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Research Article

Long-Term Efficacy of Combined Treatment in Idiopathic Achalasia Patients

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1. Abstract

1.1. Introduction

Several treatment strategies are available to treat achalasia. Although combined therapy has been used for several years, there are limited data on long-term outcomes. We aimed to determine its long-term efficacy in patients who were resistant or those with rapid relapse.

1.2. Methods

In this prospective study, we reviewed the records of 1100 achalasia patients, who were candidates for pneumatic balloon dilatation (PBD) in our center from 1996 to 2018. We enrolled 197 patients resistant to initial treatment or with rapid relapse of symptoms after three sessions of PBD. Clinical evaluation and time barium esophagogram (TBE) were done pre- treatment, a month afterwards, when clinical symptoms increased in order to confirm relapse, and at the end of follow-up.

1.3. Results

A total of 168 patients accepted combined therapy). The mean duration of follow-up was 9.04 years. Achalasia symptom score (ASS) dropped from 10.82 to 3.62 a month after treatment and was 3.09 at the end of follow up (P= 0.0001 and 0.001). TBE had a decrease in mean height of barium one month after treatment (9.23 vs 5.10, PV 0.001) and this reduction persisted till the end of follow up (3.39, PV: 0.001). Vantrappen score at the end of follow up showed 56 patients in excellent, 51 good, 33 moderate, and 14 in poor condition (89% acceptable response rate).

Conclusion: Our results determined long-term efficacy of combined treatment in achalasia patients who otherwise had to undergo a high-risk and costly procedure, making it a safe and effective alternative for myotomy.

2. Keywords: Therapeutics; Esophageal achalasia; Long-term care; Recurrence

3. Introduction

Idiopathic achalasia is a primary chronic motor disorder of the esophagus with incomplete or absent relaxation of the lower esophageal sphincter (LES) during swallowing and a peristalsis of the esophageal body [1]. Histopathologic data of the achalasic esophagus showed a loss of ganglionic cells in the my enteric (Auerbach's) plexus. The primary pathophysiology seems to be losing inhibitory ganglion cells which secrete nitric oxide (NO) and vasoactive intestinal peptide (VIP) and the persistence of cholinergic stimulatory cells [2].

Several treatment strategies are available to decrease the LES pressure, such as pharmacological drugs, pneumatic balloon dilatation (PBD), botulinum toxin (BT) and

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ethanol amine oleate injections, and endoscopic or surgical myotomy [3,4]. Pneumatic balloon dilatation (PBD) is a common method of treatment that provides good to excellent symptomatic relief with a response rate of approximately 90%. Several studies have compared the efficacy of PBD, BT, and the combined method (pneumatic balloon dilation 1month after botulinum toxin injection). PBD is effective in a majority of achalasia patients, however, the combined method (BT and PBD) provides a better response rate [5]. Botulinum toxin induces LES relaxation by inhibiting acetylcholine release from the nerve endings and decreasing unopposed cholinergic stimulation of the LES. Studies have shown a low sustained effect with only about 30% response at 12 months [6]. Heller myotomy is a safe and effective second-line treatment for achalasia (after PBD or BT injections), but it seems to be less satisfactory in those previously treated with BT in long-term evaluations [7]. Although combined therapy has been used for several years as achalasia treatment, there are limited data on the long-term outcomes of patients treated with this procedure. Hence, we aimed to determine the long-term efficacy of BT injection before PBD in controlling symptoms of achalasia in patients who were resistant to therapy or those with rapid relapse.

4. Patients and Methods

4.1. Patients

In this prospective study, we reviewed the records of 1100 patients previously diagnosed with achalasia, who were candidates for PBD in our center from January 1996 to May 2018. Diagnosis was established based on 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 alternatives.

4.2. Study Design

Patients resistant to initial treatment and those with rapid relapse of symptoms after three sessions of PBD were enrolled. Achalasia Symptom Score (ASS) >4 and retention of barium in timed barium esophagogram (TBE) during six months after the last PBD were used to define resistance or rapid relapse. Overall, 197 patients with achalasia were enrolled in our study (**Figure 1**).

