ELSEVIER

Journal of the Neurological Sciences 239 (2005) 5 – 10

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

A randomized placebo controlled trial of ranitidine versus sucralfate in patients with spontaneous intracerebral hemorrhage for prevention of gastric hemorrhage

U.K. Misra [a,*], J. Kalita [a], S. Pandey [a], S.K. Mandal [b], M. Srivastava [b]

[a] *Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, PGIMS, LKO Raebareily Road, Lucknow 226014, India*
[b] *Department of Biostatistics, Central Drug Research Institute, LKO, India*

Received 20 September 2004; received in revised form 8 July 2005; accepted 10 July 2005
Available online 22 September 2005

Abstract

Aim: Due of paucity of studies on stress ulcer prophylaxis in intracerebral hemorrhage (ICH), we have evaluated the usefulness of ranitidine and sucralfate in preventing gastric hemorrhage (GH) in patients with ICH.
Subjects and methods: In a hospital-based randomized placebo-controlled study, patients with CT-proven ICH within 7 days of ictus were randomized into ranitidine 50 mg i.v. eight hourly, sucralfate 1 g six hourly and placebo groups. Patients were conservatively managed. Primary endpoint was occurrence of GH within 15 days of ictus and secondary endpoint 1-month mortality.
Results: The mean age of the patients was 57.2 (range 25–90) years and 40 were females. There were 45 patients in ranitidine, 49 in sucralfate and 47 in placebo group. Demographic, clinical and radiological features were not significantly different in 3 groups. GH occurred in 11 (23.4%) patients in placebo, 5 (11.1%) in ranitidine and 7 (14.3%) in sucralfate group, which was not significant. Only one female had GH. There were 13 (27.7%) deaths in placebo, 5 (11.1%) in ranitidine and 12 (24.5%) in sucralfate group. Pneumonia occurred in placebo group in 5 (10.6%), ranitidine in 2 (4.4%) and sucralfate in 5 (10.2%) patients, which was not significantly different.
Conclusion: Ranitidine and sucralfate do not seem to significantly prevent GH or reduce 1-month mortality.

Keywords: Stroke; ICH; Gastric hemorrhage; Malena; Hematemesis; Sucralfate; Ranitidine; Stress ulcer; Randomized control trial

1. Introduction

Stress ulcers are common in neurology and neurosurgical practice. Depending on the severity of illness and co-morbidity, their frequency has widely ranged between 0.1% and 54% [1,2]. In stroke patients, the incidence is quite variable. In a study on 16,612 stroke patients, 17 had GH of whom 14 had infarction and 3 ICH [2]. In a prospective study on GH in 612 stroke patients, the incidence of GH was 3% [3]. These studies included a mixed population of ischemic and hemorrhagic strokes. This difference in incidence in GH in stroke could be attributed to the difference in the severity of illness, associated morbidity and therapy. Intracerebral hemorrhage may be associated with higher incidence and greater severity of GH because of associated acute rise in intracranial pressure, which may result in excessive cholinergic activity leading to gastric erosion [4]. In our earlier study, 30% ICH patients had GH [5]. In another study, the ICH patients with GH had higher mortality compared to those without GH [1]. The therapy and prevention of the stress ulcers is controversial. A meta-analysis has revealed beneficial results in favor of prophylaxis but most large randomized controlled trials do not conclusively support the use of antacid, H2 receptor blockers, proton pump inhibitors (PPI) and sucralfate [6,7]. In ICH, there is no randomized controlled trial evaluating

* Corresponding author. Fax: +91 0522 2668017.
E-mail addresses: ukmisra@sgpgi.ac.in, drukmisra@rediffmail.com (U.K. Misra).

0022-510X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2005.07.011

the role of H2 receptor blockers or sucralfate in preventing GH. We therefore report the results of a randomized placebo-controlled trial of ranitidine and sucralfate in preventing GH in patients with ICH.

2. Subjects and methods

Patients with CT-proven ICH within 7 days of ictus were included. The patients with arteriovenous malformation, aneurysmal bleed, bleeding and coagulation disorders, hepatic and renal failure, history of peptic ulcer and those on antiplatelet and anticoagulation therapy were excluded.

