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ENDOSCOPIC INJECTION OF DILUTED ADRENALINE FOR TREATMENT OF BLEEDING DUODENAL ULCER IN COMPARISON WITH SURGERY.

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Abstract

Peptic ulcer disease is a common and life threatening emergency. The management of patients with bleeding gastroduodenal ulcer (BGDU) has evolved over the past two decades. For many years, surgery was the only treatment for BGDU. Endoscopic techniques have emerged as a successful alternative with constant improvement. Endoscopic therapy is effective in controlling 80-95% of actively bleeding ulcers and it lowers the mortality rate from BGDU by 30-40%. No study has compared surgery with endoscopic therapy; most trials of endoscopic therapy define the need for a surgical operation as a treatment failure of endoscopic haemostasis. Aim of our study is to evaluate endoscopic treatment of bleeding duodenal ulcers using injection of diluted adrenaline in comparison with surgical treatment. This is a prospective study conducted at Basrah General Hospital during the period between Jan.2004-July 2006. Twenty patients were treated by endosopic injection of diluted adrenaline (1:10000), the injection group (group I), compared with 28 patients treated by surgery, the surgically treated group (group S). The mean age was 55 and 57 years in I group and S group respectively. There were no statistically significant differences in demographic, clinical and endoscopic findings between both groups. High rate of successful initial haemostasis was achieved in group I (95%). Injection therapy failure was encountered in one patient (5%) while other two patients (10%) developed rebleeding in group I, giving overall success rate of 85% (17 patients out of 20). Two patients (7.14%) developed rebleeding in group S and one of them died. Other non-bleeding complications developed in 3 patients in group I and in 14 patients in group S. One patient (5%) died in group I from non-bleeding cause representing the total mortality. Seven patients died in group S from non-bleeding cause giving overall mortality rate of 28.5% (8 out of 28 patients). There were statistically significant differences in complication and mortality rates between the two groups. There was statistically significant difference in the amount of blood transfusion between the study groups. There was no statistically significant difference in the length of the hospital stay. Conclusion: Our results show that endoscopic injection of diluted adrenaline for patients with actively bleeding duodenal ulcer is associated with less complication and mortality rates as well as less amount of blood transfusion in comparison with surgical treatment.

Introduction

Bleeding peptic ulcer is a common and life threatening emergency accounting for 50-70% of cases of acute nonvariceal upper gastrointestinal haemorrhage[1,2]. Eighty percent of all bleeding from peptic ulcers stop spontaneously without any specific intervention[1]. However, in subgroup of patients (10-20%), the bleeding does not stop with a mortality rate of 6-10% despite recent advances in therapy[3-6]. The management of patients with bleeding gastroduodenal ulcer (BGDU) has evolved over the past two decades[7]. For many years, surgery was the only treatment for BGDU. Endoscopic techniques have meanwhile emerged as a successful alternative with a constant

improvement[8]. Early stratification of patients into low-and high-risk categories for rebleeding and mortality, based on clinical and endoscopic criteria is important for proper management[1,2,9,10]. The endoscopic therapy available for patients who have major stigmata of recent haemorrhage can be classified as those based on injection, application of heat (thermal) and mechanical clips[11]. Endoscopic therapy is effective in controlling 80-95% of actively bleeding ulcers. Recurrent bleeding occurs in 10-20% of these cases and it is the single most important adverse prognostic factor[11-13]. The choice between endoscopic modalities remains controversial[12]. Endoscopic therapy lowers the mortality rate from BGDU by 30-40%[1,13]. No study has compared surgery with endoscopic therapy; most trials of endoscopic therapy define the need for a surgical operation as a treatment failure of endoscopic haemostasis[3,4,14]. Aim of our study is to evaluate endoscopic treatment for bleeding duodenal ulcers using injection of diluted adrenaline in comparison with surgical treatment.

