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Article type : Original Manuscript

PROSPECTIVE MULTI-CENTRE STUDY ON BARBED REPOSITION PHARYNGOPLASTY STANDING ALONE OR AS A PART OF MULTILEVEL SURGERY FOR SLEEP APNEA.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/coa.13001

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Short Title: Barbed Reposition Pharyngoplasty for obstructive sleep apnea

ABSTRACT

Objectives: The aim of this study was to demonstrate in a prospective multi-centre study that Barbed Reposition Pharyngoplasty (BRP) procedure is safe and effective in management of obstructive sleep apnea/hypopnea syndrome (OSAHS) patients.

Design: prospective study

Setting: multicenter study.

Participants: patients suffering from obstructive sleep apnea.

Main outcomes measures: values of post-operative apnea-hypopnea index(AHI), oxygen desaturation index (ODI), epworth sleepiness scale (ESS).

Results: 111 BRP procedures standing alone or as a part of multilevel surgery for OSAHS, performed between January and September 2016, were analyzed in 15 different centers. The average hospitalization period was 2.5 ± 0.5 days. The mean patient age was 46.3 ± 10.5 years. The average BMI at the time of the procedure was 27.9 ± 3.2 and the majority of the patients were men (83%). The mean pre-operative and post-operative apnea/hypopnea index was 33.4 ± 19.5 and 13.5 ± 10.3, respectively ($p < 0.001$). The mean pre-operative and post-operative epworth sleepiness scale score was 10.2 ± 4.5 and 6.1 ± 3.6, respectively ($p < 0.001$). The mean pre- and post-operative oxygen desaturation index was 29.6 ± 20.7 and 12.7 ± 10.8, respectively ($p < 0.001$).

Conclusions: Patients undergoing BRP standing alone or as part of a multilevel approach for the treatment of OSAHS have a reasonable expectation for success with minimal morbidity.

Keywords: Pharyngoplasty; Sleep Apnea; Technique; Surgery; Complication

INTRODUCTION

The main mechanism of the most classic palatal techniques for obstructive sleep apnea/hypnea syndrome (OSAHS) was basically the shortening of the soft palate by trimming the free edge or pulling up the uvula and the soft palate. The main and most used over time palatal procedure is the uvulopalatopharyngoplasty(UPPP). In the last years, many new palatal surgical techniques for snoring and OSAS were devised to address mainly the lateral pharyngeal wall and to enlarge laterally the oropharyngeal inlet such as lateral pharyngoplasty[1], Z-palatoplasty[2], uvulopalatopharyngoplasty (UP2)[3], expansion sphincter pharyngoplasty (ESP)[4] and relocation pharyngoplasty[5]. As the palate component of multilevel procedure, ESP proved to be superior to UPPP[6]. In the last years, surgeons have been trying to modify the approach to lateral pharyngeal wall/retropalatal airway switching from ESP to less invasive procedures. In our experience, the relocation pharyngoplasty according to Li[5], was modified with some different solutions of experienced surgeons developing a new technique named as Barbed Reposition Pharyngoplasty(BRP).

The details of technique are described previously[8] and following summarised:

1. ‘‘Barbed’’ which refers to the use of knotless bidirectional absorbable sutures introduced for similar purposes by Mantovani et al[9].
2. ‘‘Reposition pharyngoplasty’’ because it displaces the posterior pillar (palatopharyngeal muscle) in a more lateral and anterior position to enlarge the oropharyngeal inlet as well as the retropalatal space.
3. Suspension of the posterior pillar to the pterygomandibular raphe.
4. Initial weakening of the inferior aspect of the palatopharyngeal muscle.

5. The multiple lateral sustaining suture loops of BRP proved to be more stable than the single pulling tip suture of ESP, with no risk of tearing the muscle fibers losing the entire pulling force.

After publishing a pilot study on the first treated ten cases[8], we decided to perform a multicenter prospective analysis of results and complications in a larger group of patients representing 15 different worldwide centres. The aim of this study was to evaluate the effectiveness and the safety of BRP in a multi-centre setting and to create benchmarks for evaluating clinical outcomes and complications of BRP.

