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Efficacy of dual therapy (APC & Adrenaline) in high risk peptic ulcer bleeding

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A B S T R A C T

Upper endoscopy, in addition of diagnosis, is also important in treatment and prognosis of gastrointestinal bleeding. Ease of using argon plasma coagulation (APC) has increased the trend to use it. Several studies, so far in far, were in favor of effectiveness of APC in peptic ulcer bleeding (PUB). In this study, the effectiveness rate of dual therapy associated with APC and adrenaline was evaluated on the gastric and duodenal ulcers with major stigmata of recent hemorrhage. In a clinical trial without a control group, conducted at the Internal Medicine Department in Medical Sciences of Tabriz University on 456 patients with gastrointestinal bleeding in the period of 2012-2013, the effectiveness rate of dual therapy associated with APC and adrenaline was evaluated on the gastric and duodenal ulcers with major stigmata of recent hemorrhage. Of 456 patients with Gastrointestinal bleeding (GIB), 211 patients with PUB were selected and from the risk of rebleeding, were divided in two groups: high risk and low risk. In high risk group of 82 patients, dual therapy with adrenalin and APC was used, and in case of rebleeding, treatment was again repeated and if not controlled, the patient was referred to surgery. In 36 patients out of 82 patients, rebleeding was observed that the risk of rebleeding in an active bleeding was 44%, which was similar to non-intervention. There is a doubt about the value of using endoscopic dual therapy (APC and adrenalin) in reduction risk of rebleeding and the requiring surgery in high risk PUB specially in active bleeding. It is recommended the use of other methods like hit probe coagulation (HPC) and Hemoclins.

Introduction

Upper Gastrointestinal Bleeding (UGIB) is defined as a common medical emergency which is expensive with high risk of morbidity (1). UGIB refers to the origin of excessive bleeding before Treitz ligament (1).

The annual incidence of hospital admissions for UGIB in the United States and is approximately 100 in 100000 adults population (2). The most common causes of UGIB include Peptic Ulcer Disease (PUD), esophageal varices, esophagitis, erosive

gastritis, Mallory Weiss syndrome, angiodysplasia, cancer and polyp and dieulafoy lesions (the most common cause of PUD) (3).

Upper endoscopy can provide information about the prognosis of UGIB besides the diagnosis and treatment (4). Endoscopic therapy for high risk of recurrent bleeding ulcers had a better outcome compared to medical and surgical treatment (5).

According to Forrest classification, the stigmata of hemorrhage observed at endoscopy can be classified as: High-risk lesions (active bleeding, Non bleeding visible vessel (NBVV) or adherent clot) and low-risk lesions (Flat pigmented spot and clean base).

The accepted treatment for high-risk ulcer includes intravenous proton pump inhibitors (PPI) for 72 hours along with a dual endoscopic therapy (7). The dual therapy includes the methods such as thermal coagulation, Hemo clips and argon plasma coagulation (APC) associated with the diluted adrenaline injection. The adrenaline injection is not singly recommended in terms of the increased risk of re-bleeding (8).

In this study, the effectiveness rate of dual therapy associated with APC and adrenaline was evaluated on the gastric and duodenal ulcers with major stigmata of recent hemorrhage.

Materials and methods

In a clinical trial without a control group, conducted at the Internal Medicine Department in Medical Sciences of Tabriz University on 456 patients with gastrointestinal bleeding in the period of 2012-2013, the effectiveness rate of dual therapy associated with APC and adrenaline

was evaluated on the gastric and duodenal ulcers with major stigmata of recent hemorrhage.

Clinical protests include: Hematemesis, melena, rectorrhagia, weakness, dizziness and unexplained drop in hemoglobin. After history taking, physical examination and initial manufacturing hospital file for each patient, the initial treatment conducted as follows: at least two peripheral venipunctures, hydration, the pack cell if necessary, Pantoparazole (IV) and blood sampling for initial examinations.

Upper endoscopy was performed on the 456 patients in the first 24 hours of hospitalization after stabilization of hemodynamic symptoms. Finally the gastric and duodenal ulcers with major stigmata were observed in 82 patients who were selected for the study.

Major Stigmata includes active bleeding, non Visible Vessel bleeding and oozing + adherent clot. Therapeutic endoscopic intervention was performed as dual therapy (injection of 3-15 cc adrenaline 1 /10000 associated with APC). The patients were monitored for 72 hours in terms of re-bleeding. Dual therapy was secondly repeated for the patients with recurrent hemorrhage the same as first method.

The patients with the unsuccessful endoscopic intervention or recurrent hemorrhage were referred to the surgical department. The demographic information, Clinical and laboratory findings, and the endoscopic results of each patient were recorded and the percentage frequency distribution was analyzed by SPSS.

