

Giant Peptic Ulcer Hemorrhages: Epidemiology, Treatment, and Outcome in the Teaching Hospital of Tartu

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Key words: giant peptic ulcer; hemorrhage; epidemiology; treatment; outcome.

Summary. The aim of the study was to analyze the management and outcome in the case of giant peptic ulcer hemorrhage (GPUH).

Material and Methods. We analyzed the data of all 372 cases of 348 patients treated for acute peptic ulcer hemorrhage during 2005–2007. The source and intensity of hemorrhage was assessed endoscopically according to the Forrest classification: class I+II, persistent hemorrhage or signs of recent hemorrhage; and class III, ulcer without signs of recent hemorrhage. Of the 372 cases, 64 (17%) were GPUH (diameter, ≥ 2 cm) (group 1) and the remaining 308 (83%) were peptic ulcer hemorrhages of a standard size (SPUH) (diameter, < 2 cm), which formed the control group (group 2).

Results. Forrest class I+II hemorrhage occurred significantly more frequently in the group 1 as compared with the group 2 (97% [62/64] vs. 77% [238/308]), as well as endoscopic hemostasis, (80% [51/64] vs. 57% [175/308]), repeat hemostasis procedures (22% [11/51] vs 6.3% [11/175]), and operative treatment (27.6% [16/58] vs 1.7% [5/290]) were needed more frequently in the group 1. No postoperative in-hospital deaths occurred in either group. Five patients died: 2 (3.4% [2/58]) in the group 1 and 3 (1.0% [3/290]) in the group 2.

Conclusions. GPUHs were more intensive as compared with SPUHs and needed more endoscopic hemostasis, including repeat procedures and operative treatment. Endoscopic hemostasis and operative treatment allowed reducing mortality due to GPUH to 3.4%.

Introduction

Despite the introduction of effective medical treatment of peptic ulcer disease, hemorrhage remains the most frequent complication with in-hospital or 30-day mortality reaching 10% (1–4). Previous data show that patients with giant ulcers compared to those with ulcers of a standard size are at higher risk of developing life-threatening complications including hemorrhage (4, 5) and poorer outcome (6, 7). Therefore, studies on the management of giant peptic ulcer hemorrhage (GPUH) should be considered essential, so much the more as such research has not been undertaken earlier in this area. The aim of the present study was to analyze epidemiology, treatment strategies, including operative treatment, and outcome in the case of GPUH.

Material and Methods

We assessed the data of 348 patients (372 cases) aged ≥ 15 years, treated for acute peptic ulcer hemorrhage (PUH) in the Clinic of Surgery, Tartu University Hospital, during 3 years (2005–2007). The data were gathered from the electronic database, endoscopy records, and autopsy records. The medical records of all patients were evaluated to determine their characteristics and outcome. Endoscopic diag-

nostics and endoscopic treatment of alimentary tract hemorrhages is the responsibility of four experienced general surgeons of the Clinic of Surgery, and this kind of 24-hour medical care has been provided since 1988. In the present study, all patients underwent endoscopy within the first 24 hours after admission. As a rule, before endoscopic investigation, a single dose of 40 mg of a proton pump inhibitor (PPI) was administered, and after the procedure, it was administered continuously at a dosage of 40–80 mg per day. Ulcer hemorrhages were classified as gastric ulcer hemorrhage (GUH) and duodenal ulcer hemorrhage (DUH) (prepyloric, pyloric, and duodenal bulb ulcers) as described elsewhere (8). GPUH was defined as hemorrhage from an ulcer with a diameter of 2 cm or more. Ulcer size was estimated at endoscopy using biopsy forceps or on the basis of operative findings or autopsy as described in previous studies (9). Of the 372 cases, 64 cases (58 patients) were GPUH (group 1) and the remaining 308 cases (290 patients) were SPUH (ulcer less than 2 cm in diameter) forming the control group (group 2). The intensity of hemorrhage was assessed endoscopically according to the Forrest classification: class I, ulcer with persistent hemorrhage; class II, ulcer with signs of recent hemorrhage; and class III,

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ulcer without signs of recent hemorrhage. To stop hemorrhage, the injection method was used in endoscopic treatment: a combination of adrenalin and ethanol in half of the cases, ethanol in one-third of the cases, and adrenalin in the remaining cases. The choice of the injection method depended on endoscopic findings and state of the patient as well as on individual preferences of the endoscopists. Any information or data about drug use potentially associated with poor outcome of bleeding (nonsteroidal anti-inflammatory drugs, low-dose or high-dose aspirin, systemic corticosteroids, vitamin K antagonists) were obtained from medical records.

