High Doses of Methylprednisolone in the Management of Caustic Esophageal Burns

WHAT’S KNOWN ON THIS SUBJECT: Corrosive substance ingestion is a public health issue in developing countries. Stricture formation is a late complication of corrosive substance ingestion. The role of corticosteroids in preventing corrosive-induced strictures is controversial.

WHAT THIS STUDY ADDS: High doses of methylprednisolone therapy lead to less frequent stricture formation in grade IIb esophageal burns in children who ingested caustic substances and may improve prognosis.

abstract

OBJECTIVE: Caustic substance ingestion in childhood is a public health issue in developing countries, and several management protocols have been proposed to prevent the resulting esophageal strictures. The role of corticosteroids in preventing corrosive-induced strictures is controversial. Our aim was to study the influence of high doses of corticosteroids in preventing esophageal strictures.

METHODS: Eighty-three children with a mean age of 4.10 ± 2.63 years and with grade IIb esophageal burns (an esophagogastroscopy was performed within 24–48 hours of injury) due to corrosive substance ingestion were enrolled in our study between 2005 and 2008. Forty-two children (study group) received methylprednisolone (1 g/1.73 m² per day for 3 days), ranitidine, ceftriaxone, and total parenteral nutrition. Forty-one children (control group) were administered the same regimen excluding methylprednisolone. Stricture development was compared between groups based on endoscopic and radiologic findings.

RESULTS: During the endoscopic examination, stricture development was observed in 4 patients (10.8%) in the study group and in 12 patients (30%) in the control group. The difference was statistically significant (P = .038). The stricture development rate in the upper gastrointestinal system with barium meal was 14.3% and 45.0% in the study and control groups, respectively. The difference was statistically significant (P = .004). The duration of total parenteral nutrition was shorter in the study group compared with the control group (P = .001). High doses of methylprednisolone were well tolerated in the study group without any side effects.

CONCLUSIONS: High doses of methylprednisolone used for the management of grade IIb esophageal burns may reduce stricture development. Pediatrics 2014;133:e1518–e1524

AUTHORS: Merve Usta, MD,a Tulay Erkan, Professor Dr.b Fugen Cullu Cokugras, Professor Dr.b Nafiy Urganci, Associate Professor Dr.b Zerrin Onal, MD,c Mahir Gulcan, Assistant Professor Dr.a and Tufan Kutlu, Professor Dr.b

aDepartment of Pediatric Gastroenterology, Hepatology and Nutrition, Sisli Etfal Education and Research Hospital, Istanbul, Turkey; bDepartment of Pediatric Gastroenterology, Hepatology and Nutrition, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey; cDepartment of Pediatric Gastroenterology, Hepatology and Nutrition, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey; and dDepartment of Pediatric Gastroenterology, Hepatology and Nutrition, Acibadem University Medical Faculty, Istanbul, Turkey

KEY WORDS
caustic, corticosteroid therapy, stricture, children

ABBREVIATIONS
CI—confidence interval
GIS—gastrointestinal system
IV—intravenous
TPN—total parenteral nutrition

Dr. Usta conceptualized and designed the study, designed the data collection instruments, carried out the initial analyses, coordinated and supervised data collection at 2 of the 4 sites, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr Kutlu conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and revised and reviewed the manuscript; Drs Erkan, Cullu Cokugras, Urganci, Onal, and Gulcan carried out the initial analyses and revised and reviewed the manuscript; and all authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT02002078).

www.pediatrics.org/cgi/doi/10.1542/peds.2013-3331
doi:10.1542/peds.2013-3331
Accepted for publication Feb 21, 2014

Address correspondence to Merve Usta, MD, Department of Pediatric Gastroenterology, Sisli Hamidiye Etfal Education and Research Hospital, 34377 Sisli/Istanbul, Turkey. E-mail: mervokesim@yahoo.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Esophageal burn due to corrosive substance ingestion in childhood is a public health issue in developing countries. Corrosive ingestion may lead to clinical manifestations varying from no injury to fatal outcome. Besides perforation, the most serious complication of corrosive damage to the esophagus is stricture formation. The role of corticosteroids in preventing corrosive-induced strictures is controversial. The frequency of esophageal stricture in corrosive esophagitis is 5%, and this ratio increases to 47% in severe cases. Centers have proposed various treatment protocols to prevent stricture formation, such as early dilatation before the occurrence of strictures, different types of esophageal stents, and steroid therapy, mostly in combination. Steroids have been shown to significantly reduce the incidence of strictures in animal experiments. However, even though steroids have been widely used in various doses in humans since the 1950s, the results have been variable and often disappointing. In a prospective study, Anderson et al found that corticosteroid treatment had no significant effect on stricture formation. Conversely, Howell et al reported that corticosteroid therapy reduces stricture development in grade II and III cases based on the analysis of 13 studies. After conducting a meta-analysis in 2005, Peclova et al reported that they do not recommend corticosteroid therapy in the management of corrosive substance ingestion. In a multicenter study that included our department, methylprednisolone therapy at a dose of 2 mg/kg/day has been found to be ineffective in preventing stricture formation. In recent years, studies conducted using high doses of corticosteroids have reported reduced frequency of stricture formation. In grade IIb esophagitis in particular, the prognosis is better with high-dose corticosteroids, and no mortality or morbidity has been observed in association with the therapy.