2.1. Evaluation and therapy

The consciousness was assessed by Glasgow coma scale (GCS) and severity of stroke by Canadian Neurological Stroke (CNS) scale [8]. The presence of hyperventilation, pupillary asymmetry, decerebration, decortication and motor signs on the nonhemiplegic side was recorded and considered as a surrogate marker of raised intracranial tension. The presence of cranial nerve palsy, muscle power, tone and reflexes was noted and sense of joint position and pinprick were assessed in them who could cooperate for these tests. The presence of pneumonia and septicemia during the hospital stay was noted. The diagnosis of septicemia or systemic inflammatory response syndrome was based on at least two of the following: (1) temperature more than 38 °C or below 36 °C, (2) heart rate above 90/min, (3) respiration more than 24/min, (4) leucocyte count more than 12,000/mm [3] or below 4000/mm [3] or more than 10% band forms [9]. Hemoglobin, leucocyte counts, hematocrit, serum chemistry, prothombin time and activated partial thromboplastin time, radiograph of chest and ECG were carried out in all the patients. Plain CT scan was obtained on a spiral CT scanner taking 10 mm axial sections parallel to orbitomeatal line. The location, size and ventricular extension of hematoma and midline shift were noted. The size of hematoma was calculated as $A \times B \times C/2$ where A refers to the largest diameter of hematoma in centimeters, B refers to diameter in centimeters at right angle to A and C refers to number of slices showing parenchymal hemorrhage. The hematoma was classified into small (<20 ml), medium (20–40 ml) and large (>40 ml) [10]. The patients were managed conservatively receiving about 2000 calories, 2–2.5 L fluids and antihypertensive medications to maintain BP below 180/110 mm of Hg. Temperature was kept below 38 °C by paracetamol injection and cold sponging. Hyperglycemia was managed by soluble insulin maintaining blood sugar below 160 mg/dl. Phenytoin or carbamazepine was used to control seizures. All the patients were managed in the general ward and none of them was on ventilator. The patients were randomized using computer-generated random table number into 3 groups: (1) ranitidine group receiving ranitidine 50 mg eight hourly i.v.; (2) sucralfate group receiving 1 g six hourly p.o. and (3) placebo group receiving placebo solution. To prevent bias, randomization was done by one investigator (JK) and evaluation by another (SP) who was unaware about the treatment arm. The blinding was done by giving placebo injection (saline) or solution (starch).

Primary outcome was occurrence of gastric hemorrhages (gross blood, coffee ground aspirate from nasogastric tube, hematemesis or malena) [2] during 15 days of ictus. Secondary end point was 1-month mortality. If the patient developed GH in the placebo group, he was again randomized to one of the treatment options, i.e. ranitidine or sucralfate. If patients on therapy developed GH, he was given a combination of ranitidine and sucralfate. The project was duly approved by the local ethics committee. Informed consent was obtained from the patients or their immediate relatives if they were unconscious, aphasic or uncooperative.

2.2. Statistical analysis

The therapy has been considered significantly effective if there was 20% reduction in GH and based on this, sample size was calculated to be 40 patients in each group. The group comparison was done by Z test of proportion and various categorical variables were evaluated by χ^2 test. Interim analysis was planned after recruiting 60 patients. The study was planned to be terminated if there was significant benefit or serious side effects.

3. Results

During 2001 and 2003, 176 patients with ICH were recruited; 35 of whom were excluded because of late admission or GH at presentation (23), anticoagulant bleed (6), peptic ulcer (3) and lack of consent (3). Our results are therefore based on 141 patients. The age ranged between 25 and 90 (mean 57.2) years and 40 were females. Eighty-five patients were admitted within 48 h, 32 between 48 h and 5 days and 24 after 5 days. The delay in admission was due to late referral. The mean admission GCS score was 9.8 (range 3–15) and mean CNS score was 3.1 (range 2–9). The clinical features of raised intracranial pressure were present in 36 patients, which included hyperventilation in 34, pupillary asymmetry in 5 and decerebration in 3 patients. The location of hematoma was thalamic in 26, putaminal in 85, lobar in 10, caudate in 6 and cerebellar in 9 patients. The remaining 5 patients had brainstem and another 2 had primary intraventricular hemorrhage. The hematoma was large in 32, medium in 46 and small in 63 patients. Midline shift on CT scan was present in 61 and the hematoma extended into the ventricular system in 71 patients. One patient each in study and control group was not available for follow up; therefore, they have been excluded from