Considering the previous studies and due to the high risk of hemorrhage and mortality in

the absence of endoscopic intervention, the control group was selected with endoscopic intervention so the effectiveness rate of endoscopic intervention (dual therapy with adrenaline and APC) was performed without a control group and compared with other studies. Therapeutic endoscopic intervention was performed by two gastroenterologist fellowships and the direct supervision of teachers and the material and devices are as follows:

Endoscopic machine- Pentanx model, APC-generating device-AA model and adrenaline-1/10000.

This study was performed on the supervision and approval of Digestive Disease Research Center, Tabriz.

Results and Discussion

The mean age of patients with gastric ulcer and duodenal ulcer was respectively 60.95 (between 19-89 years old) and 58.69 (between 16-89 years old). 127 patients with gastric ulcer and 84 patients with duodenal ulcer were identified among 211 patients referred with ulcer symptoms. 67 out of the 127 patients with gastric ulcer a history resume NSAIDs and whereas 43 patients (51%) with duodenal ulcer was reported the same experience.

The incidence of macroscopic lesions and their classification are shown in Table 1. Patients were divided into two groups:

1. The first group consisted of 129 low-risk patients who were not in the therapeutic endoscopic intervention such as (clean base and flat pigmented spot)
2. The first group consisted of 82 high-risk patients who were in the therapeutic endoscopic interventions such as (dual therapy with APC and adrenaline)

The results of endoscopic therapy, the rate of bleeding, the number of patients referred for surgery and the mortality of gastric and duodenal ulcer are respectively shown in Tables 2 and 3. Totally, the re-bleeding occurred in 11 out of the 13 patients (84.6%) with active hemorrhage was in dual therapy with APC and adrenaline. the surgery was finally necessary for 7 patients (53.8%) but 6 cases were died (46%) (Table 4). Risk of rebleeding before and after endoscopy therapy in PUD was show in table 5.

APC is a non-contact method which leads to coagulation and tissue homeostasis by using high-frequency devices and Argon gas ionization to liquid (Plasma) (5). The tissue coagulation induced by APC is relatively superficial (maximum depth 1-3 mm) and therefore unable to coagulate deep vessels (6). In a study conducted by Karaman and colleagues on the 85 patients divided into two groups with 43 and 42 patients suffered from UGIB caused by high risk ulcers, After examining the effectiveness of APC along with hit probe coagulation (HPC), adrenaline, they stated that the efficacy of APC and HPC was respectively 97% and 81% to prevent the occurrence of re-bleeding (1).

In the study conducted by Wang et al on 135 UGIB patients in order to compare the primary homeostasis efficiency among these patients by using APC and adrenaline with distilled water. They proved that the effectiveness of APC and distilled water were respectively 97% and 91%, the Re-bleeding rate in APC and distilled water was respectively 11 % and 27% which indicates that APC is more effective than distilled water to prevent the occurrence of re-bleeding (5).

Table.1 Frequency of ulcer type in Gastric and Duodenal ulcers

		Gastric Ulcer	Duodenal ulcer	Total	Total
Low Risk	Clean base	52(24.64%)	34(16.11)	86(40.75%)	129(61.13%)
	Flat Pigmented spot	31(14.69%)	12(5.68%)	43(20.38%)	
High Risk	Adherent clot + oozing	17(8.05%)	22(10.42%)	39(18.48%)	82(38.87%)
	NBVV	20(9.47%)	10(4.74%)	30(14.21%)	
	Active bleeding	7(3.31%)	6(2.84%)	13(6.16%)	
Total		127(60.19%)	84(39.81%)	211(100%)	

Table.2 Frequency of Rebleeding, Surgery and Mortality in Gastric ulcer

	Patients count	Dual therapy	Rebleeding	Surgery	Mortality
Active bleeding	7(15.90%)	7(15.90%)	6(13.63%)	4(9.09%)	4(9.09%)
NBVV	20(45.45%)	20(45.45%)	9(20.45%)	1(2.27%)	1(2.27%)
Adherent clot	17(38.63%)	17(38.63%)	6(13.63%)	1(2.27%)	3(6.81%)
Total	44(100%)	44(100%)	21(47.72%)	6(13.63%)	8(18.18%)

Table.3 Frequency of Rebleeding, Surgery and Mortality in Duodenal ulcer

	Patients count	Dual therapy	Rebleeding	Surgery	Mortality
Active bleeding	6(15.8%)	6(15.8%)	5(13.1%)	3(7.9%)	2(5.26%)
NBVV	10(26.3%)	10(26.3%)	3(7.9%)	0(0%)	1(2.63%)
Adherent clot	22(57.9%)	22(57.9%)	7(18.4%)	0(0%)	1(2.63%)
Total	38(100%)	38(100%)	15(39.4%)	3(7.9%)	4(10.52%)