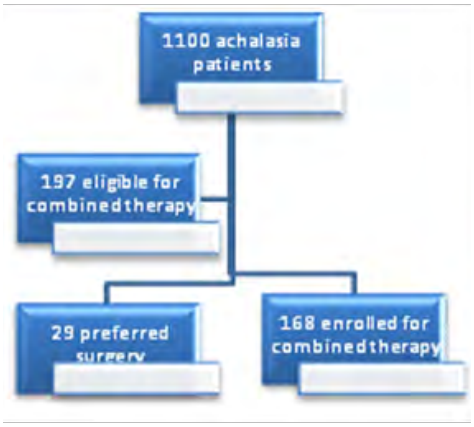

Figure 1: Patients arrangement

Surgical myotomy and combined therapy was completely explained to each patient. Of these, 168 patients preferred combined therapy (PBD 1 month after BT) with the following protocol:

All patients had botulinum toxin injection (Dysport 500 units) into the LES and PBD was performed a month later using a 35mm Rigiflex balloon. Clinical assessment and TBE were performed one month after the combined therapy and patients were followed by clinical evaluation every six months. If the ASS increased to more than four, TBE was repeated to confirm relapse. Treatment was repeated for those with barium retention at 5 minutes.

Patients developing clinical relapse in less than a year underwent retreatment with BT and PBD with a 40-mm Rigiflex balloon. Those with relapse after a year received retreatment with BT and PBD, again using a 35-mm Rigiflex balloon. The study protocol was reviewed and approved by the Ethics Committee of Digestive Disease Research Center at Tehran University of Medical Sciences and an informed consent was obtained from all patients.

4.3. Clinical Evaluation

Clinical evaluation was done prior to treatment and a month afterwards, being repeated every six months. The severity of symptoms was evaluated based on 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 (**Tables 1, 2**) [9,10]. The highest obtainable score was 18, where clinical response was defined as a symptom score ≤4 without severe dysphagia (accompanied with regurgitation) and those with a symptom score >4 were considered to have relapsed. Patient's symptoms were

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evaluated by Vantrappen score at the end of their follow up, expressed as: excellent, good, moderate, or poor (**Table 3**).

Table 1: Cardinal symptoms score in achalasia

Symptom	Each meal	Daily	Weekly	None
Dysphagia to solids	3	2	1	0
Dysphagia to liquids	3	2	1	0
Active regurgitation	3	2	1	0
Symptom	Daily	Weekly	Monthly	None
Passive regurgitation	3	2	1	0
Chest pain	3	2	1	0

Table 2: Severity score of dysphagia for every swallow

Severity	Score	Description
No dysphagia	0	Normal passage of food from LES zone
Mild dysphagia	1	Sensation or short delay of passage of food from LES, without need of water
Moderate dysphagia	2	Need of water for passage of food from LES zone
Severe dysphagia	3	Accompanied with passive or active regurgitation

Table 3: Vantrappen Scoring System in achalasia

Class	Dysphagia
Excellent	Completely free of symptoms
Good	Occasional (less than once a week) dysphagia or pain of short duration defined as retrosternal hesitation of food lasting from 2–3 s to 2–3 min and disappearing after drinking fluids
Moderate	Dysphagia more than once a week lasting less than 2–3 min and not accompanied by regurgitation or weight loss
Poor	Dysphagia more than once a week or lasting 2–3 min or longer or accompanied by regurgitation or weight loss

4.4. Timed Barium Esophagogram

TBE was performed before combined therapy, one month after PBD, anytime during follow-up when clinical symptoms increased (ASS>4) in order to confirm relapse, and at the end of follow-up. Patients were told to swallow 200ml of low density barium sulfate suspension (81% weight/volume) while standing over 30-45 seconds. X-rays from the left posterior oblique view were taken at 1, 3, and 5 minutes afterwards. Barium column height, defined as the distance from the most distal part of the esophagus to the proximal barium level, was measured in centimeters. The volume of retained barium (mL) was calculated as follows: $(\text{mean radius})^2 \times 3.14 \times \text{height of column}$.

The initial TBE in our patients showed barium retention at 1,3, and 5 minutes, a dilated esophagus, and a beak-like narrowing at the GE junction. Differences in retained barium height and volume at 5 minutes pre- and post-treatment were calculated.

