

Comparison of Pneumatic Dilatation with Pneumatic Dilatation Plus Botulinum Toxin for Treatment of Achalasia

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Received: 7 Apr. 2009; Received in revised form: 4 Oct. 2009; Accepted: 8 Nov. 2009

Abstract- Among the therapeutic options for achalasia are pneumatic dilatation (PD), an appropriate long-term therapy, and botulinum toxin injection (BT) that is a relatively short-term therapy. This study aimed to compare therapeutic effect of repetitive pneumatic dilatation with a combined method (botulinum toxin injection and pneumatic dilatation) in a group of achalasia patients who are low responder to two initial pneumatic dilations. Thirty-four patients with documented primary achalasia that had low response to two times PD (<50% decrease in symptom score and barium height at 5 minute in timed esophagogram after 3month of late PD) were randomized to receive pneumatic dilatation (n=18) or botulinum toxin injection and pneumatic dilatation by four weeks interval (n=16), PD and BT+PD groups respectively. Symptom scores were evaluated before and at 1, 6 and 12 months after treatment. Clinical remission was defined as a decrease in symptom score $\geq 50\%$ of baseline. There were no significant differences between the two groups in gender, age and achalasia type. Remission rate of patients in BT-PD group in comparison with PD group were 87.5% vs. 67.1% ($P = 0.7$), 87.5% vs. 61.1% ($P = 0.59$) and 87.5% vs. 55.5% ($P = 0.53$) at 1, 6 and 12 months respectively. There were no major complications in either group. The mean symptom score decreased by 62.71% in the BT-PD group ($P < 0.002$) and 50.77% in the PD group ($P < 0.01$) at the end of the first year. Despite a better response rate in BT+PD group, a difference was not statistically significant. A difference may be meaningful if a large numbers of patients are included in the study.

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Acta Medica Iranica 2010; 48(2): 107-110.

Key words: Balloon dilatation; botulinum toxins; esophageal achalasia

Introduction

Achalasia is a primary esophageal motor disorder characterized by incomplete relaxation of the lower esophageal sphincter on swallowing and aperistalsis of the esophageal body (1). The primary etiology of achalasia remains unknown but the pathophysiology results in the loss of inhibitory neurons in the esophageal myenteric plexus (1). Despite being a rare disorder, affecting one per 100 000 subjects, achalasia can cause significant symptoms including dysphagia, chest pain, regurgitation and heartburn (2). The mainstay of therapy is directed towards the reduction of lower esophageal sphincter pressure resulting in improved esophageal emptying by gravity. Pharmacological therapy, endoscopic dilatation, botulinum toxin injection and surgical myotomy are the primary therapeutic modalities. Pneumatic balloon dilata-

tion is a commonly used treatment modality. Studies have found that balloon dilatation provides well to excellent symptomatic relief in 86-100% of cases (3-6). Intrasphincteric injection of botulinum toxin has been used in as an alternative to balloon dilatation or surgical myotomy. Several controlled trials have compared the efficacy of PD, BT and myotomy. Pneumatic dilatation is found to be the most effective medical treatment for majority of achalasia patients (7,8). However, long-term follow-up indicated that more than half of patients relapse in 5 years after treatment (9,10). In case of relapse, patients can be retreated with pneumatic dilatation; however, it remains a matter of debate how often patients can be re-dilated before the patient should be referred to the surgeon. Recently, Zerbib *et al.* (11) presented data indicating that those patients responding to the first treatment, can be managed with repeated dilata-

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tion on a long-term basis with excellent results (>90% remission). Because surgical myotomy and repeated dilatations during lifetime are unsatisfactory for the most patients, improvement in therapy is being sought. Radek *et al.* (12) showed that the effect of combined therapy of BT+PD is longer than BT or pneumatic dilatation alone compared to the literature. Our previous studies in naïve achalasia patients showed that botulinum toxin injection before pneumatic dilatation may increase the effectiveness of treatment and 1 year clinical response (13, 14). However, there was not any study in patients with low response to initial pneumatic dilatation and some studies suggest that PD performed in a graded fashion has a high success rate in these patients (15). Here, we report the results of a prospective randomized-controlled trial to compare therapeutic effect of repetitive pneumatic dilatation with a combined method (botulinum toxin injection and pneumatic dilatation) in a group of achalasia patients that had unsatisfactory response to two time's pneumatic dilatation.