Table.4 Frequency of Rebleeding, Surgery and Mortality in Gastric and Duodenal ulcer

	Patients count	Dual therapy	Rebleeding	Surgery	Mortality
Active bleeding	13(15.85%)	13(15.85%)	11(13.41%)	7(8.53%)	6(7.31%)
NBVV	30(36.58%)	30(36.58%)	12(14.63%)	1(1.22%)	1(1.22%)
Adherent clot	39(47.56%)	39(47.56%)	13(15.85%)	1(1.22%)	4(4.87%)
Total	82(100%)	82(100%)	36(43.90%)	9(10.97%)	11(13.41%)

Table.5 Risk of rebleeding before and after endoscopy therapy in PUD

	Frequency	Rebleeding	Risk of rebleeding after endoscopy therapy
Active Bleeding	12	90%	15-30
NBVV	22	50%	15-30
Adherent clot	24	33%	0-5
Flat pigmented	10	7%	Unknown
Clean base	32	3%	Unknown

There was no significant advantage for APC compared to other endoscopic homeostasis methods in a meta-analysis conducted by Havanond and colleagues (9). Active bleeding is one of the predictors of re-bleeding in the initial endoscopic treatment in a meta-analysis of García-Iglesias et al (10). Kujawski and et al who compared different endoscopic treatment methods of PUD indicated the 78% initial homeostasis rate in general. The Hemoclips singly is effective in homeostasis compared to the HPC and adrenaline or APC and adrenaline (11). The statistical studies related to reducing the risk of bleeding have totally been presented in all researches. But there is no study conducted by APC and adrenaline based on the ulcer type. Therefore, a recent research is one of the few studies that separately evaluate the efficacy of APC and adrenaline on the basis of the ulcer type(12).

As it is shown in Table 4, the re-bleeding rate was extremely high in active bleeding after initial homeostasis and the re-bleeding was found in 11 out of the 13 patients after initial homeostasis (85% of cases) which is as the same as non-intervention condition (90%). It is likely that the initial provisional effects in homeostasis control are associated with the effectiveness of tamponade and epinephrine during active bleeding and use or disuse of APC neither have difference in the re-bleeding rate.

Thus it can be concluded that dual therapy with epinephrine and APC, has no tangible impact on the prevention of re-bleeding in these ulcers. Considering the presence of NBVV in the ulcers, the re-bleeding was occurred in 12 out of the 30 patients (40%) and it should be noted that the APC and epinephrine have no significant effectiveness on the ulcers due to the possibility of 50% re-bleeding without any intervention. In

Table 5, it was shown that the HPC could reduce the risk of re-bleeding less than 20%. Considering the oozing ulcers with adherent clots, the re-bleeding was occurred in 13 out of the 39 patients (33%) which is approximately the same as the non-intervention cases (Table 5). The results are almost the same as above while the analysis is according to differentiate between a Gastric ulcer and a duodenal ulcer (85% of duodenal ulcer with active bleeding and 83% of gastric ulcer with active bleeding).

Despite the number of studies that have demonstrated the similar efficacy for dual endoscopic therapy (with APC - epinephrine) and HPC in the patients with the high risk peptic ulcer bleeding (PUB), in this study the effectiveness of this method in homeostasis of PUB (especially in the cases with active bleeding) is clearly controversial which is the same as non-intervention cases. It also seems that the APC and the adrenaline have no effect in reducing the need for surgery.

The surgery is finally required for 9 out the 82 patients (11%) with high risk PUB which is more significant in the cases with active bleeding (7 out of 13 patients).

The mortality rate was 11 patients (13.4%) among patients with high risk PUB but it will change into 6% while the total patients (211 cases) with high risk PUB and low risk PUB are considered.

This study has the following limitations:

Firstly, this research was conducted without a control group; our results were compared with confirmed results of previous studies and gastrointestinal textbooks as a control group. It is not morally correct to choose the control group as Placebo.

Secondly, the ulcer size as an accepted factor in order to assess and predict the risk of re-bleeding, other factors such as NSAID consumption, age, hemodynamic instability were not considered as confounding factors in the risk of bleeding. It was performed on the basis of the endoscopic classification and the appearance of the ulcer.

Thirdly, there is little possibility that the inadequate training or insufficient proficiency affected the results, because the procedure is performed by Gastroenterology fellowship under the supervision of lecturers with 10 years experiences.

Conclusion

The need for surgery especially in the active bleeding cases and the dual therapy with APC and adrenaline to reduce the risk of re-bleeding is completely controversial. Other techniques such as HPC and Hemo clips are recommended in order to endoscopic therapy for high risk PUB, especially ulcers with active bleeding.

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