another study with a similar methodology confirms once again that the use of PPI therapy does not determine such clinically relevant outcomes as mortality, rebleeding, or need of surgery, although it shows that PPI therapy prior to endoscopy in patients with ulcerative upper gastrointestinal hemorrhage remarkably reduces the number of patients with endoscopic stigmata of recent bleeding and hemorrhage risk (13).

As our institution has an assistant digestive physician on call, all patients attending our hospital with an episode of acute gastrointestinal hemorrhage undergo emergency endoscopy (within less than 6 h), and endoscopic therapy is applied whenever required. In the present study, a new endoscopy was systematically performed after 24-48 hrs of the initial endoscopy, which is known as an endoscopic “second-look”, in order to detect lesions with a high risk of rebleeding and to apply a second endoscopic treatment, which has proved to reduce the risk of recurrent hemorrhage (14). The results of this endoscopic “second look” do not reveal any significant differences when comparing patients treated with PPIs with patients receiving conventional therapy in order to achieve profound acid suppression, which has significant cost-saving implications. Despite the results of the aforementioned in vitro studies, our results may be explained by the fact that the caliber of any artery inducing a high risk for hemorrhage ranges between 1.5 and 3.4 mm vs. 0.1-1.8 mm for mild and controlled hemorrages, which means that it may be necessary to employ a physical method, more important than any drug therapy for acid suppression, in order to stop hemorrhage and prevent its recurrence in this type of lesions (15).

Therefore, patients with ulcerative gastrointestinal hemorrhage require individualized therapy adapted to each environment and particular healthcare facility. However, in those cases in which early and effective endoscopic therapy could be applied (16), the use of PPIs at maximum doses does not seem to have obtained better results than therapy with conventional doses.

Apart from the results of the present study, some recent reports denounce the high prevalence of inadequate PPI use, and recommend a more reasonable use of these medications to provide patients with more effective care and to avoid side effects and interactions with other drugs (17).

REFERENCES