METHODS

Local ethics committees or institutional review boards approved the study. The multicenter prospective study investigated the effectiveness of BRP for OSAHS as well as the prevalence and type of reported complications. The studied group included patients who underwent consecutive BRP surgeries for OSAHS at fifteen institutions of Otolaryngology – Head and Neck surgery in different countries (Head and Neck Department – ENT & Oral Surgery Unit – G.B. Morgagni - L. Pierantoni Hospital, Forlì – Infermi Hospital, Faenza - ASL of Romagna, Italy; Department of Otolaryngology Head and Neck Surgery, Fazzi Hospital, Lecce, Italy; Department of Otorhinolaryngology, Alexandria University, Alexandria, Egypt; Department of Otorhinolaryngology, Grupo Medico San Pedro, Monterrey, Mexico; Department of Otolaryngology, Fabrizio Spaziani Hospital, Frosinone, Italy; Department of Otolaryngology, Department of Clinical Sciences and Community Health, Fondazione I.R.C.C.S. Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; Department of Otorhinolaryngology, Doctor Peset University Hospital, Valencia, Spain; Department of Otolaryngology, Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal; Department of Otolaryngology, S. Pio X Hospital, Milan, Italy; Ear Nose Throat-

Head and Neck Surgery Department, Faculty of Medicine, Hacettepe University, Ankara, Turkey; Department of Otolaryngology, San Bassiano Hospital, Bassano del Grappa, Vicenza, Italy; Department of Otolaryngology Head Neck Surgery, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; Department of Otolaringology, University of Navarra, Campus Universitario, Pamplona, Spain; Otorhinolaryngologic Unit, San Giovanni di Dio e Ruggi d' Aragona University Hospital, Salerno, Italy; First Otorhinolaryngologic Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy). The BRP were performed between January and September 2016. All patients had signed the informed consent. The preoperative Drug induced sleep sedation (DISE) is perfoermed according to the European Position Paper on DISE[7]. Inclusion criteria were: patients diagnosed with mild to severe OSAHS (AHI $\geq$ 5), having the main site of obstruction at the retropalatal level with or without retrolingual obstruction; patients not accepting or unwilling to use of continuous positive airway pressure(CPAP) treatment; failures of previous surgery; age between 21 and 75 years; body mass index (BMI) $\leq$ 35; ASA $\leq$ 2. Exclusion criteria were: patients $\geq$ 75 years and/or with severe medical illness; patients with significant craniofacial anomalies affecting airway; BMI $\geq$35; patients with limited mouth opening (interincisive distance $\leq$ 2 cm); ASA $\geq$ 2; and patients with less than 6 months of follow-up including post-operative polisomnography (PSG) and Epworth Sleepiness Scale(ESS) data. A total number of 111 patients were included. A careful general, ear, nose and throat (ENT) history of each patient was taken with particular attention given to sleep history. The collected data included the following:

Preoperative data:

1) Age and sex

2) Complete history including associated medical diseases

3) Complete ENT examination, including Fiberoptics and Müller maneuver to identify the collapsable sites

4) Pre-operative Epworth Sleepiness Scale (ESS)

5) Pre-operative apnea-hypopnea index (AHI) & oxygen desaturation index (ODI)DISE data would be included if available

Intra-operative evaluation:

1) Operative time of palatal procedure

2) Intra-operative complications

Post-operative evaluation:

1) Post-operative hospital stay

2) Post-operative complications, including evaluation of the swallowing function with MD Anderson Dysphagia Inventory (MDADI) questionnaire which each patient had to fill in a preoperative visit, during first week and after 1 month postoperatively.

3) 6 months post-operative PSG, ESS and BMI

A detailed description of the surgical technique is previously published[8]. All the procedures were performed with patients under general anesthesia and orally intubated, exposed by a Boyle-Davis mouth gag together with or without lateral cheek retractors to give wide access to the surgical field. The patient was positioned in supine position with under shoulder inflatable bag to keep the neck hyperextended. In most of the cases BRP was a single procedure including if required tonsillectomyand a nasal procedure. The tonsillectomy is

necessery to expose the palatopharyngeal muscle; in patients already had tonsillectomy a superficial removal of mucosa overlying the muscle is performed. In few cases a tongue base surgery or a thyro-hyoidopexy have been performed as part of multilevel surgery for sleep apnea. We have used for the procedures reabsorbable Polydioxanone (PDO), bidirectional, size 0 (tensile strength size 2-0), 24x cm length, not cutting edge (taper point), needle 36 mm or 26 mm(Quill Sutures, Research Triangle Park, NC).

The description of levels of success criteria are reported in the Table 1.

Statistical Analysis

Associations between variables and endpoints were tested with the Fisher exact or t tests, as appropriate. A 2-tailed P value less than 0.05 was regarded as statistically significant. T Statistical analysis was performed with STATA 12.0 software (Stata Corp., College Station, TX, USA).

