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Synopsis

Study Code: D1843R00056
Study Report Version: 2.0 Version Date: 14 Dec 2016

Study title:

China Survey of Stress Ulcer Bleeding in Critically Ill Neurosurgical Patients

Participating sites:

12 sites across Chinese mainland.

Study duration:

12 months

Date of Fist Subject Enrolled: 28 Jan 2015

Date of Last Subject Last Visit: 27 Jul 2015

Objective:

(1) Primary objective: To estimate the overall incidence of upper gastrointestinal (GI) bleeding in critically ill neurosurgical patients in China.

(2) Secondary objectives:

- To estimate the incidence of upper GI bleeding with clinically significant complications in critically ill neurosurgical patients in China.
- To estimate the incidence of any overt upper GI bleeding without clinically significant complications in critically ill neurosurgical patients in China.
- To assess time to upper GI bleeding after a cerebral lesion.
- To investigate potential risk factors associated with upper GI bleeding, and assess how common certain risk factors occurred in upper GI bleeding patients.
- To assess the overall incidence of upper GI bleeding in critically ill patients by different risk factors for upper GI bleeding.
- To investigate the drugs, the route of administration, the doses and the duration commonly used for stress ulcer prophylaxis.
- To investigate the proportion of ICU patients with nasogastric tube, and the duration of nasogastric tube.

Study design：

A Multicenter, Retrospective, Observational Study

Inclusion criteria：

The subject population included in the non-interventional study were the consecutive discharged patients≥18 years old who were hospitalized to Neurosurgical departments. Those whose GlasgowComa Scale (GCS) ≤10 within 24 hours of lesion/admission were defined as critically ill patients. Three kinds of cases included: brain trauma critically ill patients, cerebral haemorrhage critically ill patients or postoperative brain tumour critically ill patients.

Exclusion criteria：

Subjects were ineligible if they had below conditions:

1) Those who were likely to swallow blood (for example, those with severe facial trauma or epistaxis;
2) Patients with previous total gastrectomy;
3) Known upper GI lesions that might bleed (e.g., varices, polyps, tumours, etc);
4) Evidence of active GI bleeding including oesophageal and gastric variceal bleeding, Peptic Ulcer Disease (PUD).

Number of subjects：

1468 subjects were screened from 45391 patients who were hospitalized to Neurosurgical departments at the beginning, and finally 1416 subjects enrolled were included in FAS according to the data integrity.

Efficacy variables：

Not applicable.

Safety variable：

Not applicable.

Efficacy assessment criteria：

Not applicable.

Statistical methods：

For continuous data, descriptive statistics was presented as number of patients (n), mean, standard deviation (SD), median, minimum and maximum. For categorical data, the frequency and percentage of patients in each category were presented. Counts that were zero were displayed as “0”. Percentages were based on non-missing data unless otherwise

specified. The incidence of overall (any overt upper GI bleeding with or without clinically significant complications) bleeding, overt bleeding with clinically significant complications, and overt bleeding without clinically significant complications, respectively, up to 14 days after lesion, were estimated using Kaplan-Meier survival methodology. Cox proportional hazard model was employed to investigate the impact of risk factors on the occurrence of upper GI bleeding.

Results：

Primary objective

The primary objective of this NIS was to estimate the overall incidence of upper GI bleeding in critically ill neurosurgical patients in China. Among 1416 subjects, there were 182 subjects presented with upper GI bleeding in critical ill neurosurgical patients during the first 14 days after the cerebral lesion, the incidence of upper GI bleeding was 12.9%.

Secondary objective

1) **Upper GI bleeding with clinical significant complications in critically ill neurosurgical patients during the first 14 days after cerebral lesion:** Among 1416 subjects, 10 subjects had experienced upper GI bleeding with clinical significant complications in critically ill neurosurgical patients during the first 14 days after cerebral lesion and the incidence was 0.7%.

2) **Upper GI bleeding without clinical significant complications in critically ill neurosurgical patients during the first 14 days after cerebral lesion:** Among 1416 subjects, 171 subjects had experienced upper GI bleeding without critical significant complications in critically ill neurosurgical patients within the first 14 days after cerebral lesion and the incidence was 12.1%.