Statistical analysis was conducted using the software Statistica 8.0. Continuous variables are presented as mean (SD), and categorical variables are presented as percentages (%). Data were analyzed using the unpaired *t* test or the nonparametric Mann-Whitney *U* test; categorical data were analyzed using the Fischer exact test. A value of $P \leq 0.05$ was considered to indicate statistical difference; all *P* values were two-sided.

Results

The data in Table show that GPUH (group 1) accounts for 17% ($n=64$) of the 372 cases. At the same time, the mean age of the patients in the group 1 was somewhat higher compared with the mean age of the patients in the group 2 (65.4 [SD, 14.5] vs. 61.4 [SD, 17.0] years), and the proportion of patients older than 65 years was larger (54% vs. 48%, not significant).

The use of drugs associated with peptic ulcer

bleeding was nonsignificantly higher in the group 1 compared with the group 2 (61% [39/64] vs. 50% [155/308] of the cases). At the same time, among the patients in the group 1 who had been repeatedly hospitalized for hemorrhage, the rate of drug usage was significantly higher accounting for 73%.

In the group 1, GUH occurred significantly more frequently compared with the group 2 (69% [44/64] vs. 33% [103/308]), as well as Forrest class I+II hemorrhages (97% [62/64] vs. 77% [238/308]). Endoscopic hemostasis was used significantly more frequently in the group 1 as compared with the group 2 (80% [51/64] vs. 57% [175/308]), the same as repeated hemostasis procedures (22% [11/51] vs. 6.3% [11/175]). Endoscopic treatment was proved to be ineffective more frequently in the group 1 as compared with the group 2: 25.5% (13/51) and 2.3% (4/175) of the cases, respectively ($P < 0.001$). At the same time, there was no significant difference in the ineffectiveness of endoscopic hemostasis comparing all three different injection methods. The need for blood transfusion was higher in the group 1 than group 2 (91% of cases [58/64] vs. 74% [228/308]) as well as the number of doses of blood transfusion (median of 6 doses vs. 4 doses).

In the groups 1 and 2, 16 (27.6%) of the 58 patients and 5 (1.7%) of the 290 patients, respectively, underwent surgery without postoperative in-hospital death cases in either group. In the group 1 among 16 patients, the indications for surgery were ineffective conservative and endoscopic treatment in 13 cases and early elective surgical treatment for preventing recurrent hemorrhage in hospital in 3 cases. Among

Table. Data of the 372 cases of peptic ulcer hemorrhage

Characteristic	Group 1 N=64	Group 2 N=308	<i>P</i> value
Males	39 (61)	207 (67)	0.31
Age, mean (SD), years	65.4 (14.5)	61.2 (17.0)	0.08
Age ≥ 65 years	35 (55)	148 (48)	0.28
DRU	39 (61)	155 (50)	0.10
GUH	44 (69)	103 (33)	<0.0001
DUH	20 (31)	205 (67)	<0.0001
Forrest I+II*	62 (97)	238 (77)	<0.0001
Endoscopic treatment	51 (80)	175 (57)	0.0004
including repeat endoscopic treatment	11 (22)	11 (6.3)	0.002
Blood transfusion	58 (91)	228 (74)	0.0006
Blood transfusion doses, median	6	4	0.0004
Surgical treatment (% of patients)	16/58** (27.6)	5/290** (1.7)	<0.0001
Postoperative death	0	0	
Death (% of patients)	2/58** (3.4)	3/290** (1.0)	0.11

Values are number (percentage) unless otherwise indicated. Group 1, giant peptic ulcer hemorrhage; group 2, standard size peptic ulcer hemorrhage.

