

Endoscopic Hemostasis of Gastrointestinal Hemorrhage by Local Application of Absolute Ethanol: A Clinical Study

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ASAKI, S., NISHIMURA, T., SATOH, A., OHARA, S., SHIBUYA, D., OGITSU, Y. and GOTO, Y. *Endoscopic Hemostasis of Gastrointestinal Hemorrhage by Local Application of Absolute Ethanol: A Clinical Study.* Tohoku J. exp. Med., 1983, 141 (4), 373-383 — The procedure of endoscopic hemostasis with topical injection of absolute ethanol has been developed and applied since 1975 for the control of postoperative hemorrhage associated with diathermic polypectomy. Since June 1979, upper gastrointestinal hemorrhages other than varices have also been subjected to this procedure. This method is based on the principle of dehydration and fixation of the tissue with absolute ethanol. In this procedure, the bleeding vasculatures are dehydrated and fixed with consequent vasoconstriction and necrosis of the vascular wall including its endothelial lining, thereby thrombogenesis and hemostasis are facilitated. The troubled blood vessels fixed in vivo are disintegrated and disappeared. Rebleeding from the ulcer has been extremely rare with this method since the necrotized tissue seldom defoliates but often constitutes a part of the white coating and protects the base of ulcer. Treatment by this method has been successful in all 23 cases of upper gastrointestinal hemorrhage associated with endoscopic diathermy, and none has developed rebleeding. The hemostasis has also been successful in 51 cases (72 hemorrhagic lesions) with fresh blood clots adhering to the lesion, exposed blood vessels in the lesion or an actively bleeding lesion out of 126 cases referred for emergency endoscopic examination because of upper gastrointestinal hemorrhage during the 3-year period from June 1979 to May 1982. After hemostasis, however, 3 patients received an elective operation and one patient was also operated due to perforation of the gastric wall. Rebleeding occurred in 3 cases more than a week after the hemostasis; one of these was the above-described operated case of perforation. The rebleeding occurred in stress ulcers following surgery for femoral fracture. The other two were at the terminal stage of malignancy and complicated with DIC respectively. Of the patients treated by this method, 8 died by causes other than gastrointestinal hemorrhage. All the rest of 39 cases attained cure of ulcer by the non-surgical treatment alone. ————— G-I bleeding; endoscopy; endoscopic hemostasis; topical injection; absolute ethanol

TABLE 1. *Endoscopic hemostatic methods*

I.	Clotting factor (Linscheer and Fazio 1979)
II.	Hemostatic clip (Hayashi et al. 1975)
III.	Na-Epinephrin (Hirao et al. 1982)
IV.	Electro-coagulation (Papp 1975 ; Matek et al. 1979)
V.	Laser radiation (Frühmorgen et al. 1976 ; Kiefhaber et al. 1977)
VI.	Pure ethanol (Asaki 1981)

Since the application of emergency endoscopy for gastrointestinal hemorrhage was advocated by Palmer (1969) gastrointestinal endoscopy has been of great value as a diagnostic means to determine the location and nature of the lesion and of assessing the degree of bleeding. However, the application has been solely diagnostic and has hardly led to a substantial reduction in mortality from gastrointestinal hemorrhage. There have been prevailing inveterate views that emergency endoscopy entails considerable technical difficulty and involves a danger of aggravating hemorrhage. With the recent advancement in fiberoptic instruments for endoscopy, especially the advent of slim-type panendoscopes, nevertheless, emergency endoscopy has become a non-invasive and a simple procedure. And, on account of a development in transendoscopic treatment the emergency endoscopy is no longer a mere diagnostic procedure but is applied also therapeutically as endoscopic hemostasis. The current techniques of endoscopic hemostasis for gastrointestinal hemorrhage are listed in Table 1.

We have developed a transendoscopic method of hemostasis based upon the mechanisms of dehydration and fixation of the ruptured blood vessel by means of perivascularly applied absolute ethanol with consequent constriction and necrotization of the vessel, and thrombogenesis. The results of basic assessments of this technique have been reported elsewhere. The present report presents the data obtained with the transendoscopic procedure in the treatment of hemorrhage associated with gastrointestinal diathermy or biopsy and in the control of gastrointestinal bleeding other than that from esophageal varices, viz. postoperative stress ulcer, peptic ulcer, Mallory-Weiss syndrome, carcinoma of the stomach, submucosal tumor, anastomotic ulcer, sarcoma and erosion.

