A revised risk analysis of stress ulcers in burn patients receiving ulcer prophylaxis

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Objective Most of the literature about Curling's ulcer was published from 1960 through 1980. Therefore, an updated study of Curling's ulcer is needed. We analyzed the risk factors affecting ulcer incidence in burn patients.

Methods We retrospectively analyzed the medical records of burn patients who were admitted to two burn centers. We collected information about the general characteristics of patients, burn area size, abbreviated burn severity index, whether surgery was performed, endoscopy results, and the total body surface area (TBSA). We performed a multivariate regression analysis predicting development of Curling's ulcer.

Results In total, 135 patients (mean age, 49.5±13.5 years) underwent endoscopy. Endoscopy revealed ulcer in 51 patients: 36 (70.6%) with gastric ulcers, 9 (17.6%) with duodenal ulcers, and 6 (11.8%) with both ulcer types. Burn area, burn depth, epigastric pain, melena, intensive care unit admission, burn area >20% of TBSA, and undergoing surgery for the burn were significantly different between the ulcer and non-ulcer groups. Multivariate analysis showed two independent factors significantly associated with ulcer: epigastric pain (odds ratio [OR]: 4.55, 95% confidence interval [CI]: 1.74 to 11.90), major burn (TBSA > 20%)(OR: 4.31 ,95% CI: 1.34 to 13.85).

Conclusion For burn patients, presence of epigastric pain and major burn with TBSA > 20% showed significant association with ulcer development.

Keywords Burns; Stomach ulcer; Duodenal ulcer

Capsule Summary

What is already known
Burn size and preexisting sepsis have been related to the development of Curling's ulcer. Most of the literature about Curling's ulcer was published from 1960 through 1980, and since then, only a few articles about this topic have been written.

What is new in the current study
Our study provides fundamental and updated data about ulcers in burn patients. We retrospectively analyzed 135 patients with burns who underwent endoscopy. The rate of ulcer was higher in patients who had burn area >20% of total body surface area. The rate of ulcer was also higher in patients with epigastric pain.

INTRODUCTION

Erosive gastric mucosal changes or ulceration with bleeding can result from shock, sepsis, massive burns, severe trauma, or head injury. Generally, stress-induced ulcers are most commonly observed in the acid-producing portions (fundus and body) of the stomach. Elevated gastric acid secretion as well as mucosal ischemia and breakdown of normal protective barriers of the stomach play an important role in the pathogenesis of ulcers.[1]

In 1823, Swan was the first to recognize the relationship between cutaneous thermal injury and gastrointestinal (GI) mucosal damage in a patient with severe burns.[2] In 1842, Curling reported acute duodenal ulcers (subsequently known as Curling's ulcers) in 10 patients who had severe burns.[3] Burn injuries increase the risk of GI mucosal damage and ulceration. Burn shock leads to splanchnic hypoperfusion and gastric mucosal ischemia, which causes mucosal atrophy, decreased capacity to neutralize hydrogen ions, and impaired mucosal healing. These alterations cause mucosal ulceration.[4]

In a study of 323 burn patients, Pruitt et al.[5] suggested that burn size and preexisting sepsis were related to the development of Curling's ulcer. According to their report, the incidence of Curling's ulcer amounted to 40% in burn patients with burns covering 70% of total body surface area (TBSA). Ulcer prophylaxis with histamine-2 (H2)-receptor blockers and early enteral nutrition has dramatically reduced the incidence of Curling's ulcer in recent decades.[6,7] Therefore, the question arises how often Curling's ulcers occur in burn patients under ulcer prophylaxis. Furthermore, how often do ulcers with life-threatening bleeding occur? Most of the literature about Curling's ulcer was published from 1960 through 1980, and since then, only a few articles about this topic have been written.[8] Therefore, more updated evidence is needed. Subsequently, we reviewed the medical records of burn patients who underwent endoscopy for suspected ulcers, with an aim to provide basic epidemiologic data about Curling's ulcer compared with data from previous studies and analyze the risk factors affecting the incidence of this type of ulcer.