Patients and Methods

This is a prospective study that was conducted at Basrah General Hospital during a period between Jan.2004-July 2006. A total of 25 patients who were admitted to the surgical ward either referred from emergency department or from medical wards complaining of upper gastrointestinal bleeding were proved to be caused by duodenal ulcers by endoscopy. Five cases were excluded from the study. The duodenal bleeding in one of them proved to be due to local invasion of malignant pancreatic tumour and in another patient it was due to invasion of advanced gallbladder tumour. The other three patients presented with massive bleeding from the duodenum that prevented proper visualization at endoscopy and they were transfered immediately to the operating theater for surgical treatment. The patients were resuscitated and a maintained haemodynamic state was achieved before endoscopic interventions using the ABC steps of the Advanced Trauma Life Support System (ATLS)[1,5].The remaining 20 patients, were treated by injection of diluted adrenaline (1:10000), and represented the injection group (group I). The adrenaline was further diluted to 10 -20 ml using 0.9% NaCl. We used a GIF Q40 endoscop (Olympus-Tokyo-Japan) and LM 10 or NM-8L injector for treatment. Irrigation and suction with normal saline was used through a nasogastric tube if the stomach contained fresh blood or clots that prevented clear vision. The bleeding duodenal ulcer was assessed depending on the revised Forrest ulcer classification[13,15] and if any of the endoscopic stigmata of recent haemorrhage was present, the endoscopic injection commenced. We inject an average of 12 ml of diluted adrenaline (range 8-20ml) around and in the bleeding ulcer. Successful haemostasis was achieved if no further bleeding appeared from the ulcer and this was assessed by target irrigation of the ulcer and watching for a couple of minutes. If continuous bleeding or oozing still appeared after the injection of a maximum amount of diluted adrenaline, treatment failure was considered at index endoscopy and the patient underwent emergency surgery. After injection therapy the patients were transferred to the Intensive Care Unit for continuing monitoring and further treatment. Rebleeding was defined as any fresh bleeding that appeared in nasogastric tube , emesis or per rectum or any drop in the haemoglobin level to less than 100g/l after its stabilization to a normal level

or the need for increasing number of blood transfusion units to maintain normal haemodynamic status in the first 72 hours post injection. All patients received cimitidine 200mg intravenously 8 hourly then 40 mg oral omeprazol twice a day when they started oral intake with a standard H. Pylori eradication treatment. The collected data included age, sex, concurrent use of nonsteroidal anti-inflammatory drugs (NSAID), associated comorbidity and the clinical and endoscopic findings in addition to the parameters used to assess the endoscopic treatment like, initial haemostasis, rebleeding rate, amount of blood transfusion, hospital stay, complications and mortality rate. The patients were observed for these parameters for 30 days post treatment. All the data were compared with 28 patients admitted or referred to surgical units complaining of bleeding duodenal ulcers and were treated by surgery during the period from 2003-2006 in the same hospital. They represent the surgically treated group (group S). A written consent was taken from all the patients about the acceptation of endoscopic injection, failure of the procedure and the possible need of surgery at any time the patient's condition demanded. Chi square, Fisher's exact test and paired t test were used, when appropriate, for statistical analysis and P value <0.05 was considered significant.

Results

A total of 48 patients included in the study, 20 of them represent the injection group (group I) and 28 patients represent the surgically treated group (group S). The mean age was 55 and 57 years in group I and group S respectively. Seventy percent and 67% of patients were male in group I and group S respectively. About 40% of patients in both groups presented with shock state (BP<100mmHg and pulse rate>100 beat/minute). Comorbidity was present in half of the patients in both groups and cardiorespiratory diseases were the predominant. About 60% of patients in both groups were on concurrent NSAID use. One third of the patients in both groups developed bleeding during their admission to hospital for other illnesses. The endoscopic findings were comparable in both groups and in more than 85% of patients the stomach contained fresh blood or clots. There were no statistically significant differences in demographic, clinical and endoscopic findings between both groups. Table I, shows the clinical and endoscopic characteristics of the patients in both groups and their statistical significance. Table II shows the outcome parameters that were used to compare the two study groups. High rate of successful initial haemostasis was achieved (95% and 100% in group I and group S respectively). Injection therapy failure was encountered in one patient (5%) with big size, (2Cm), actively bleeding ulcer who was subsequently treated successfully by emergency surgery. Two patients (10%) developed rebleeding in group I and were managed successfully by surgery. The overall success rate of endoscopic injection was 85% (17 patients out of 20). Two patients (7.14%) developed rebleeding in group S and one of them died. Other non-bleeding complications developed in 3 patients in group I and in 14 patients in group S. One patient (5%) died in group I from nonbleeding cause representing the total mortality. Seven patients died in group S from nonbleeding cause giving overall mortality rate of 28.5% (8 out of 28 patients). Table III shows the complications and the causes of death in both groups. There were statistically significant differences in complication and mortality rates between the two

groups (P value 0.028 and 0.04 respectively). There was statistically significant difference between the study groups regarding the amount of blood transfusion (P value 0.012).There was no statistically significant difference in the length of the hospital stay.