MATERIALS AND METHODS

Patient population

As shown in Table 2, thirty cases were classified into the patients bled after endoscopic treatment or biopsy. Among them, 23 were caused by transendoscopic diathermy (12 gastric polyps, 2 gastric epithelial atypia, 1 carcinoma of the stomach and 8 submucosal tumor of the stomach or the duodenum). One patient bled due to laser irradiation of carcinoma of the stomach. Of the 6 post-biopsy bleedings, 1 patient had a gastric polyp, 3 had submucosal tumor and 2 had carcinoma of the stomach. Four out of the 29 bled mildly ; perhaps from the vein or capillary. Twelve cases bled moderately and a zonal blood clot over the lesion was formed. Fourteen cases were impending over oligemic shock

TABLE 2. *Hemostatic effect of local pure ethanol injection for the hemorrhage after biopsy and endoscopic treatment with electrocautery or laser irradiation*

Subjects	Number of cases	Complete cessation of bleeding
Bleeding after electrocautery	23	23
Hyperplastic polyp	12	
Atypical epithelium	2	
Cancer	1	
Gastric submucosal tumor	7	
Duodenal submucosal tumor	1	
Bleeding after biopsy	6	6
Hyperplastic polyp	1	
Gastric invasion of pancreatic cancer	1	
Gastric cancer	1	
Gastric submucosal tumor	3	
Bleeding after laser irradiation	1	1

TABLE 3. *Symptoms of bleeding*

Symptoms	Number of cases	(%)
Hematemesis	8	(16)
Hematemesis & melena	17	(33)
Melena	26	(51)

* Hemorrhagic shock were seen in 23 cases (45%).

TABLE 4. *Complicating diseases seen in 45 cases*

Disease	Number	(%)
Post major surgery	20	(44)
Malignant tumor	23	(51)
Diabetes mellitus	5	(11)
Liver cirrhosis	3	(7)
Chronic renal failure	3	(7)
Others	10	(22)

TABLE 5. *Erythrocyte counts in 34 cases*

Counts ($10^4/\text{mm}^3$)	Number	(%)
< 150	1	4 (12)
$150 \leq < 200$	3	
$200 \leq < 300$	19	(56)
$300 \leq < 400$	10	(29)
$400 <$	1	(1)

due to severe gastric hemorrhage. Their ages ranged between 21 and 78 years (mean age of 58).

Fifty-one patients who had fresh blood clot, exposed blood vessels in the basin of the lesion, or bleeding from the lesion, were classified as gastrointestinal hemorrhage (Fig. 2). They consisted of 38 males and 13 females. Three patients were under 30 years of age, 5 in their thirties, 7 in their forties, 11 in their fifties and 25 over 60 years of age; hence about half the number of patients were elderly. The age ranged from 28 and 83, with an average of 57 years. Table 3 shows the incidence of hematemesis and melena and the occurrence of hemorrhagic shock in the present series. Eight patients (16%) had hematemesis, 17 patients (33%) both hematemesis and melena and 26 patients (51%) melena. Of these 51 patients, 23 (45%) developed hemorrhagic shock. There were 6 patients (12%) who had no appreciable underlying disorder while the remaining majority (45 cases, or 88%) had one or other serious underlying diseases (Table 4). In 20 patients (44%), hemorrhage was from stress ulcer which occurred after surgery for malignant tumors, kidney transplantation or cholelithiasis. Malignant tumors were the most frequent underlying disease (23 cases, or 51%), followed, in order, by advanced diabetes mellitus, cirrhosis of the liver, and chronic

TABLE 6. *Serum protein levels in 22 cases*

Serum protein (g/100 ml)		Number	(%)
$4 \leq$	< 4	1	} 7 (31)
	< 5	6	
$5 \leq$	< 6	9	(40)
$6 \leq$	< 6.5	1	(4)
$6.5 \leq$		5	(25)