DRU, drug use potentially associated with poor outcome of hemorrhage; GUH, gastric ulcer hemorrhage; DUH, duodenal ulcer hemorrhage.

*Forrest class I+II, Forrest I (persistent hemorrhage) + Forrest II (signs of recent hemorrhage).

**Number of patients.

5 patients of the group 2, the same indications were for 4 cases and 1 case, respectively. In the group 1, 8 (20%) of the 39 GUH patients were operated on: 7 patients underwent Billroth type I gastric resection, and oversewing of the bleeding vessels in the ulcer base was performed in 1 patient. In the group 2, 8 (42%) of the 19 DUH patients underwent the following surgical procedures due to a giant ulcer in the duodenal posterior wall penetrating into the pancreas: oversewing of the bleeding vessels and exteriorization of the ulcer base with duodenal bulb resection (3 cases) or antrectomy (3 cases), both methods combined with vagotomy, and oversewing of the bleeding vessels in the giant ulcer base (2 cases). In one of these cases, recurrent hemorrhage developed, which was stopped using angiographic embolization.

In the group 2, 5 patients were operated on: 2 GUH patients underwent ulcer suturation, and definitive operations were performed in 3 DUH patients (Billroth type I gastric resection; ulcer excision + pyloroplasty and vagotomy; and antrectomy + vagotomy).

Table shows that although mortality was somewhat higher in the group 1 than group 2 (3.4% and 1%, respectively), this difference was not statistically significant. Death occurred in 5 patients; 4 of them had undergone endoscopic treatment. In the group 1, 2 GUH patients, aged 74 and 89 years, who were considered inoperable due to concomitant severe diseases, died. In the group 2, death occurred in 3 patients: one 69-year-old patient died in the intensive care unit 30 minutes after admission due to hemorrhage (autopsy revealed GUH); the other two patients, aged 62 and 84 years, died of brain infarction and worsening cardiovascular insufficiency (hemorrhage caused by DUH and GUH, respectively, was stopped endoscopically).

Discussion

According to our data, GPUH was found in 17% of the study cases, and it occurred significantly more often in men than women (61% vs. 39%), the percentages being similar with those of SPUH cases.

Previous data have shown that admission rates for PUH increase among the elderly (10), and time trends demonstrate a continuous increase in the proportion of the elderly (11).

In our study, the mean age of GPUH patients was 65 years, and those older than 65 years account for more than half of the cases, i.e., 55%, which was somewhat but not significantly higher as compared with the mean age of SPUH patients.

It is known that the incidence of PUH shows a declining trend in younger subjects but is increasing in the elderly, primarily in users of nonsteroidal anti-inflammatory drugs (12, 13) and anticoagulant

agents (14, 15). According to our data, the drug use potentially associated with poor outcome of hemorrhage was somewhat but not significantly higher among GPUH patients compared with SPUH patients, accounting for 61% of the cases. However, it was as high as 73% among the GPUH patients who had been repeatedly hospitalized for hemorrhage, which is consistent with recent data (16).

In our study, the cause of GPUH was GUH in 69% of the cases and DUH in 31% of the cases. The situation is significantly different for SPUH groups where DUH is clearly more predominant accounting for 67% of the cases.

In previous studies focusing on treatment of both uncomplicated giant ulcers and giant ulcers complicated with hemorrhages, giant gastric ulcers predominated, which occurred in slightly more than half of the cases (9).