Patients and Methods

Patients

All patients with documented primary achalasia that were low responder to two times PD with 3 and 3.5cm Rigiflex balloons (<50% decrease in symptom score and barium height at 5 minute in timed esophagogram after 3month of late PD) were enrolled in this prospective study. The diagnosis of achalasia was established based on the clinical, radiological, endoscopic as well as manometric criteria. Exclusion criteria included age <18 years, cardiovascular disability (functional class III or IV) and coagulopathy. Informed consent was obtained from all patients after a full discussion of the risks, benefits and alternative treatments.

Study design

This study was designed as a randomized prospective controlled trial. All the patients [based on age, 50 >age>50 and achalasia type(classic vs. vigorous)] were randomized to receive pneumatic dilatation with 4cm Rigiflex balloon or botulinum toxin injection and pneumatic dilatation with the same Rigiflex balloon (4cm diameter) by four weeks interval, PD and BT+PD groups respectively. Symptom scores were evaluated before and at 1, 6 and 12 months after treatment. Clinical remission was defined as a decrease in symptom score \geq 50% of baseline (at the time of enrollment in study). The study protocol was reviewed and approved by the Ethic Committee of Digestive Disease Research Center of Tehran

University of Medical Sciences and informed consent was obtained from all patients.

Clinical evaluation

Clinical evaluation was conducted initially and at 1, 6 and 12 months after treatment. The severity of symptoms was evaluated on the basis of five clinical symptoms; solid and liquid dysphagia, active and passive regurgitation and chest pain. The severity of each of these symptoms was scored on a scale of 0–3 as described elsewhere (0 none; 1 weekly; 2 daily, 3 in each meal) for solid dysphagia, liquid dysphagia and active regurgitation, and (0 none; 1 monthly; 2 weekly, 3 daily) for passive regurgitation and chest pain (16, 17). The highest obtainable score was 15. Clinical remission was defined as a decrease in symptom score \geq 50 of baseline.

Botulinum toxin injection

Botulinum toxin has been injected in patients in the BT+PD group, 1 month before receiving the PD. Upon upper gastrointestinal endoscopy, the LES was identified by visualization of the sphincter rosette at the squamocolumnar junction. Clostridium botulinum type A toxin-hemmagglutinin complex (Dysport; IPSEN, Berkshire, UK) was injected through a 5-mm sclerotherapy needle into each quadrant of the LES. Four hundred units of Dysport were diluted in 4-mL normal saline. Two 50-U aliquots (0.5 mL) were injected in each quadrant for a total dose of 400 U.

Pneumatic dilatation

After a clear liquid diet for 12 h and an overnight fast, PDs were performed using 4cm Rigiflex balloon in both groups. Following a complete upper gastrointestinal endoscopy, balloon dilators were passed over a guide wire and were positioned such that LES places at the midpoint of the balloon under videoendoscopic guide. Rigiflex balloons was gradually inflated up to 10 psi in 30 s and maintained for another 60 s. After emptying and pulling out the balloons, patients were endoscoped again to assess the LES opening (relaxation) and any evidence of bleeding or perforation and were discharged after a 6-h observation if remained asymptomatic.

Results

Of 34 patients enrolled in the study, 18 underwent PDs (PD group) and 16 received BT injection 1 month prior to PD (BT+PD group). The baseline characteristics were similar for the two groups (Table 1).

Table 1. Baseline Characteristics of patients with achalasia

Group	BT+PD	PD	P value
No	16	18	NA
Age (mean \pm SD)	31.3 \pm 9.7	33 \pm 8.6	0.59
Sex (F/M)	8/8	12/6	NS

The mean symptom score of the PD group decreased by 74% at 1 month ($P < 0.001$) and remained decreased at 12 months. Similarly, in the BT+PD group, there was a significant reduction (85%) in mean symptom score at 1 month ($P < 0.001$) and this reduction was sustained over 12 months after therapy.

Remission rate of patients in BT-PD group in comparison with PD group were 87.5% vs. 67.1% ($P = 0.7$), 87.5% vs. 61.1% ($P = 0.59$) and 87.5% vs. 55.5% ($P = 0.53$) at 1, 6 and 12 months after treatments respectively. The mean symptom score decreased by 62.71% in the BT-PD group ($P < 0.002$) and 50.77% in the PD group ($P < 0.01$) at the end of the first year.