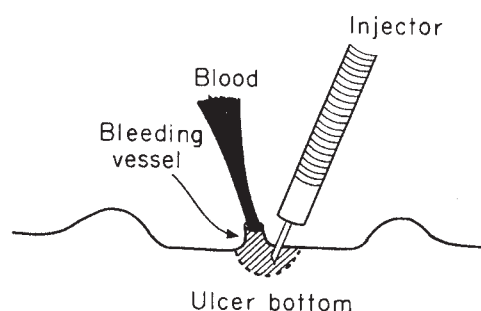
TABLE 7. *Bleeding focus*

Disease	Number	(%)
Gastric ulcer	27	(53)
Duodenal ulcer	13	(25)
Gastric & duodenal ulcer	3	(6)
Mallory Weiss syndrome	1	(2)
Gastric cancer	2	(4)
Metastatic gastroduodenal malignant lymphoma	2	(4)
Stomal ulcer	1	(2)
Gastric erosion	1	(2)
Gastric submucosal tumor	1	(2)
Total	51	(100)

TABLE 8. *Bleeding state at emergency endoscopy*

State	Number of bleeding foci	(%)
Projectile	3	(5)
Pulsatile	6	(8)
Clot	48	(67)
Venous. capillary	15	(20)
Total	72	(100)

* Exposed vessel in 14 cases (27%).



1~2 mm away from bleeding vessel
0.1~0.2 ml at a time
3 or 4 points

Fig. 1. Technique of local absolute ethanol injection.

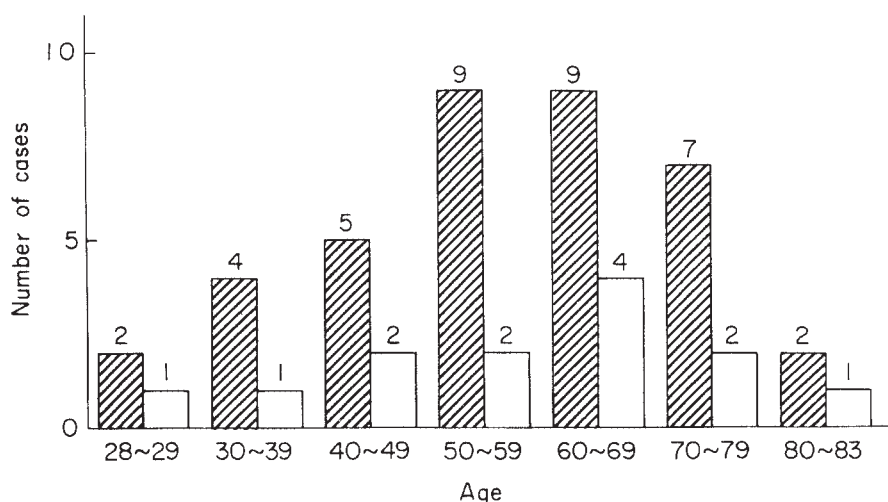


Fig. 2. Sex and age distribution. Mean age, 57 years. ▨, male; □, female.

renal insufficiency. The hematological and blood biochemical findings in the patients at emergency endoscopic examination were as follows: Erythrocyte counts revealed that 4 patients (12%) were markedly anemic ($<150 \times 10^4$ in 1 case and ≥ 150 to $<200 \times 10^4$ in 3 cases), 19 patients (56%) moderately anemic (≥ 200 to $<300 \times 10^4$), 10 patients (29%) slightly anemic (≥ 300 to $<400 \times 10^4$) while 1 patient showed a count of $>400 \times 10^4$ (Table 5). As seen from Table 6, there were 7 patients (31%) who were found to have marked hypoproteinemia with serum total protein levels of <4 g/100 ml (1 case) to 5 g/100 ml (6 cases), 9 patients (40%) moderate hypoproteinemia with serum levels of ≥ 5 to <6 g/100 ml, 1 patient (4%) mild hypoproteinemia with serum levels of ≥ 6 to <6.5 g/100 ml and 5 patients (25%) normal serum levels of ≥ 6.5 g/100 ml. The source of bleeding subjected to hemostasis by this procedure was gastric ulcer in 27 cases (53%), followed, in order of decreasing frequency, by duodenal ulcer in 13 cases (25%), concurrent ulcers in 3, gastric carcinoma in 2, metastatic gastroduodenal sarcoma in 2 cases, and Mallory-Weiss syndrome, anastomotic ulcer, submucosal tumor, and gastric erosion in 1 case each (Table 7). The distribution of patients by severity of gastrointestinal hemorrhage is shown in Table 8. Of a total of 72 hemorrhagic lesions subjected to treatment in the 51 patients, 3 hemorrhages in 3 patients were spouting, 6 in 5 patients pulsatile, 48 in 35 patients blood clots adhering to lesions, and 15 in 8 patients venous and/or capillary bleeding. Ruptured blood vessels were seen exposed in 14 lesions (27%).