Discussion

Peptic ulcer disease remains the commonest cause of non-variceal upper gastrointestinal tract bleeding[1,2,16]. Although hospitalization and surgery for uncomplicated duodenal ulcers have decreased over the past two decades, the number of hospital admission for haemorrhage associated with ulcers has remained relatively unchanged [5,6,17,20]. It represents a substantial clinical and economic burden [1]. The management of patients with bleeding duodenal ulcers has evolved over the past decades and endoscopic techniques have emerged as a successful alternative to surgery with a constant improvement[7,8,13]. The choice between endoscopic modalities remains controversial and combination of two modalities confers additional success in treatment[4,11-14]. For injection therapy, no solution is superior to another for haemostasis[1,18]. In our study, we used diluted adrenaline as it is the injection agent of choice[12]. It is non-tissue damaging, without risk of life threatening necrosis produced by sclerosants, cheap, effective, safe even if large volume used[11,12,19-21]. In our hospitals the interventional endoscopy is in evolution and that is why our study sample is small. The age is one of the clinical factors that is associated with increase in incidence of ulcer bleeding, rebleeding and mortality[11,12,22]. In the literatures, the age of 60 years is used as a cut point between low-and high- risk patients for rebleeding and death[1,2,11,12,22]. The mean age in our study was slightly less than 60 years in both groups and it was associated with comparable rebleeding and mortality rates that was reported by other studies[1-6,13]. Yasuharu et al[23] concluded that increased age may no longer be a risk factor for rebleeding and death after endoscopic injection therapy. Other clinical and endoscopic parameters to stratify patients into low- and high- risk for rebleeding and death that were used in our study showed no statistically significant differences between both groups. This can give an idea that our study groups were comparable. Initial endoscopic haemostasis was achieved in 95% of our patients and this in consistence with other studies [1-6,18,19,24,25]. One (5%) injection therapy failure was encountered in a patient with a big size (2cm) actively bleeding ulcer. This goes in line with the importance of ulcer size as a predictor of injection therapy failure, although it was not considered in Forrest ulcer classification, yet it was mentioned by many other authors[1,5,26-29]. Two patients (10%) in our study developed rebleeding after successful initial injection therapy. The reported rebleeding rate after successful initial injection therapy ranges from 10-20%[1,5,13,14,24,25]. The two patients developed rebleeding at 24 and 36 hours post injection and were successfully managed by emergency surgery without delay or doing another endoscopic trial. Both of them survived without complications. The active management of the two patients who developed rebleeding by doing early surgery might have influenced their survival without complication. In case of rebleeding, many studies suggest that surgery should not be delayed when indicated[1,2,30,31].There is little controversy concerning the management course of patients with active bleeding ulcer that fail to stop at index interventional endoscopy, most