Twelve months after a single treatment, 10 patients treated with PD and 14 treated with BT-PD were still in symptomatic remission. Total symptom scores decreased significantly in both groups after treatment. There was no statistically significant difference in symptom scores between two groups at the various time intervals (Table 2).

Discussion

Despite several studies comparing primary therapeutic options in achalasia, this is the first randomized control trial comparing the efficacy of the combined treatment of BT and PD with PD in treatment of low responder achalasia patients.

The recurrence of symptoms in achalasia usually occurs in the first year of treatment and follow up in this period is valuable, thus the subjective parameters of response in all patients have been studied over 1 year. Although the statistical analysis was performed blindly, but the study design was not blinded.

We did not find statistically significant difference between the efficacy of the combined treatment (BT+PD) and PD in treatment of low responder achalasia patients at one year follow up, although decline in symptom score (≥ 50) and satisfaction in BT+PD group were more than PD group in the follow up period. It appears that greater numbers of patients with BT+PD treatment have longer duration of remission as compared to PD treatment alone. The difference between the results of our study is not meaningful due to relatively small number of patient; however, if a large scale of patients was included in this study the results may be different.

Hep A *et al.* (18) demonstrated that combination therapy in 9 patients with primary achalasia possibly resulted in longer duration clinical remission than that one. Although, their study was done in a small number of naïve achalasia patients and did not have any control group.

With regarding "mean symptom score decline" at the end of the first year, 62.7% of BT+PD-treated patients were in symptomatic remission compared with 50.77% of PD group. Although, there was a greater decline in mean symptom score in BT+PD group but this did not reach statistical significance. Mean symptom score declined in both groups at 1, 6 and 12 month after treatment compared to pre-treatment score but symptoms in PD group were more severe than BT+PD treated patients. Timed esophagogram (barium column height in 3 and 5 minutes) was done in some patients (whom completed objective follow up) in both groups. From this objective standpoint, there was no significant difference ($P = 0.38$) between two groups. In this study we applied 4cm balloon (the largest Rigiflex balloon) in all patients. The reports of the success rate for pneumatic dilation in achalasia patients vary widely however graded pneumatic dilation and use of larger balloons in repeat dilations can result in greater efficacy and long duration of remission (6, 10, 19). Unfortunately, there was no any study in literature similar to our study. However, combined treatment (BT+PD) - in study of Radek *et al.* (12) - had longer duration of remission than BT or pneumatic

Table 2. Symptom scores before and 1, 6 and 12 months after treatment

Group	BT+PD	PD	P value
SS (mean \pm SD) Before treatment	12.19 \pm 2.9	12.94 \pm 3.2	NS
SS (mean \pm SD) After 1 month	4.6 \pm 1.9	5.61 \pm 3.4	NS
SS (mean \pm SD) After 6 month	4.2 \pm 2.4	6.61 \pm 3.4	NS
SS (mean \pm SD) After 12 month	4.3 \pm 3.02	6.5 \pm 2.9	NS

dilatation alone in naïve achalasia patients compared to the literature. Although, Radek study had no control group, but their study had sufficient number of patients and a long duration (average: 21 month) of follow up and half of whom followed more than two years. We previously conducted two study about the efficacy of combined (BT+PD) treatment in naïve achalasia patients. In the first retrospective study we compared two groups of patients that had been underwent (BT+PD) and PD treatment. Each group consisted of 12 patients and PD had been performed with 3cm Rigi-flex balloon. The cumulative remission rate was significantly higher in the (BT+PD) group compared with the PD group ($P < 0.01$) (13), but in the second study that had been designed prospectively the difference was not statistically significant and only there was a trend for better response rate in elder patients (>40 years) in the (BT+PD) group in one year follow up (14). In according to this study and our previous studies it appears that combined therapy has possibly more efficacy than PD alone. The decision that which treatment is best for achalasic patients with low response to initials PD need more investigation because our study result is not confirmatory due to low numbers of patients in both groups. In conclusion, despite a better response rate in BT+PD group, a difference was not statistically significant. A difference may be meaningful if a large numbers of patients are included in the study.

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