TABLE 9. *Results in 51 cases (72 foci)*

Complete hemostasis was achieved in all cases.
Re-bleeding occurred in 3 cases (6%).
Elective surgery in 3 cases (6%).
Perforation in one case (2%).

Procedure

For local injection of ethanol, endoscopic local injectors, 1- to 2-ml disposable plastic syringes, along with a slim GI panendoscope GIF-Q (Olympus) or FGI (Machida), or a forward-oblique viewing panendoscope GIF-K₂ (Olympus) for emergency fiberoptic endoscopy, and either 99.5% or absolute ethanol were prepared. In case where it was found difficult to carry out local hemostasis with any of these forward-viewing fiberscopes, the system was promptly switched to the side-viewing gastro-fiberscope (e.g. GF-B₃).

Ethanol was injected locally in amounts of 0.1-0.2 ml into areas around the bleeding blood vessel as illustrated in Fig. 1. The injection might be made also into the bleeding vessel if it had a large diameter.

Approximately 0.2 ml of the absolute ethanol was applied into the perivascular region and then additional local injections of 0.1 ml each at a few sites to stop hemorrhage from an artery as large as about 3 mm in diameter. In case of a lesion where complete hemostasis could hardly be accomplished with the initial attempt, the endoscope was temporarily withdrawn, and 15-30 min later the local injection with doses of 0.1 ml at a few sites was repeated for a complete arrest of bleeding.

In 3 out of 51 patients studied, a transient increase in severity of hemorrhage was observed after a local injection at one site, but additional 1 or 2 injections to different sites in a dose of 0.2 ml provided a fairly satisfactory control of bleeding. Subsequent injections of 0.1 ml each at a few additional sites accomplished the hemostasis.

In order to permit its sufficient effect upon the bleeding vessels, it is most advisable to inject ethanol slowly. The average dosage of ethanol to be used is approximately 0.6 to 0.8 ml. Precaution must be exercised to avoid de novo extension of ulcer resulting from local effect of ethanol. Caution must also be observed against the danger of perforation which may be caused by deep injection of a large amount. Depth of the needle may be controlled by complaints of pain by patient. Thereafter, a serial injections of 0.2 ml each into a fresh blood clot at the site of hemorrhage is performed in order to get a prompt blackening of the clot. Then a few more injections are added into the bleeding vessel in the clot-adhered ulcer base to secure the hemostasis. Finally, a local irrigation of the area under endoscopy is performed in order to confirm the completion of the procedure.

RESULTS

The attempts of hemostasis were successful in all these cases as shown in Table 9. Late rebleeding occurred more than a week after the treatment in 3 cases (6%). One patient treated for hemorrhage from carcinoma of the stomach developed rebleeding 3 weeks later due to DIC. Another patient treated for hemorrhage from a metastatic lesion of malignant lymphoma in the gastroduodenal region developed an episodic late rebleeding (4 times during 11 weeks course of anticancer chemotherapy). All 3 but the last hemorrhage at the terminal stage were controlled satisfactory by the endoscopic hemostasis. The third case rebled on three separate occasions from a large perforating ulcer at the gastric angle