4.5. Botulinum Toxin Injection

Botulinum toxin was injected one month before PBD. The LES was identified by visualizing the sphincter rosette at the squamocolumnar junction during esophagogastroduodenoscopy. Five hundred units of Clostridium botulinum type a toxin-hem agglutinin complex (Dysport; IPSEN, Berkshire, UK) diluted in 5-mL normal saline was injected through a 5-mm sclera therapy needle into the LES in ten injections of 0.5ml. These injections were done circumferentially at the gastro esophageal junction up to 2cm above the Z-line.

4.6. Pneumatic Balloon Dilatation

After a clear liquid diet for 48 h and an overnight fast, PBDs were performed using a 35-mm Rigiflex balloon. Following a complete esophagogastroduodenoscopy, balloon dilators were passed over a guide wire and were positioned in the middle of the LES using video endoscopic guide. The balloons were gradually inflated up to 15 psi in 30 s and this pressure was maintained for 60 s. Afterwards, esophagoscopy was repeated to assess the LES opening (relaxation) and any evidence of bleeding or perforation. They were discharged after a 6-h observation.

4.7. Statistical Analysis

Descriptive statistics are provided as the median and inter quartile range for age, symptom score, LES pressure, and barium height and volume. Quantitative variables are presented as medians and ranges. SPSS version 21 was used for the statistical analysis. The Kaplan-Meier method was used to assess symptomatic recovery. *P* values < 0.05 were considered significant.

5. Result

A total of 168 patients (90 males and 78 females; median age, 40 years), with previously diagnosed achalasia treated with combined therapy (PBD following injections of botulinum toxin), were enrolled from January 1996 to May 2018. The mean duration of follow-up was 9.04 years. Fourteen patients had surgery during follow-up due to symptom relapse. Up to 2008, manometry was done using conventional manometry and we had 85 patients with the classic and 6 with the vigorous type. After implementing high resolution manometry in our center, the frequency of achalasia subtypes were 13,62, and 2 for types 1,2, and 3, respectively. The mean LES resting pressure was 32.61 mmHg. ASS dropped from 10.82 to 3.62 a month after treatment and was 3.09 at

the end of follow up (P= 0.0001 and 0.001) (**Table 4**). Timed barium esophagram had a decrease in the mean height of barium one month after treatment (9.23 vs 5.10, PV 0.001) and this reduction persisted till the end of follow up(3.39, PV:0.001) (**Table 5**)

Vantrappen score was used to evaluate patients at the end of their follow up, where 56 patients were in excellent, 51 good, 33 moderate, and 14 in poor condition (**Table 6**). During follow up, 109 patients underwent BT-PBD once (64.8%), 49 patients twice (29.1%), and 10 patients three times (5.9%). The rate of relapse was 35% during this long term follow-up (PV: 0.042) (Figure 2). Interesting to note, among those who had surgery during follow-up (14 patients), five developed symptom relapse. BT-PBD was done again for them with excellent and good responses, according to the Vantrappen score, seen in 3 and 2 patients, respectively.

Table 4: Achalasia Symptom Score before and after the combined therapy

ASS		Mean (±SD)	P. Value*
Before therapy		10.82±2.97	-
1 month	after therapy	3.62±3.57	0.0001
6 months		3.74±3.45	0.0001
12months		3.09±3.15	0.0001

Table 5: Timed Barium Esophagram in combined treatment for resistant and rapid relapse achalasia patients

TBE Volume and Height		Mean(±SD)	P. Value*
Volume (ml)	Before therapy	66.98 ±34.24	-
	1 month after therapy	34.24±58.25	0.001
	End of follow up	22.02±50.48	0.0001
Height (cm)	Before therapy	9.23±5.755	-
	1 month after therapy	5.10±6.262	0.01
	End of follow up	3.88±5.459	0.001

Table 6: Timed Barium Esophagram in combined treatment for resistant and rapid relapse achalasia patients

Vantrappen score	Frequency	Percentage
Excellent	56	36.36
Good	51	33.11
Moderate	33	21.42
Poor	14	9.09
Total	154	100