METHODS

Study design and population

This study was performed after obtaining the permission of the Institutional Review Board. We conducted a retrospective analysis of the medical records of burn patients who were admitted to two burn centers from January 2009 to December 2014. Both burn centers were designated as specialized burn centers by the Korean Ministry of Health and Welfare and have approximately 120 beds each. According to the data of the National Health Insurance Ser-

vice and Korea Workers' Compensation and Welfare Service, our burn centers treat approximately 25% of burn patients in Korea.

Patients who were admitted for plastic and reconstruction surgery or had a history of chronic peptic ulcer disease were excluded. We obtained the general characteristics of patients, burn area, burn depth, type of burn, details about intensive care unit (ICU) admissions, application of ventilation, abbreviated burn severity index (ABSI), whether surgery was completed, number of surgeries, results of endoscopy, and the numbers of patients whose burn area was > 20% of TBSA and > 30% of TBSA.

All enrolled patients were over 16 years old. Endoscopies were performed within 48 hours if patients had 1) hematemesis, 2) melena/hematochezia, 3) related GI symptoms (epigastric pain, dyspepsia, heartburn, or nausea/vomiting), 4) a drop in hemoglobin level, 5) shock, or 6) miscellaneous reasons. Generally, a drop in hemoglobin was defined as hemoglobin dropping more than 3 g/dL from baseline without any specific reason. All patients with miscellaneous causes, except one, were burn patients who had no symptom but wanted to undergo endoscopy, and only one patient underwent an endoscopy to evaluate a tracheoesophageal fistula. All burn patients were administered H2-receptor blockers within 48 hours, and ICU patients were started on enteral nutrition. The ABSI was used to examine the correlation between the severity of the burn and the incidence of ulcers.[9]

Statistical analysis

All analyses were performed with SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA). Nominal variables are presented as frequencies and percentages. Continuous variables are presented as means and standard deviations for data with a normal distribution. Data are presented as medians and interquartile ranges for variables that did not follow a normal distribution. We used the Shapiro-Wilk normality test. The Kruskal-Wallis test was used to assess the differences among three independently sampled groups on non-normally distributed continuous variables. For nominal variables, the chi-square test was used to identify differences between groups. If the expected frequencies were < 5, we used Fisher's exact test. A multivariate logistic analysis was performed to identify variables that affected ulcer development in burn patients. Receiver operating characteristic curves were constructed to determine the accuracy of the ABSI in predicting ulcers. P-values < 0.05 were considered statistically significant.