3) **Time to upper GI bleeding after cerebral lesion:** The average time to upper GI bleeding after cerebral lesion was 2.9 ±3.37 days, the median was 1 day. The average time to upper GI bleeding after cerebral lesion of brain trauma patients was 3.6±3.79 days, the median was 2 days. The average time to upper GI bleeding after cerebral lesion of cerebral haemorrhage patients was 2.6±3.26 days, the median was 1 day. The average time to upper GI bleeding after cerebral lesion of brain tumour patients was 4.4±3.89 days, the median was 3 days.

4) **Risks factors associated with upper GI bleeding and the most common risk factors for upper GI bleeding:** Among all the 19 risks factors: mechanical ventilation over 48

hours, GI ulcer or upper GI bleedind history and administration of anticoagulants or anti-platelet drugs (heparin, warfarin, aspirin, clopidogrel) were the relatively important factors, patients with these three risk factors had a higher risk of developing an upper GI bleeding.

5) The overall incidence of upper GI bleeding of critically ill patients with different risk factors:

Mechanical ventilation over 48 hours, GI ulcer or upper GI bleeding history and administration of anticoagulants or anti-platelet drugs were the relatively important factors. The following are the overall incidence of upper GI bleeding in patients with these three risk:

The overall incidence of upper GI bleeding was 59/ 265(22.3%) in critically ill neurosurgical patients in which mechanical ventilation was used at least 48 hours; The overall incidence of upper GI bleeding was 123/1151(10.7%) in critically ill neurosurgical patients otherwise.

The overall incidence of upper GI bleeding was 2/2(100.0%) in critically ill neurosurgical patients with GI ulcer or upper GI bleeding history; The overall incidence of upper GI bleeding was 180/1414 (12.7%) in critically ill neurosurgical patients without GI ulcer and upper GI bleeding history.

The overall incidence of upper GI bleeding was 49/194 (25.3%) in critically ill neurosurgical patients in which anticoagulants or anti-platelet drugs were administrated; The overall incidence of upper GI bleeding was 133/1222(10.9%) in critically ill neurosurgical patients in which anticoagulants or anti-platelet drugs were not administrated.

6) Commonly used stress ulcer prevention drug types, route and dose of administration, and course of treatment:

In In this study, the most commonly used stress ulcer prophylactic drug was acid-related drugs and hemostatic drugs. 1119 (79.0%) subjects received acid-related drug for stress ulcer prophylaxis. 574 (40.5%) subjects received hemostatic drugs for stress ulcer prophylaxis. 539 (38.1%) subjects received both acid-related drugs and hemostatic drugs for stress ulcer prophylaxis.

To summarize the acid-related drugs used for stress ulcer prophylaxis in subject ended without bleeding: the most commonly used drugs were esomeprazole, omeprazole, pantoprazole and lansoprazole, most of these drugs were administered through injection. Among subjects who ended without bleeding and received acid-related drugs for stress ulcer prophylaxis, 434 subjects (42.5%) received esomeprazole, the mean duration of esomeprazole was 4.7±5.24 days, and the mean dosage was 40.5 ± 5.83mg; 339 subjects (33.2%) received omeprazole, the mean duration of omeprazole was 6.4±6.35 days, and the mean dosage was 40.8±8.3mg; 298subjects (29.2%) received pantoprazole, the mean duration of pantoprazole was 8.2±8.07 days, and the mean dosage was 53.4±18.86mg; 106 subjects (10.4%) received lansoprazole, the mean duration of lansoprazole was 6.3±5.92 days, and the mean dosage was 31.0±5.4mg.

To summarize the acid-related drugs used for stress ulcer prophylaxis by subjects with bleeding: the most commonly used drugs were esomeprazole, omeprazole, pantoprazole and lansoprazole as well, most of these drugs were administered through injection. Among subjects who ended with bleeding and received acid-related drugs for stress ulcer prophylaxis, 37 subjects (38.1%) received pantoprazole, the mean duration of pantoprazole was 5.7±3.53 days, and the mean dosage was 48.0±16.18mg; 31 subjects (32.0%) received omeprazole, the mean duration of omeprazole was 4.9±3.10 days, and the mean dosage was 41.8±7.69mg; 26 subjects (26.8%) received esomeprazole, the mean duration of esomeprazole was 4.9±2.97 days, and the mean dosage was 40.0±0.00mg; 13 subjects (13.4%) received lansoprazole, the mean duration of lansoprazole was 5.5±3.10 days, and the mean dosage was 30.0±0.00mg.