RESULTS

The mean pre-operative and post-operative apnea/hypopnea index were 33.4 ± 19.5 and 13.5 ± 10.3, respectively ($p < 0.001$). The mean pre-operative and post-operative Epworth Sleepiness Scale score were 10.2 ± 4.5 and 6.1 ± 3.6, respectively ($p < 0.001$). The mean pre- and postoperative oxygen desaturation index were 29.6 ± 20.7 and 12.7 ± 10.8, respectively ($p < 0.001$) (see Fig 1.)

The primary outcomes were defined as a significant postoperative reduction of the pre-operative AHI and ESS. In order to have a more detailed and clinically relevant distribution of outcomes, we stratified our post-operative results into 4 different levels (Table 2). According to these criteria, 73% of the outcomes were considered as success, and 27% were

unsuccessful with different degrees of severity. The mean pre-operative and post-operative BMI was 27.9 ± 3.2 and 27.3 ± 3.0. The mean operative time of palatal procedure was 25 ± 4.2 minutes (shorter in centers with high volume activity).

All patients were allowed to restore the oral feeding within the second day after surgery. Intra-operative and post-operative complications are summarized in Table 3. There were no intra-operative complications recorded in 103 patients (93% of the cases), in 3 patients we had partial thread extrusion, in 3 patients intra-operative self-limited bleeding, once the needle was broken during surgery and in 1 case a surgeon experienced intraoperative suture rupture. There were no post-operative complications recorded in 75 patients (68% of the cases), The most common patient complaint was a transient dysphagia (21%), which recovered within 6 days in all patients. The preoperative mean MDADI score was 3.67±2.58, whilst the postoperative first week and 1-month scores were 11.18±4.32 and 5.06±1.83, respectively. Partial thread extrusion was the second most common complication (6% of the procedures). Post-operative bleeding was a complication in 6 patients (5% of the procedures). In 4 of these 6 patients, late postoperative bleeding was self-limited and did not require operative intervention. Only 1.8% of the patients required an additional surgical procedure to control the bleeding.

DISCUSSION

In this prospective study, we report the largest multi-centrereview of efficacy and safety of BRP with or without concomitant procedures for OSAS. These data can be used as a benchmark for evaluating clinical outcomes and complications. AHI, lowest oxygen saturation and ESS were significantly improved without evidence of a reduction in the BMI. There were minimal complications reported with no significant long-term morbidity.

Dysphagia is common after pharyngeal surgery and it is reported even after a conventional tonsillectomy. Dissecting pharyngeal muscles is not necessary while performing BRP and it allows post-operative pain and dysphagia recover faster than other techniques. It is crucial to underline that the main complication (suture extrusion) is more common at the beginning of the experience. Especially in Centres with lower volume cases a partial extrusion of the suture was reported. In this case, the patient complains of pain and it is possible to remove the small portion of the thread by using scissors in the outpatient clinic without compromising the result of the procedure. It is important to keep in mind that the insertion of the suture during the procedure should be within the muscular layer to avoid extrusions. The 'typical' patient of the present study is middle-aged, overweight, male, suffering from moderate to severe AHI with associated significant daytime sleepiness and non-compliant to continuous positive airway pressure (CPAP). Anatomically, there is evidence of significant palatal obstruction in all these patients. Careful preoperative planning including office fiberoptic examination in awake and during DISE if available ensure that patients have received the appropriate surgical treatment. In the present study, BRP was applied primarily in OSAS cases; however, the patients with simple snoring may be approached with this technique in order to guarantee a reduction of palatal vibration.

The standard for surgical success is a 50% reduction in the preoperative AHI and AHI below 20. For patients to safely come off CPAP, their AHI should be below 15 and there should be no associated daytime somnolence[10]. Using these more strict criteria for success, the current study demonstrates that 62.2% of the patients who underwent BRP surgery no longer required CPAP. Using traditional measures of success, 73% of the patients would be considered to have had a successful result. 10.8% of these patients who had a "successful" surgery would still require CPAP. The BRP technique might be considered a valid alternative to traditional

UPPP for the management of palatal/oropharyngeal obstruction as well as the ESP. Conceptually, the techniques modelling the oropharyngeal cavity in 3D fashion are superior to UPPP or other palatal procedures addressing only the borders of soft palate. Further a recent meta-analysis showed that OSAS patients had greater benefit from the ESP technique compared to the traditional UPPP or adeno-tonsillectomy[11]. However, the BRP is an emerging technique thus currently the amount of data in literature do not allow to perform a meta-analysis; although compelling results are becoming known[7,12,13].