would agree that those patients should undergo surgical treatment[24]. On the other hand, the preferred line of management of ulcer rebleeding after initial endoscopic haemostasis is not yet clearly defined[1,2,24]. Many studies[1-8,19,25,32-38] suggest different management lines for treating patients with recurrent bleeding after initial endoscopic haemostasis. These lines reduce the rebleeding rate, the need for surgery, with its inherent risk, and mortality rate. These management lines include; The addition of another endoscopic haemostatic modality after adrenaline injection like, heater probe or mechanical clips, the use of scheduled second look endoscopy, endoscopic retreatment for rebleeding and the use of intravenous proton plump inhibitors as a bolus dose or infusion. The above lines of management are not available in our hospitals and its availability and utilization in the future might further improve the results. In our study we used intravenous cimitidine 200 mg 8 hourly because of its availability and depending on the results of Selby et al[39] that shows reduction in rebleeding rate and the need for surgery but not the mortality rate[40]. Recent studies appreciate the effect of oral proton plump inhibitors in reducing the rebleeding rate[41,42], But the time of starting oral intake is a question that still needs an answer. In our study we started oral omeprazol in a dose of 40 mg 12 hourly, 24-48 hours post injecion. BGDU is not an automatic contraindication to enteral feeding but sometime it needs to be withheld for 48 hours until the risk of rebleedig is minimal[43]. Two patients (7.14%) developed rebleeding in group S after surgical haemostasis. Both of them underwent salvage second surgery, one of them died 48 hours postoperatively from irreversible shock and organ failure. This might indicate that salvaged second surgery carries increased mortality but its statistical significance was inconclusive because of small number of the patients. The difference in rebleeding rate between group I and group S was not statistically significant (P value 0.72). If we exclude the rebleeding from the complications, 3 patients (15%) developed non-bleeding complication in group I compared with 14 patients (50%) in group S, a difference which was statistically significant (P value 0.028). There are no study comparing the complication rate between endoscopic treatment and surgery and most of the studies consider the need for surgery as an endoscopic treatment failure[3,4,14,25]. Most of the complications that developed in group S were operation- related complications. One patient (5%) died in group I due to myocardial infarction 7 days post injection. Eight patients (28.5%) died in group S, 7 of them died from non bleeding causes. This indicates that blood loss and emergency surgery is intolerable by patients who are poor surgical candidates because of their age and coexisting illnesses[11-15]. Thomopoulos et al[43] stated that two thirds of deaths were not caused by the bleeding but from other causes a great number of which were unpreventable. Table III shows the complications and the causes of deaths in our study.This indicate that endoscopic injection is a logical treatment and offers significant reduction in complications and mortality. There was a difference in the mean number of blood transfusion units between the two groups and it was statistically significant (P value 0.017) .Operative treatment usually associated with some inevitable blood loss that could explain the difference in the blood transfusion requirement. There was no statistically significant difference in the length of hospital stay between the study groups (P value

0.28). This is consistent with many studies[11-14,25].

In conclusion, these results indicate that endoscopic injection of diluted adrenaline for patients with actively bleeding duodenal ulcer is associated with less complication and mortality rates and required less amount of blood transfusion in comparison with surgical treatment.

It is therefore recommended that: Adoption of generally accepted management protocol for patients with BGDU in our hospitals. Training programs for interventional endoscopy need to be conducted. Improvement of our endoscopy unit facilities including the current haemostatic modalities. Intravenous proton pump inhibitors need to be available in our hospitals.

Table I: The clinical and endoscopic characteristics of the patients in both groups and its statistical significance.

Characteristic	Injection group	Surgical group	significance
Age(year) mean ± SD	55 ±12	57 ±14	NS
Sex: *Male* *Female*	 14 (70%) 6 (30%)	 19 (67.8%) 9 (32.2%	NS
Shock at presentation	8 (40)	11 (39.2%)	NS
Haemoglobin(g/l) mean ±SD	8.5 ± 2	8.2 ± 2	NS
Comorbidity: *Cardiac* *Respiratory* *Renal* total	 4 (20%) 4 (20%) 2 (10%) 10(50%)	 7 (25%) 6 (21.4%) 1 (3.5%) 14 (50%)	NS
NSAID	12 (60%)	17 (60%)	NS
Bleeding during hospitalization	6 (30%)	10 (35%)	NS
Endoscopic findings: *Actively bleeding or oozing ulcer* *Fresh clot overlying ulcer base* *Fresh blood or clot in stomach*	 15 (75%) 5 (25%) 17 (85%)	 22 (78.6%) 6 (21.4%) 25 (89.2%)	NS

SD = Standard deviation. NS= Not significant, P value>0.05.

Table II: The outcome parameters of the patients in both groups:

Parameter	Injection group	Surgical group	Significance
Initial haemostasis	19(95%)	28(100%)	NS
Failed treatment	1(5%)	0(0%)	NS
Rebleeding	2(10%)	2(7.14%)	NS
Complications	3(15%)	14 (50%)	S
Mortality	1(5%)	8(28.5%)	S
Units of blood transfusion mean ± SD	6 ± 2	8 ± 3	S
Hospital stay(days) mean ± SD	10 ± 5	12 ±7	NS

S = Significant, P value<0. 05, **NS =** Not significant, P value> 0.05.

Table III: Complications within in both groups and the cause of death.

Complications	Injection group No. (death)	Surgical group No. (death)
Myocardial infarction	1 (1)	1 (1)
Stroke	1	0
Chest infection	0	3 (1)
Respiratory failure	0	2 (2)
Wound complications	0	4 (1)
Acute renal failure	1	0
Intraabdominal sepsis	0	4 (2)
Rebleeding	2	2 (1)
Total *	5 (1)	16 (6)

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