RESULTS

As is indicated in Fig. 1, during the study period, 11,609 patients were admitted to the two burn centers. Of these patients, 869
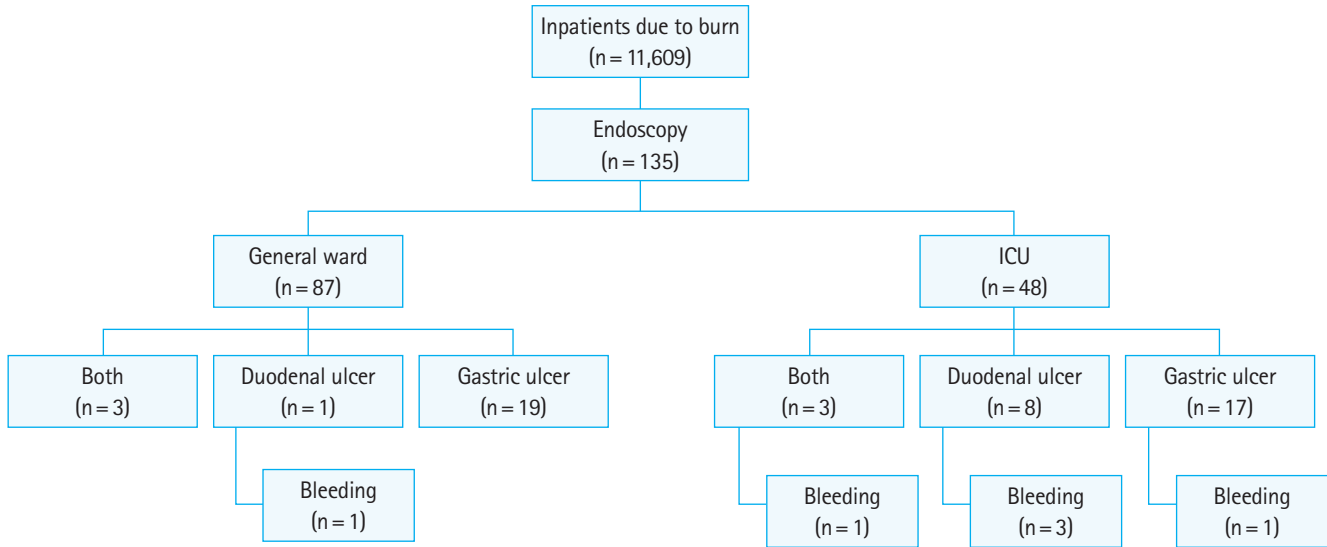
Fig. 1. Flow diagram of enrolled patients. ICU, intensive care unit.

were admitted to the ICU. A total of 135 patients underwent endoscopy, 48 of whom were in the ICU. The patients' mean age was 49.5 ± 13.5 years. The median burn area was 10% of TBSA (interquartile range, 4% to 25%). Only one patient died.

Using endoscopy, ulcers were detected in 51 patients, and of these, 36 (70.6%) had gastric ulcers, nine (17.6%) had duodenal ulcers, and six (11.8%) had both types of ulcer. Ulcers with bleeding were detected in six patients: one had a gastric ulcer, four had duodenal ulcers, and one had both ulcer types. Table 1 shows the differences in variables between patients according to the presence or absence of ulcers. There were significant differences between the ulcer group and the non-ulcer group for the following variables: burn area, burn depth, epigastric pain, melena, ICU admission, burn area > 20% of TBSA, and burn surgery.

Table 2 shows differences in patient variables according to type of ulcer. Patients with duodenal ulcers had a larger burn area, a higher incidence of bleeding, and more frequent melena than patients with other types of ulcers.

The results of logistic regression of variables affecting gastric or duodenal ulcer formation in burn patients are shown in Table 3. Gender, old age, epigastric pain, melena, deep burn, burn area > 20% of TBSA, and ICU admission were used as covariates. The odds ratios of ulcer incidence were 4.55 and 4.31, respectively, if patients had epigastric pain and if burn area was > 20% of TBSA. A receiver operating characteristic analysis was conducted to examine whether ABSI could predict the incidence of ulcer. The area under the curve for predicting ulcers according to the ABSI was 0.736 (95% confidence interval, 0.648 to 0.824). Table 4 shows the diagnostic accuracy of the ABSI for predicting ulcers in burn patients comparing three different cutoff values.