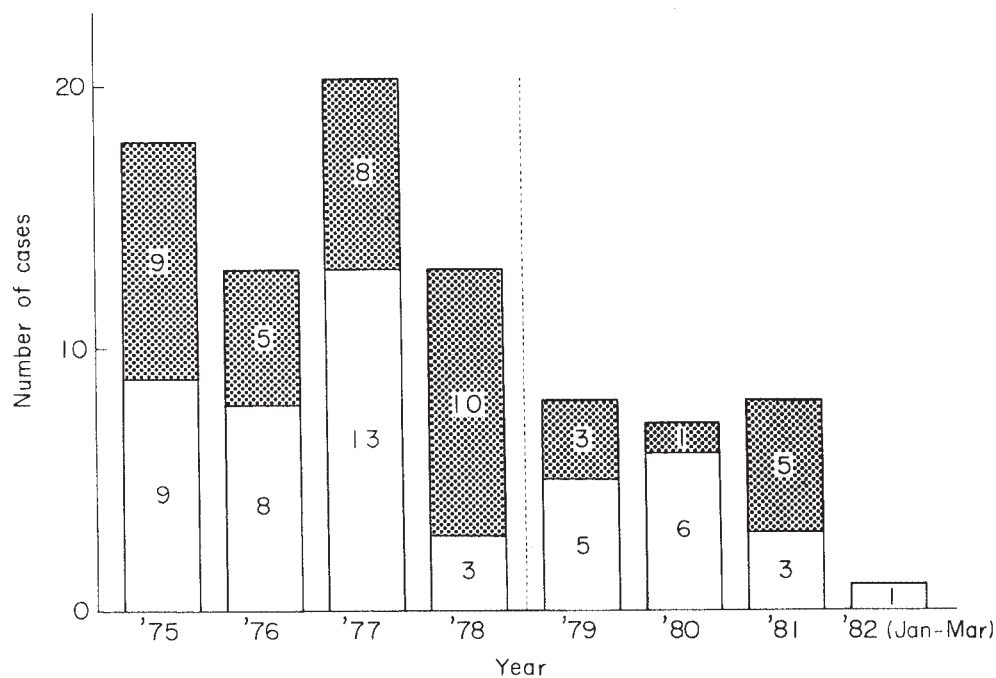


Fig. 3. Massive hemorrhaged gastro-duodenal ulcer or cancer cases with needed surgery or died of the bleeding in Tohoku University Hospital. ■, operation case; □, autopsy case.

gastric angle during a period of about 1 month following an operation for fracture of the femur. The rebleedings were all treated satisfactorily by the transendoscopic ethanol injection. However, the patient was subjected to gastrectomy because of perforation located distant from the sites of ethanol injection. Since the patient developed sharp pain a few hours before the third hemostatic attempt on, one possible explanation is that he has already in a state of perforation before ethanol. Histopathologic study of the resected specimen of the stomach from this patient revealed that the perforation was not directly associated with the local ethanol injection. There were 3 patients on whom elective operations were performed sometime after the hemostasis was completed by this procedure. No cases needed an emergency operation due to gastrointestinal hemorrhage. Eight patients have expired after the endoscopic attempts, but all of them died due to conditions other than hemorrhage, e.g. malignant tumors, complicated DIC, etc. Six treated were complicated by carcinomatous peritonitis, ileus associated with ascites and metastatic carcinoma of the liver after surgical removal of carcinoma of the colon, but the endoscopic hemostasis was successfully completed with no rebleedings in all the cases.

Shown in Fig. 3 are cases in which gastric or duodenal ulcer, and carcinoma of the stomach were treated surgically at the Tohoku University Hospital during the period since 1975. Beside the gastrointestinal diseases, many patients had various underlying diseases such as collagen diseases and cardiopulmonary disorders among them. Thirty-two patients were surgically treated and 33 patients autopsied (total: 65 cases) during the 4-year period from 1975 to 1978

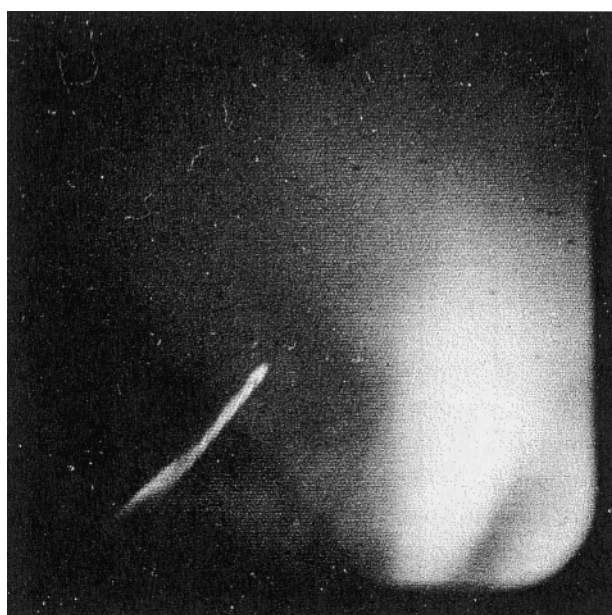


Fig. 4. Endoscopic picture showed a sprouting hemorrhage from an exposed blood vessel in the base of a large ulcer locating on the anterior wall of the upper gastric body.