The majority of BRP cases were performed as a single procedure including if required tonsillectomy and a nasal procedure (94.6 % of the patients), and in only 5.4% of the cases, BRP was used as a part of multilevel surgery for sleep apnea (4 cases underwent Hyoid Suspension and 2 cases Tongue Base Reduction as well).

Recently, Camacho et al[14] showed that AHI was the only factor that independently remained significant on multivariate analysis for both surgical cure and surgical success in OSAS patients who had only tonsillectomy. A significant effect for AHI (< 30 events/hour vs. > 30 events/ hour) on the likelihood of surgical cure was registered. However, tonsil size was not a predictor of success in this meta-analysis. Hence, the role of tonsillectomy in post-operative results in patients who had BRP should be marginal.

The average length of hospitalization was (2.5 ± 0.5 days) reflecting the different hospital policies in different countries. Primary outcomes (AHI, ODI and ESS) showed a statistical improvement after 6 months. Confounding influences such as a change in BMI were not significantly different at the time of the post-operative sleep study.

This study had some limitations; first, our study was not randomized, but was designed as only a prospective study, second, long-term outcomes and complications could not be examined because of the short follow-up period. During the observation period, registered complications were limited in number and severity. In our study, the efficacy is just one of the topics; the key points are feasibility, safety and teachability in centres with low and high volume patients treated. Patients who performed BRP with or without concomitant procedures had a significant improvement in their AHI, ODI and ESS in all these centres. Our results suggest that BRP would be considered an additional option for treating OSAHS related to obstruction in the soft palate.

CONCLUSIONS

BRP in this prospective multicenter study proved to be an easy to learn, quick, safe and effective new palatopharyngeal procedure. The key points that must be considered are the use of a knotless re-absorbable suture technology, the minimal and targeted muscle manipulation, the use of the pterygomandibular raphe as sustaining structure. The minimal muscle and mucosa resection and the absence of knots in the pharynx is well accepted by the patients in terms of invasiveness. The minimal required manipulations and the knotless technique mean for the inexperienced surgeon a technique easy to learn, quick and safe to perform, included in a simultaneous multilevel procedure if required. Further studies are needed to elucidate long term outcomes of BRP for OSAS.

CONFLICT OF INTEREST

None to declare

ACKNOWLEDGEMENTS

Claudio Vicini designated the study, critically revisioned and approved the manuscript. Filippo Montevecchi and Giuseppe Meccariello draft and revisioned the manuscript, Elisabetta Firinu, Mohamed Salah Rashwan, Michele Arigliani, Michele De Benedetto, Antonio Palumbo, Yassin Bahgat, Ahmed Bahgat, Rodolfo Lugo Saldana, Andrea Marzetti, Lorenzo Pignataro, Mario Mantovani, Vittorio Rinaldi, Marina Carrasco, Filipe Freire, Ines Delgado, Fabrizio Salamanca, Alessandro Bianchi, Metin Onerci, Paolo Agostini, Luigi Romano, Marco Benazzo, Peter Baptista, Francesco Salzano and Iacopo Dallan collected data. Simona Nuzzo made statistical analyses.

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Figure Legend

Figure 1. Post-operative outcomes.

Table 1. Definition of success and unsuccess criteria

Criteria	**Definition**
Cured	AHI<5 and ESS<10 and reduction>50%
No more CPAP needed	AHI<15 and ESS<10 and reduction>50%
Success	AHI<20 and ESS<10 and reduction>50%
Failure	AHI>20 and any ESS value and reduction<50%

Table 2. Outcomes			
Criteria	**No. of Patients**	**Proportion**	**Cumulative**
Cured	23	20,7%	20,7%
No more CPAP needed	46	41,4%	62,2%
Success	12	10,8%	**73,0%**
Failure	30	27,0%	**27,0%**

Table 3. Complications		
INTRA OPERATIVE COMPLICATIONS		
	No. of cases	%
No complications	103	93%
Partial thread extrusion	3	3%
Intraoperative bleeding	3	3%
Needle broken	1	1%
Suture rupture	1	1%
POST OPERATIVE COMPLICATIONS		
	No. of cases	%
No complications	75	68%
Partial thread extrusion	7	6%
Postoperative bleeding	6	5%
Dysphagia	23	21%