Table 1. Differences in variables according to the presence or absence of ulcers

Variable	No ulcer (n = 84)	Ulcer detected (n = 51)	P-value
Male	44 (52.4)	35 (68.6)	0.063
Age (yr)	48.5 ± 13.4	50.9 ± 13.7	0.322
Burn area, % (IQR)	5 (2–15)	23.5 (6–40)	< 0.001
Burn depth			< 0.001
Superficial second degree	15 (17.9)	2 (3.9)	
Deep second degree	35 (14.7)	10 (19.6)	
Third degree	28 (33.3)	36 (70.6)	
Fourth degree	6 (7.1)	3 (5.9)	
Symptoms			
Epigastric pain	16 (19.0)	18 (35.3)	0.035
Melena	5 (6.0)	11 (21.8)	0.006
Type of burn			0.74
Contact burn	8 (9.5)	1 (2.0)	
Chemical burn	4 (4.8)	3 (5.9)	
Electrical burn	6 (7.1)	3 (5.9)	
Flame burn	28 (33.3)	29 (56.9)	
Friction burn	2 (2.4)	3 (5.9)	
Scalding burn	34 (40.5)	11 (21.6)	
Other	2 (2.4)	1 (2.0)	
ICU admission	20 (23.8)	28 (54.9)	< 0.001
Use of ventilator	4 (4.8)	4 (7.8)	0.462
Burn area > 20% of TBSA	19 (22.6)	30 (60.0)	< 0.001
ABSI (IQR)	5 (4–6.3)	7 (6–9.3)	< 0.001
Burn surgery	52 (61.9)	49 (96.1)	< 0.001
No. of surgeries	1 (0–2)	2 (1–4)	< 0.001

Values are presented as number (%), mean ± standard deviation, or number (IQR) unless otherwise indicated.
IQR, interquartile range; ICU, intensive care unit; TBSA, total body surface area; ABSI, abbreviated burn severity index.

DISCUSSION

Pruitt et al.[5] evaluated patients who were treated from 1954 to 1969; their study is significantly different from our study. First,

Table 2. Differences in patient variables according to type of ulcer

Variable	Gastric ulcer (n = 36)	Duodenal ulcer (n = 9)	Both (n = 6)	P–value
Male	22 (61.1)	8 (88.9)	5 (83.3)	0.285
Age, yr (IQR)	54 (50–63.5)	45 (35–47)	46 (42–50)	0.029[a]
Tukey's test[b]	a	b	b	
Burn area, % (IQR)	21 (5–25.2)	40 (31–50)	20.5 (7–42)	0.013[a]
Tukey's test[b]	a	b	a	
Symptoms				
Epigastric pain	11 (30.6)	2 (22.2)	5 (83.3)	0.043
Melena	4 (11.1)	6 (66.7)	1 (16.7)	0.003
Hemorrhagic ulcer	1 (2.8)	4 (44.4)	1 (16.7)	0.004
ICU admission	17 (47.2)	8 (88.9)	3 (50.0)	0.07
Ventilator apply	1 (2.8)	3 (33.3)	0 (0)	0.02
ABSI (IQR)	7 (5.5–8)	9 (8–11)	9.5 (5–10)	0.022[a]
Tukey's test[b]	a	b	b	

Values are presented as number (%) unless otherwise indicated.
IQR, interquartile range; ICU, intensive care unit; ABSI, abbreviated burn severity index.
[a]Statistical significances were tested by Kruskal-Wallis test among groups. [b]The same letters indicate nonsignificant differences between groups based on post hoc analysis.

Table 3. Logistic regression of variables affecting gastric or duodenal ulcer formation in burn patients

Variables	Odds ratio	P–value	95% CI
Female	0.75	0.531	0.30–1.86
Old age (≥ 65 yr)	0.72	0.477	0.30–1.76
Epigastric pain	4.55	0.002	1.74–11.90
Melena	3.06	0.089	0.85–11.10
Deep burn (≥ deep 2nd degree)	2.65	0.240	0.52–13.46
Burn area > 20% of TBSA	4.31	0.014	1.34–13.85
ICU admission	1.18	0.785	0.36–3.86

CI, confidence interval; TBSA, total body surface area; ICU, intensive care unit.