Fig. 5. Immediately after injection, hemorrhage was successfully stopped.

prior to application of the transendoscopic hemostatic procedure, and the numbers of cases became remarkably reduced during the period from 1979 to 1982 (7 surgically treated and 15 autopsied; total: 22). After this trial, there has been no case of emergency operation for gastrointestinal hemorrhage at this hospital since June 1981.

Case Male, 66 years of age.

Past history: Treated for diabetes for the last 5 years.

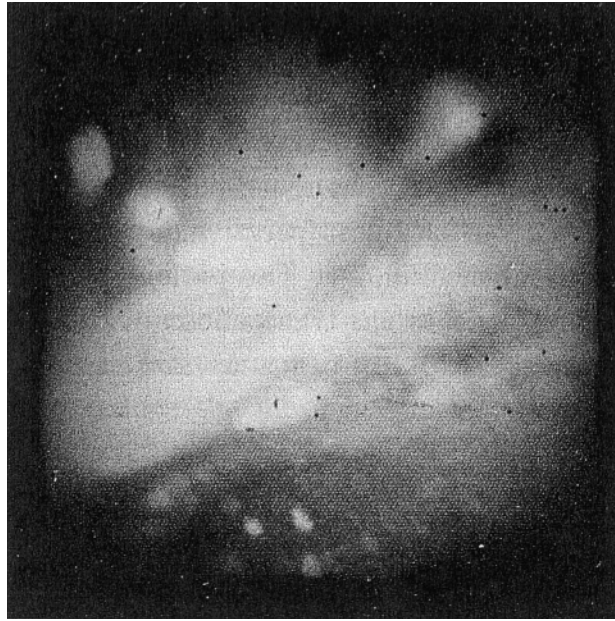


Fig. 6. The ulcer base was found completely free of hemorrhage on the following day.

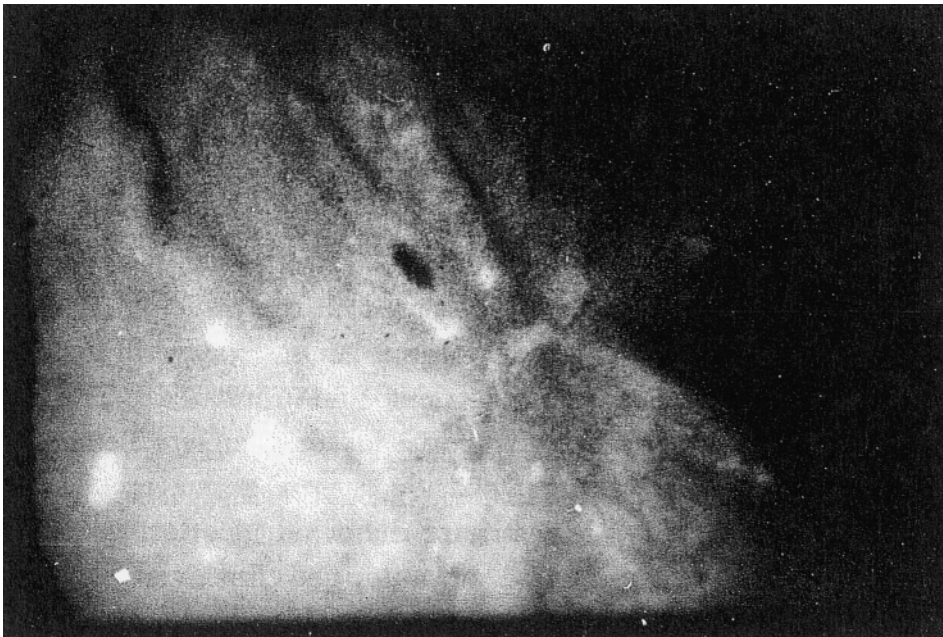


Fig. 7. The ulcer became noticeably contracted in 20 days.