Our study shows that treatment of GPUH is much more complicated than treatment of SPUH in several aspects. In GPUH, higher-risk Forrest class I+II hemorrhage occurred in 97% of the cases, while endoscopic treatment was required in 80% of the cases, and repeated endoscopic hemostasis procedures were required in 22% of the cases. These figures were significantly higher than those characterizing SPUH. Also, in GPUH, blood transfusions were needed more often, i.e., in 91% of the cases, and the number of doses of blood transfusion was significantly higher in GPUH compared with SPUH. In the management of PUH, we used proton pump inhibitors in combination with endoscopic treatment, which significantly reduces the in-hospital risk of recurrent hemorrhage as shown previously (17). However, despite the use of such a strategy, in GPUH, 22% of the cases in our study required repeat endoscopic treatment, while in SPUH, the corresponding percentage was as low as 6%. Repeat endoscopic treatment is considered highly important in the case of Forrest class I+II hemorrhages (18). The most common cause of the failure of endoscopic hemostasis is the difficulty to access the lesion for injections: extensive scarring due to ulcer, presence of a giant ulcer, particularly duodenal posterior wall ulcer (19, 20), as well as other factors like hypotension and concomitant diseases. Previous data have also shown that the failure of endoscopic treatment occurs more frequently in DUH cases than GUH cases (46% vs. 7%) (21) and likewise more frequently in cases of giant DUH than smaller DUH. Our study confirms such findings as an indication for surgical treatment as the failure of endoscopic therapy was significantly more frequent in the case of giant DUH than giant GUH.

The failure of endoscopic and conservative therapy is the main indication for surgical treatment. At present, the need for surgical treatment in PUH

ranges from 5% to 10% of cases irrespective of ulcer size (22, 23). However, there are no data about the modern treatment of PUH, including endoscopic treatment, based on the analysis of the effectiveness and outcome of treatment of GPUH versus SPUH. According to our data, endoscopic treatment was proved to be ineffective in 25.5% of the GPUH cases (in only 2.3% of the SPUH cases), which was also the main indication for surgical treatment. In a few cases (3 GPUH patients and 1 SPUH patient), we applied the so-called early elective surgery in patients at high risk of rebleeding, according to recommendations (24). Namely, early surgical therapy for preventing rebleeding reduces mortality (25).

In 27% of the GPUH patients, we used operative treatment successfully with no in-hospital deaths. It should be noted here that in our study, the need for operative treatment was twice as high in giant DUH than in giant GUH. The reason for this is significantly more complicated endoscopic treatment of posterior wall ulcer penetrating into the pancreas in giant DUH and consequent scarring, which leads to recurrent hemorrhage and poor treatment outcome (26), compared with giant GUH.

In the case of PUH, the type of emergency surgery to be undertaken is controversial and related to the type and severity of the pathology, the condition and risk factors of the patients, and experience of the operator. In the literature, more centers prefer nondefinitive methods such as oversewing or ulcer excision alone (27–29). Other authors advocate a definitive approach, vagotomy and pyloroplasty or partial gastrectomy (30).

Our data clearly show that in the case of both giant and smaller ulcer hemorrhage, we used, as a rule, definitive operations and considered removal of the source of hemorrhage as an important step.

As it is known that in GUH, gastric resection results in significantly fewer recurrent hemorrhages compared with oversewing (31, 32), we employed Billroth type I gastric resection in 7 of the 8 giant GUH cases and oversewing of the bleeding vessel at the ulcer base in only one case. At the same time, it should be kept in mind that although medical therapy of benign giant gastric ulcers is often effective (33), the duration of such therapy is usually much longer than it is in the case of standard size ulcers and it requires clinical and endoscopy-based follow-up to ensure healing (9). Surgical therapy in the case of DUH varies from oversewing to acid-reducing procedures (34): in the United States, vagotomy was employed in 45% of DUH cases in 2003 (35). However, it is known that in the case of DUH, oversewing of ulcer results in early recurrent hemorrhages in 3% to 20% of cases as well as in high mortality (36). The current literature on surgical

management of acute DUH lacks reports on prospective randomized trials on the outcome of non-definitive versus definitive surgery, moreover, those involving giant DUH cases. Surgical management of massive giant DUH, where ulcer is localized in the posterior duodenal bulb wall and has pancreatic penetration, as was also the case with our study patients, is complicated.