Table 4. Diagnostic accuracy of the ABSI for predicting ulcer in burn patients

	ABSI above 5		ABSI above 6		ABSI above 7	
	Yes	No	Yes	No	Yes	No
Ulcer (n)	40	11	34	17	24	27
Non-ulcer (n)	39	45	20	64	11	73
Sensitivity (95% CI)	78.40 (64.68–88.71)		66.67 (52.08–79.24)		47.06 (32.93–61.54)	
Specificity (95% CI)	53.57 (42.30–64.53)		76.19 (65.65–84.81)		86.90 (77.78–93.28)	
PPV (95% CI)	50.63 (39.14–62.08)		62.96 (48.74–75.71)		68.57 (50.71–83.15)	
NPV (95% CI)	80.36 (67.57–89.77)		79.01 (68.54–87.27)		73.00 (63.20–81.39)	
Likelihood ratio (+)	1.69 (1.29–2.22)		2.80 (1.82–4.30)		3.59 (1.93–6.70)	
Likelihood ratio (−)	0.40 (0.23–0.70)		0.44 (0.29–0.66)		0.61 (0.46–0.80)	
Area under the ROC curve (95% CI)	0.736 (0.648–0.824)		0.736 (0.648–0.824)		0.736 (0.648–0.824)	

ABSI, abbreviated burn severity index; CI, confidence interval; PPV, positive predictive values; NPV, negative predictive values; ROC, receiver operating characteristic.

the incidence of ulcers and mortality rate had decreased between Pruitt's study and ours from 11.7% to 0.4% and from 77% to 1.9%, respectively. These reductions can be attributed to several causes, including a decrease in the number of major burn patients and improved treatment modalities for these patients. Moreover, ulcer prophylaxis had been introduced. Early enteral nutrition and ulcer prophylactic therapies with H2-receptor blockers have become the most important means of preventing gut dysfunction and GI ulceration in burn patients.[10-12] Prophylactic pharmacologic therapies could have reduced the incidence of ulcers with severe bleeding by 50%.[13]

The decreased mortality rate can also be attributed to the improvement in endoscopic devices, which have enabled more accurate diagnosis and made endoscopic bleeding control possible since the invention of the first fiber optic endoscopy in 1957.[14] In Pruitt's study,[5] 13% (42/323) patients underwent surgery for ulcer treatment, and of these, 64% (27/42) died, whereas, in our study, there were only six patients with bleeding ulcers: five patients (83%, 5/6) who were successfully treated with endoscopic bleeding control and only one patient (16%, 1/6) who underwent surgery and died.

Furthermore, the types of ulcer included in the two studies were different. Gastric ulcers were slightly more frequent (47.1%) than other types of ulcer in Pruitt's study.[5] However, gastric ulcers were much more frequent in our study (70%). Interestingly, there were no significant differences between gastric ulcer (22%) and duodenal ulcer (28%) incidence in Czaja et al's study.[15] We are unable to explain the differences in gastric ulcer incidence between our study and these other studies. More investigation is needed to explain the differences.

In our study and Pruitt's study,[5] burn areas in the ulcer and non-ulcer groups were significantly different. Pruitt's study showed the incidence of Curling's ulcer increased with increasing burn size, and our study showed that patients with a major burn (burn

area > 20% of TBSA) had a higher incidence than those with a minor or moderate burn. The definition of major burn in this study was in accordance with the guidelines of the American College of Surgeons.[16] In our study, burn patients with ulcers had a larger burn area compared with patients without ulcers, and patients with a burn area > 20% of TBSA had a 4.31 times higher probability of ulcers than those with a burn area < 20% of TBSA. The American Society of Health-System Pharmacists suggested that patients with thermal injury of > 35% of TBSA were at risk for stress-related mucosal disease.[17] Their finding was different from ours, probably because although their study included only ICU patients, our study included patients in the general ward as well as the ICU. Apart from burns, more than 20% of burn patients with epigastric pain or melena had, respectively, a 4.55 and 3.06 times higher probability of ulcers than patients without those conditions. A median 20 days (interquartile range, 10 to 34) elapsed from the accident before burn patients with ulcers underwent endoscopy. All patients except one were diagnosed with an ulcer using endoscopy 3 days after the burn. These results were consistent with those of Czaja et al.[15] indicating that 74% (17/23) of acute ulcers were detected 72 hours after the burn.