To summarize the hemostatic drugs used for stress ulcer prophylaxis in subject ended without bleeding: the most commonly used drugs were haemocoagulase, etamsylate, aminomethylbenzoic, most of these drugs were administered through injection. Among subjects who ended without bleeding and received the hemostatic drugs for stress ulcer prophylaxis, 271 subjects (50.2%) received etamsylate, the mean duration of etamsylate was 1.9±1.51 days; 254 subjects (47.0%) received aminomethylbenzoic, the mean duration of aminomethylbenzoic was 1.9±1.50 days; 384 subjects (71.1%) received haemocoagulase, the mean duration of haemocoagulase was 2.0±1.71 days.

To summarize the hemostatic drugs used for stress ulcer prophylaxis in subject ended with bleeding: the most commonly used drugs were haemocoagulase, etamsylate, aminomethylbenzoic, most of these drugs were administered through injection. Among subjects who ended with bleeding and received thehemostatic drugs for stress ulcer prophylaxis, 16 subjects (47.1%) received etamsylate, the mean duration of etamsylate

was 4.6±3.76 days; 15 subjects (44.1%) received aminomethylbenzoic injection, the mean duration of aminomethylbenzoic injection was 4.2±3.59 days; 21 subjects (61.8%) received haemocoagulase, the mean duration of haemocoagulase was 6.2±4.00 days; 9 subjects (26.5%) received aminomethylbenzoic (oral), the mean duration of aminomethylbenzoic (oral) was 5.0±1.66 days.

7) **The proportion of ICU patients with nasogastric tube, and the duration of nasogastric tube:**
Among 1416 subjects, 1060 subjects (74.9%) received nasogastric tube with an average of 11.8±13.25 days.

8) **Effect on upper GI haemorrhage rate of acid-related drug and hemostatic drug:**

In patients who used neither acid-related drugs nor hemostatic drugs for prophylaxis (18.5%, 262/1416), the haemorrhage rate was 31.3% (82/262); however, in patients used both acid-related drugs and hemostatic drugs for prophylaxis (38.1%, 539/1416), the haemorrhage rate decreased dramatically to 5.8% (31/539).

In patients who received acid-related drug only (41.0%, 580/1416), the haemorrhage rate was 11.4% (66/580); in patients who received acid-related drug with or without hemostatic drug (79.0%, 1119/1416), the haemorrhage rate decreased to 8.7% (97/1119).

In patients who received hemostatic drug only (2.5%, 35/1416), the haemorrhage rate was 8.6% (3/35); in patients who received hemostatic drug with or without acid-related drug (40.5%, 574/1416), the haemorrhage rate decreased to 5.9% (34/574).

9) **Effect on upper GI haemorrhage rate of PPI and hemostatic drug:**

In patients who received PPI only (34.0%, 481/1416) for prophylaxis, the haemorrhage rate was 12.7% (61/481); in patients who received PPI with or without hemostatic drug (37.6%, 532/1416), the haemorrhage rate decreased to 5.8% (31/532).

10) **Effect on upper GI haemorrhage rate of different PPIs:**

Compared with other PPIs, esomeprazole was used more frequently and more effective for upper GI bleeding prophylaxis. The order of PPIs according to the haemorrhage rate after preventive medication from low to high was esomeprazole (6.8%, 24/353),

omeprazole (10.4%, 24/230), pantoprazole (14.6%, 26/178), and then lansoprazole (18.0%, 9/50). The haemorrhage rate of patients used esomeprazole for prophylaxis was lower than the haemorrhage rate of patients used acid-related drugs (including PPI and H2RA) for prophylaxis (8.7%).

11) **Effect on upper GI haemorrhage rate of different hemostatic drugs:**

In patients only used haemocoagulase for prophylaxis (180/1416), the haemorrhage rate was 5.6% (10/180); in patients used haemocoagulase and etamsylate for prophylaxis (17/1416), the haemorrhage rate even increased a little to 5.9% (1/17), and in patients used haemocoagulase, etamsylate and aminomethylbenzoic (208/1416), the haemorrhage rate decreased a little to 4.8% (10/208). The haemorrhage rate of patients used etamsylate and aminomethylbenzoic for prophylaxis was 8.2% (5/61).

12) **Haemorrhage rate in patients used different dosage of PPI for prophylaxis:**

In patients used PPI for prophylaxis, the haemorrhage rate in standard dose group and in large dose group was respectively 8.4% (35/418) and 9.6% (57/595), indicating that larger dose of PPI didn’t decrease the haemorrhage rate more.