Our findings demonstrate that the best solution in such cases is to employ the methods introduced by us in 1984: ulcer base-exteriorizing operations consisting of duodenal bulb resection with pyloroplasty or antrectomy, both combined with vagotomy according to Helwing or Herfarth (37, 38) in our modification (39). In the present study, this method was used as the method of choice in 6 of the 8 cases without postoperative in-hospital mortality or recurrent hemorrhage. The use of this method can be justified also owing to our previous pioneer study of long-term outcome where it yielded 90% of excellent and good results according to Visick, 11 years after operation (39). Oversewing of the giant duodenal ulcer in one patient of the two resulted in early life-threatening postoperative hemorrhage, the stopping of which with repeat endoscopic procedures failed in our study. Yet, success was achieved with angiographic embolization. It is possible that in the case of failed endoscopic treatment as well as in patients at high surgical risk, angiographic embolization is an alternative method to stop bleeding in giant DUH as described elsewhere (40, 41).

Of the GPUH patients, 2 died (in-hospital mortality, 3.4%) as inoperable due to concomitant severe diseases; in the group of SPUH, death occurred in three patients (in-hospital mortality, 1%). These results demonstrate that endoscopic treatment and strategy and methods of surgical treatment used by us allow reducing in-hospital mortality due to GPUH hemorrhages to 3.4%, which is not significantly different from in-hospital mortality due to SPUH hemorrhages.

Conclusions

Our study shows that compared to peptic ulcer hemorrhages of a standard size, giant ulcer hemorrhages occurred more frequently in the stomach than duodenum and were more complicated; hemorrhage was more intensive and needs more endoscopic hemostasis including repeat procedures. In the case of giant duodenal ulcer hemorrhage, operative treatment was required twice as frequently as in the case of giant gastric ulcer hemorrhage. Endoscopic hemostasis combined with medical and operative treatment, provided by a dedicated team, allowed reducing mortality due to giant peptic ulcer hemorrhage to 3.4%.

Kraujavimas iš gigantiškos pepsinės opos: epidemiologija, gydymas ir pasekmės Tartu universiteto klinikose

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Raktažodžiai: kraujavimas iš gigantiškos pepsinės opos, epidemiologija, gydymas, pasekmės.

Santrauka. *Tyrimo tikslas.* Išanalizuoti kraujavimo iš gigantiškos pepsinės opos kontrolę ir pasekmes.

Tyrimo medžiaga ir metodai. Išanalizavome 348 pacientų, gydytų 2005–2007 m. nuo ūminės pepsinės opos, 372 kraujavimo atvejų duomenis. Kraujavimo šaltinis ir jo intensyvumas įvertintas endoskopiškai pagal Forrest skalę: I+II – pastovus kraujavimas arba neseniai įvykusio kraujavimo požymiai; III – opa be neseniai įvykusio kraujavimo požymių. Iš 372 atvejų 64 atvejais (17 proc.) nustatyta kraujuojanti gigantiška pepsinė opa (skersmuo ≥ 2 cm) (I grupė), o kitais 308 atvejais (83 proc.), kurie sudarė kontrolinę grupę, buvo rastas mažesnės kraujuojančios opos (skersmuo < 2 cm) (II grupė).

Rezultatai. Palyginus I grupę su II grupe, Forrest I+II kraujavimas rastas žymiai dažniau, 97 proc. (62/64) palyginus su 77 proc. (238/308), kai buvo naudota endoskopinė hemostazė – 80 proc. (51/64), palyginus su 57 proc. (175/308), pakartotinės hemostazės procedūros – 22 proc. (11/51), palyginus su 6,3 proc. (11/175), ir chirurginis gydymas, 27,6 proc. (16/58) palyginus su 1,7 proc. (5/290) be pooperacinių hospitalinės mirties atvejų kiekvienoje grupėje. Penki konservatyviai gydyti pacientai mirė: 2 (3,4 proc. (2/58)) iš I grupės ir 3 (1,0 proc. (3/290)) iš II grupės.

Išvados. Gigantiškų pepsinių opų kraujavimas, palyginus su kraujavimu iš mažesnių pepsinių opų, yra intensyvesnis ir prireikia daugiau endoskopinių hemostazių, įskaitant pakartotines procedūras ir chirurginį gydymą. Endoskopinė hemostazė derinama su medikamentiniu ir chirurginiu gydymu su sąlyga, kad tam yra numatyta speciali komanda ir galima sumažinti kraujavimo iš gigantiškos pepsinės opos letališkumą iki 3,4 proc.

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