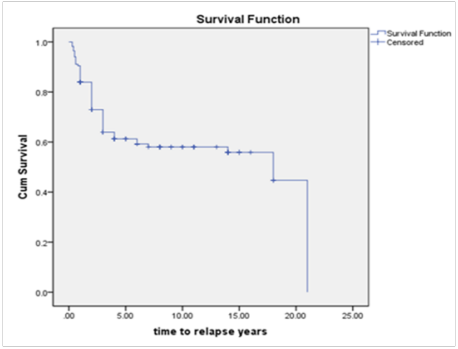

Figure 2: The rate of relapse after combined therapy in achalasia patients

6. Discussion

In our study, we showed that idiopathic achalasia patients who were potentially candidates for surgery were effectively treated in the long term with combined therapy, reducing the need for surgery in about 80% of cases. Vantrappen scoring system was used to evaluate the response rate at the end of follow-up. About two-thirds of our patients showed excellent or good response to this treatment strategy (69%). Since patients in the moderate class do not have severe dysphagia accompanied with regurgitation, we can consider them as partial responders and therefore, their response would also be acceptable; meaning an 90% response using combined therapy. The strength of our study was a relatively its duration with a mean follow up of over nine years. Treatment options for achalasia includes pharmacologic agents, PBD, intrasphincteric BT injection, and surgical or endoscopic myotomy. Several studies have compared the efficacy of these different therapeutic strategies in treatment-naïve patients, but we did not find any study on the long-term efficacy of a non-surgical therapeutic method for resistant or rapid relapse cases of idiopathic achalasia. A study revealed that PBD is more effective than botulinum toxin injections [8], and PBD is an appropriate long-term therapy. Another study showed PBD as being a good therapy for long-term relief, and BT with a relatively short term response [9]. In that study, we showed that combined therapy decreased the ASS by 76%, compared with a 53% decrease in those undergoing only PBD with a mean follow-up of about two years [9]. In this study, we have shown long-term efficacy of the combined therapy for those with rapid relapse or resistant achalasia. Ethanolamine oleate (EO) was shown to be effective in resistant achalasia in 31 patients. It was injected in the LES every two weeks for three times and they were followed

for a mean duration of 30 weeks. A good response was seen in 29 patients, in whom 12 had relapsed and were retreated with EO injections. Only minor adverse events occurred in this trial and the authors concluded that EO injection can safely be used in the treatment of resistant idiopathic achalasia [10]. A small group of patients (9 patients) with achalasia were treated with the combined therapy (250 units of Dysport followed seven days later with PBD). They were followed every three months and the longest symptom improvement was three years. Clinical and manometric improvement was seen in seven of their patients after one year [11]. A randomized clinical trial conducted on 90 patients (in three equal groups) with achalasia revealed that those who received combined therapy (100 units of Botulinum toxin injected 15 days after PBD) had a significantly better response rate at two years after treatment, compared to those who received only one of the therapeutic methods (56% compared to 35 and 13% for PBD and BT, respectively) [12]. We gave the combined therapy to 168 patients with rapid relapse and resistant achalasia and they were followed for over 9 years, with at least a partial response in about 90%. [13] Followed treatment-naïve achalasia patients for a mean duration of 48 months after using the combined therapy (200 units of BT with PBD eight days later) and 72% had a satisfactory response at their last visit. They concluded that BT prior to PBD was effective in the long term with few complications such as heart burn, but this combined therapy was not superior to doing PBD alone [13]. We enrolled 168 patients who were potentially candidates for surgical myotomy. These patients were followed for a mean duration of more than 9 years using the Vantrappen scoring system, ASS, and timed barium esophagogram (TBE). All three were significantly improved after the combined treatment with a relapse rate as low as 35%, even these patients had a good response after repeating the combined therapy. Only 18% showed a poor response to this treatment, with a poor Vantrappen score at the end of follow-up or having to do surgery. To our knowledge, we have reported the longest follow up of a combined treatment strategy in achalasia patients with resistance or rapid relapse after PBD. We enrolled a large population of these patients and followed them with clinical symptoms and TBE. Our results determined long-term efficacy of the combined treatment in achalasia patients who otherwise had to undergo a high-risk and costly procedure, making it a safe and effective alternative for myotomy in the elderly and those with co morbidities.

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