Present illness: The patient received an operation for choledocholithiasis at the Department of Surgery of this hospital on January 29, 1981, and began to have melena and fell in a shock state on the seventh postoperative day. On the following day the patient rebled thrice from the upper gastrointestinal tract. On the ninth postoperative day, a massive hemorrhage from the upper gastrointestinal tract caused a marked melena, hematemesis and shock, and the patient was referred for an emergency endoscopic examination. An emergency panendoscopy performed at the bedside revealed sprouting hemorrhage from an exposed blood vessel about

2 mm in diameter in the base of a large ulcer in the anterior wall of the upper gastric body with a large amount of fresh blood retained in the gastric lumen (Fig. 4). Injection of 0.2 ml absolute ethanol to the site promptly arrested the bleeding (Fig. 5). As seen from Fig. 6, the ulcer base was found completely free of hemorrhage on the following day. The tenth postoperative day, diet was begun safely. A picture taken at the 29th postoperative day demonstrated a remarkable contraction in size of the ulcer (Fig. 7). The patient had received a total of 30 units of blood transfusion prior to the transendoscopic hemostasis at which time the erythrocyte count was 233×10^4 per mm^3 and the hematocrit 27%. He improved progressively thereafter.

DISCUSSION

Emergency endoscopy has been of some value as a means to determine the site of hemorrhage, to indicate the nature of the lesion, and to select the method in treatment. However, it has been no more than a diagnostic means. Endoscopy became a therapeutic tool when gastric polyps or carcinomas were incinerated by transendoscopically applied high frequency currents. Various transendoscopic techniques including use of laser beams were similarly applied to arrest gastrointestinal hemorrhage with the gratifying results (Papp 1975; Matek et al. 1979; Maiman 1960; Goodale et al. 1970; Hayashi et al. 1975; Frühmorgen et al. 1976; Kiefhaber et al. 1977; Linscheer and Fazio 1979; Hirao et al. 1982), yet all left rooms for improvement in respect of hemostatic effect, safety, procedural simplicity and economy.

In contrast with them, presently described technique has resolved these problems (Asaki 1981). The procedure is based on the principle of dehydration and fixation of tissue with absolute ethanol, a common fixative in histology. By the application of ethanol vessels are constricted and necrotized. The endothelial lining thus becomes thrombogenesis which leads to complete hemostasis. The hemostasis can be performed easily at bedside even in an emergency case.

The number of patients with gastric or duodenal ulcer or carcinoma of the stomach who were surgically treated or autopsied for overt gastrointestinal hemorrhage has become remarkably reduced since the introduction of this hemostatic procedure in June 1979 at the Tohoku University Hospital.

It would be overhasty to discuss merits and demerits of any hemostatic method by mere reference to percentage of improved cases, without evaluation of the background conditions of patients. Moreover, the hemostatic therapeutic outcome is likely to vary more or less with the disposition and degree of skill of the operator particularly in transendoscopic hemostasis where the technique largely affects the outcome. Even though, it should be noticed that the hemostatic potency of this procedure and remarkably low propensity for rebleeding were measured in face of anticancer chemotherapy with a platelet count of about 2×10^4 per mm^3 , heparinization after a by-pass operation on the heart for

heart for myocardial infarction, and stress ulcer caused by various types of surgical manipulations.

Needless to say, gastrointestinal hemorrhage must be ceased as early as possible with the least invasive method. From this point of view, application of the presently described technique seems to be highly advisable one specially for the use in an emergency case and/or in the bedside practice.

In conclusion, emergency endoscopy is no longer a merely diagnostic measure but has been proving to have potential usefulness as a therapeutic weapon as well. The authors are convinced that the application of therapeutic emergency endoscopy will substantially reduce the mortality from gastrointestinal hemorrhage and the rate of cases for emergency operations.

Hemorrhages associated with diathermy or laser irradiation or after biopsy were successfully treated by transendoscopic hemostasis with local injection of absolute ethanol in all 30 patients studied, none developed rebleeding. Hemostatic attempts with this procedure were also successful for 72 gastrointestinal hemorrhagic lesions in all 51 patients treated.

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