In this study, our aim was to evaluate the efficacy of high-dose methylprednisolone treatment in preventing the late complication of stricture formation in grade IIb esophageal burns after corrosive substance ingestion.

METHODS

Eighty-three children with grade IIb esophageal burn according to the Zarugar classification were enrolled in our study between September 2005 and February 2008. The approval of the Ethics Committee of Istanbul University Cerrahpasa Medical Faculty was obtained (06.02.2007/3756).

All patients who had ingested corrosive substances underwent endoscopic examinations of the upper gastrointestinal system (GIS) in our pediatric endoscopy unit within 24 to 48 hours of injury. Grade I, IIa, and III burns were excluded from the study. All patients with grade IIb burns were hospitalized, and their medical history, age, gender, and physical examination results were recorded. Complete blood count, erythrocyte sedimentation rate, biochemical analysis, urine and blood culture values, and, when necessary, x-rays were evaluated. The patients were started on a regimen of ceftriaxone 100 mg/kg/day and ranitidine 4 mg/kg/day through the intravenous (IV) route. Oral feeding was suspended, and total parenteral nutrition (TPN) was initiated. The patients were randomized consecutively into 2 groups. The endoscopy was blinded to the patient groups at the first endoscopy. Group 1 (the study group) included 42 patients with grade IIb esophageal burns. After the endoscopic examination, the patients in the study group were administered a high dose of methylprednisolone (1 g/1.73 m²/day) for 3 days. During methylprednisolone therapy, the patients in the study group were monitored for the side effects of the treatment including hyperglycemia, high blood pressure, electrolyte disturbances, and infections.

Group 2 (the control group) included 41 patients who received the same treatment regimen but without high-dose methylprednisolone. The patients in both groups were given TPN for 1 week; when the patients tolerated oral feeding, TPN was tapered.

On the tenth day, a control esophagogastroscopy was performed on all the patients. The patients whose endoscopic findings were observed to improve (normal, grade I, IIa) and who tolerated oral feeding were discharged from the hospital to be followed up through the outpatient clinic. All patients who were discharged from the hospital were scheduled for follow-up visits at the third week of the ingestion. During the follow-up visits, patients were evaluated for the clinical symptoms and signs and any complaints such as abdominal pain, vomiting, dysphagia, odynophagia or food impaction. If there were any symptoms or signs suggestive of stricture formation, the endoscopic and radiologic examinations were repeated. None of the patients discharged from the hospital after the second-look endoscopy showed stricture formation at follow-up.

All patients were also followed up for early and late complications of caustic esophagitis. No early complication such as mediastinitis, pneumonia, upper gastrointestinal bleeding, or perforation was observed in either group. Late complications were investigated through endoscopic and radiologic examinations in patients whose endoscopic findings did not improve and whose complaints continued. At the end of the third week, an upper GIS series with barium meal was performed on patients who were suspected of stricture formation in both groups. The results were assessed by the same radiologist who remained blinded to the patient groups. In the patients whose endoscopic findings still pointed to grade IIb or grade IIa burns accompanied by clinical signs, additional...
endoscopic examinations were performed to assess the grade of the burn and the stricture formation. Both groups were compared in terms of stricture development. The patients who developed esophageal strictures were taken to the dilatation program in the pediatric surgery clinic. The flowchart is shown in Fig 1.

The study data were evaluated by using the NCSS (number cruncher statistical system) 2007 & PASS 2008 Statistical Software (Kaysville, UT) for statistical analysis. In addition to the descriptive statistical methods (mean, SD, frequency), for the comparison of the quantitative data, Student’s t test was used to compare the normal distribution of the parameters between groups, and the Mann-Whitney U test was used to compare the abnormal distribution of the parameters between both groups. $\chi^2$ test and Fisher’s exact test were used for the comparison of the qualitative data. The results were assessed within a 95% confidence interval (CI), and statistical significance was based on a value of $P < .05$.

**RESULTS**

During the study period, 345 pediatric patients were admitted to the emergency department because of corrosive substance ingestion. Among these children, 32% had grade II and III esophageal burns. Eight-three children (grade IIb esophageal burns) were included in the study. Among all the patients, 38 (45.8%) were girls, and 45 (54.2%) were boys. The male/female ratio was 1.18. The patients’ mean age was 4.10 ± 2.63 years.