We verified the validity of risk factors suggested in previous studies. Well-known risk factors for GI bleeding in critically ill patients include the use of a ventilator for more than 48 hours and the presence of coagulopathy.[18-20] Our results were not significant for two risk factors because there were not enough samples for these risk factors. In our study, a ventilator was used in four patients. However, of these, two patients required a ventilator after ulcers had developed, so the development of ulcers was not related to ventilator use. Coagulopathy often occurs early after the burn injury. Burn patients may experience thrombocytopenia, disseminated intravascular coagulation, or other coagulopathies. Later coagulopathy may occur from another cause such as sepsis.[4] In our study, no patient who underwent endoscopy had pre-existing coagulopathy or coagulopathy after burn injury.

Trauma patients with an injury severity score of more than 16 have a higher probability of developing a stress ulcer.[21,22] Similarly, we hypothesized that the ABSI might be correlated with the incidence of ulcer development because the ABSI has been widely accepted as a useful tool for predicting the mortality of burn victims since 1982.[8] Based on this idea, we examined whether the ABSI could predict the incidence of ulcer. We found that the ABSI had relatively higher sensitivity (66.67%) and specificity (76.19%) when above 6. However, the ABSI still lacked diagnostic accuracy because its area under the curve was 0.736. We examined whether diagnostic accuracy could be enhanced by adding conditions such as epigastric pain or melena. However, the diagnostic

accuracy for predicting incidence of ulcer was only 72.5% when burn patients had an ABSI of more than 6 or melena. The accuracy achieved was not significantly better than that achieved using only an ABSI of more than 6.

This study had several limitations. First, this was a retrospective study, and there was a lack of consistency in deciding when to perform an endoscopy. Although our hospital has defined criteria for performing endoscopy in burn patients, there were some differences in applying the criteria among individual physicians. If patients described vague symptoms, for example, indigestion, abdominal fullness, or abdominal discomfort, decisions about endoscopy differed between physicians. Patients with obvious symptoms such as epigastric pain or melena had a high probability of requiring endoscopy. In Pruitt's study,[5] the patients with epigastric pain represented only 4.1% (4/98) but this study showed that 35.3% of ulcer patients complained of epigastric pain. In our study, there were two reasons that epigastric pain was the most common reason for performing an endoscopy. One reason is the decreased numbers of patients with GI bleeding such as melena and hematemesis. The numbers of patients with epigastric pain seemed to increase relatively. The other reason is the ulcer patients with vague symptoms (indigestion, abdominal fullness, etc.) were excluded because they had a high probability not to receive an endoscopy.

Second, endoscopies were completed mainly for symptomatic patients in our study, and asymptomatic patients with ulcers were excluded. Moncrief et al.[23] emphasized the occult nature of gastric and duodenal ulceration, and Pruitt et al.[5] reported that 22.7% (66/291) of patients had no symptoms. Therefore, asymptomatic patients should be included in the next study. In our study, 20 asymptomatic patients underwent endoscopies, but they did not have ulcers.

The third limitation is related to the accuracy of the medical records. The most important finding was the relationship between the TBSA of burn patients and incidence of ulcer. However, the TBSA of burn patients may include personal error for each measurer because it was measured not by a precise method or technique but estimated visually. The next study should aim to minimize measurement error. Future prospective study would mitigate the first and second limiting factors.

In summary, our report provides fundamental and updated data about ulcers occurring in burn patients since ulcer prophylaxis has been widely accepted. In our study, the rate of ulcer was higher in patient who had a burn area > 20% of TBSA compared with patients with a burn area < 20% of TBSA (odds ratio, 4.31). In addition, the rate of ulcers was higher in patients with epigastric pain compared with patients without this symptom (odds ratio,

4.55). However, we need large, well-controlled prospective studies to confirm these results.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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