Alkaline chemicals (degreasers/oven cleaners) were observed as the most frequently ingested substances with a percentage of 63.9% among all the patients. Other ingested substances included lime remover in 14 patients (16.8%), household bleach in 7 patients (8.4%), hydrochloric acid in 10 patients (12%), acetic acid in 1 patient (1.2%), and dishwasher rinsing fluid in another patient (1.2%).

Burns in the oral mucosa were observed in 48.2% ($n = 40$) of patients. Among the patients, 84.3% vomited or were forced to vomit before arriving at the hospital. Respiratory symptoms were observed in only 3 patients (3.6%).

All the patients had grade IIb esophageal burns. Fourteen patients in the study group and 20 patients in the control group initially had hemorrhagic gastritis in addition to esophagitis. Fifteen patients (5 with normal findings, 10 with grade I esophageal burn) from the study group and 17 patients (2 with normal findings, 15 with grade I esophageal burn) from control group were

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**FIGURE 1**

Flowchart of the study. ES, esophageal stricture x-ray: upper GIS series with barium swallow.
discharged from the hospital at the 10th day. The patients who had grade IIa esophageal burn in both groups were discharged when they tolerated oral feeding and when they had no clinical signs. The endoscopic findings of the patients in both groups are presented in Table 1. Fifteen patients in the study group and 14 patients in the control group were found to have additional endoscopic examinations after the second look endoscopy. Another upper GIS endoscopy was performed on the patients whose endoscopic findings were still grade IIb after the second upper GIS endoscopy and whose clinical signs suggested a stricture.

The mean duration of the TPN was 9.34 ± 1.88 days in the study group and 16.83 ± 5.96 days in the control group. The difference between the 2 groups was statistically significant (P = .001).

No side effects associated with the high-dose methylprednisolone treatment were observed in the study group. All patients in the study group were monitored during the therapy, and only 1 patient was excluded from the study, due to a rash associated with chicken pox.

Patients in both groups were also monitored through the outpatient clinic for complaints including abdominal pain, dysphagia, odynophagia, vomiting, or food impaction. These complaints were observed in 21.6% of the patients in the study group and 40% of the patients in the control group. The difference was statistically insignificant (P = .08).

Esophageal stenosis was diagnosed in the patients in both groups based on the findings of the control endoscopy. Analysis of stricture formation as the endpoint over time is shown in Fig 2. When the process of stricture formation was evaluated using log-rank test, the stricture formation rate was found to be lower in the study group (P = .03).

We observed no statistically significant relationship between the stricture development and the ingested substance (P = .19).

### DISCUSSION

Corticosteroid therapy in the management of corrosive substance ingestion in children is controversial. Different corticosteroids (dexamethasone, prednisolone, methylprednisolone) were used at different doses and through different routes of administration (oral, IV) from 7 days to 4 to 6 weeks in children with corrosive esophagitis. In the current study, we used methylprednisolone at a dose of 1 g/1.73 m2/day for 3 days. In the study by Bouktir et al., methylprednisolone was administered for 19 days, and the study included 23 patients with grade IIB and III esophageal burns. The percentage of stricture formation was 45.8%. In their study, they observed stricture formation in 7 of 20 patients with grade IIb and in all patients with grade III esophageal burns. The authors commented that methylprednisolone therapy may affect the prognosis positively at that dose. In a study from Tunisia, high-dose methylprednisolone therapy was administered subcutaneously to 26 patients. The authors observed that stricture formation was reduced in their patients. In our study, all patients had grade IIB esophageal burns. Our initial aim was to suppress the initial inflammation (the first step of stricture formation) that occurs during the first 3 days of wound healing. We have used high-dose corticosteroids administered through the IV route, as recommended by Adenwalla et al., who observed a reduction in stricture formation in children with grade II esophageal burns. We believe that in the cases of grade II esophageal burns, corticosteroids can be used as part of the initial treatment to reduce inflammation.
route for better access to the burn area. Because the histologic observation of the strictures revealed acute esophagitis with fibrosis and abundant infiltration of inflammatory cells, we have considered the blockade of the initial inflammation as an important step for prevention of stricture development.\textsuperscript{18} We did not observe any side effects of corticosteroid therapy in study group during the study period.

A second-look endoscopy was performed on the tenth day, and the endoscopic findings in both groups were also compared. The results were similar in both groups, and the difference was not found to be statistically significant. All the patients in our study were administered TPN. TPN was tapered after 1 week, but if the patients did not tolerate oral feeding, TPN continued. The duration of TPN in the control group was longer than the study group, and this difference was statistically significant ($P < .01$). This leads to the conclusion that the duration of hospitalization was shorter in the study group.

Because we also aimed to evaluate the late complications including stricture formation at the end of the third week or later, the results of the second-look endoscopy performed on the tenth day were inconclusive. The duration of TPN was shorter in the study group. This means that although the difference in the endoscopic results was statistically insignificant, the patients in the study group were discharged from the hospital earlier than the control group.

The rate of stricture formation after corrosive substance ingestion is 26% to 55% in the literature.\textsuperscript{19,20} In our study, the stricture development percentage was 20.8% among all the patients. The lower percentages observed in our study compared with the literature may be associated with the exclusion of the grade IIIa and IIIb patients from our study. This

| TABLE 2 Clinical, Radiologic, and Endoscopic Findings During Outpatient Follow-up |
|----------------------------------|----------------------------------|------------------|-----------------|
| Upper GSI with barium meal       | Study Group, n (%)               | Control Group, n (%) | $P$ or OR (95% CI) |
| Abnormal                         | 5 (14.3)                         | 18 (45.0)          | .004            |
| Normal                           | 30 (85.7)                        | 22 (55.0)          | 4.90 (1.58–15.25) |
| Clinical signs$^a$ during follow-up |                                 |                   |                 |
| Yes                              | 8 (21.6)                         | 16 (40.0)          | .082            |
| No                               | 29 (78.4)                        | 24 (60.0)          |                 |
| ES with upper GIS endoscopy$^b$  |                                 |                   |                 |
| Yes                              | 4 (10.8)                         | 12 (30.0)          | .038$^*$        |
| No                               | 33 (89.2)                        | 28 (70.0)          | 3.536 (1.03–12.20). |
| Required esophageal dilatation    |                                 |                   |                 |
| Yes                              | 4 (10.8)                         | 12 (30.0)          | .038$^*$        |
| No                               | 33 (89.2)                        | 28 (70.0)          |                 |

$^*$ $P < .05$; ES, esophageal stenosis; OR, odds ratio.

$^a$ E.g., vomiting, abdominal pain, dysphagia.

$^b$ $\chi^2$ test.

**FIGURE 2**
Survival rate (stricture formation as the end point) in both groups (Kaplan-Meier analysis). Cum, cumulative.
may be considered a limitation of our study because grade IIIa and IIb patients have higher risks of stricture development. In the study by Bouktir et al., the patients’ esophageal burns were graded as IIb and III, and the duration of the therapy was longer than our study. Our study population included only grade IIb burns, and the treatment duration was shorter, which may have reduced the side effects of the therapy. We observed stricture formation in 4 patients (10.8%) in the study group. In the control group, strictures developed in 12 patients (30%). The difference between groups was statistically significant (odds ratio: 3.53; 95% CI: 1.03–12.20). This means that the 53 times greater stricture formation was observed in the control group compared with the study group.

Degreaser (oven cleaner) was the most frequently ingested substance in both groups. Twenty-eight patients (66.7%) in the study group and 25 patients in the control group (61%) had ingested degreaser. We have found no statistically significant relationship between stricture development and the ingested substance, although certain studies suggested a relationship between these factors.1,10

The patients included in the study were followed up through our clinic after they were discharged from the hospital. Clinical signs such as abdominal pain, dysphagia, or aglutition were observed in 21.6% of the study group and 40% of the control group. Although the observed difference was close to statistical significance, it remained outside the range of significance (odds ratio: 3.53 95% CI: 1.03–12.20).

The patients in whom no improvement was observed in the clinical and endoscopic findings were followed up for stricture formation through additional upper GIS endoscopies. The upper GIS series with barium meal were carried out at the end of the third week. Five patients (14.8%) in the study group and 18 patients (45%) in the control group developed esophageal strictures through the upper series with barium meal. The difference was statistically significant (P = .004). Four patients in the study group and 12 patients in the control group developed esophageal strictures during the follow-up period. In control group, stricture formation was observed in 18 patients through GIS series with barium meal, although the endoscopic examination revealed stricture formation in only 12 of them. They were transferred to the dilatation program. We believe that upper GIS endoscopy is a more precise method than radiology for the follow-up of esophageal stricture development.

**CONCLUSIONS**

Esophageal stricture is one of the most important complications that may develop after corrosive substance ingestion. In our study focusing on grade IIb esophageal burns, the stricture development rate was significantly lower in the patients treated with high doses of methylprednisolone than those who did not receive this treatment modality. This is the first randomized controlled study using high doses of methylprednisolone in the management of grade IIb corrosive esophageal burns. We believe that the prognosis may be improved and the risk of stricture formation may be reduced with high doses of methylprednisolone therapy in grade IIb esophagitis.

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Pediatrics 2014;133:e1518
DOI: 10.1542/peds.2013-3331 originally published online May 26, 2014;
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