TPM Vol. 32, No. S2, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

EVALUATION OF EFFECTIVENESS OF AMITRIPTYLINE AND PROTON PUMP INHIBITORS AS COMBINATION THERAPY FOR REFRACTORY GLOBUS PHARYNGEUS

DR.DINESH RAM R[1], DR.SHRAVANTHI MANTRA PRITHVIRAJ[2], DR.SUBAGAR ANBARASAN[3*], DR.NANDITHA S[4,]

1,2-FINAL YEAR POST GRADUATE ,DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD AND NECK SURGERY, SAVEETHA MEDICAL COLLEGE AND HOSPITALS, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES(SIMATS), CHENNAI, INDIA.
3*- ASSISTANT PROFESSOR ,DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD AND NECK SURGERY, SAVEETHA MEDICAL COLLEGE AND HOSPITALS, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES(SIMATS), CHENNAI, INDIA.
4 - UNDERGRADUATE, MBBS, SAVEETHA MEDICAL COLLEGE AND HOSPITALS, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES (SIMATS), CHENNAI, INDIA.

ABSTRACT:

Introduction: Introduction: Globus pharyngeus is characterised by a feeling of a lump in the throat that can be alleviated by eating and does not involve pain or trouble with swallowing. It presents continuous difficulties because of its persistent character, lack of response to standard therapies, and significant influence on one's quality of life. Developing consistent diagnostic and treatment guidelines for globus pharyngeus is difficult because its cause is not clear. Higher doses of the tricyclic antidepressant Amitriptyline are limited by side effects, but lower doses have shown to be effective and well tolerated for functional gastrointestinal disorders. Early attempts to use larger amounts of AMT for treating globus pharyngeus were frequently stopped because of adverse reactions, leading to further examination of smaller doses. This study aims to investigate the clinical indicators of symptom relief by combining lower-dose AMT with PPIs for globus pharyngeus patients, given the limited evidence on its effectiveness.

Materials and Methods: This research utilised a prospective RCT design, which is widely acknowledged as the most reliable method for evaluating treatment efficacy in clinical studies. Approval from the hospital ethics committee was acquired, and participants gave written informed consent before joining. Patients with globus pharyngeus, determined through thorough clinical assessment and endoscopy, were included in the study if conventional therapies had not shown improvement after six months. Thirty-four individuals were assigned randomly to receive either a combination of amitriptyline and pantoprazole or pantoprazole alone through computer-generated random selection. The evaluation criteria consisted of the Glasgow Edinburgh Throat Scale (GETS) for initial examination and the Pittsburgh Sleep Quality Index (PSQI) for further assessment. Data was systematically collected using standardised forms, and analysis was conducted using rigorous statistical methods like ANOVA and regression. Findings were presented as mean ± SD, with $P < 0.05$ considered statistically significant for better understanding of treatment results.

Results: Four weeks later, the AMT group exhibited a greater response rate (75% compared to 35.7%, with $P = 0.004$) and notable enhancements in GETS scores on days 3, 10, and week 4 (all with $P < 0.01$). AMT also had a notable enhancement on PSQI in comparison to baseline and the Conventional group ($P = 0.008$), indicating its promise in improving sleep quality for globus pharyngeus patients.

Discussion and conclusion: Low doses of AMT demonstrate promise in treating globus pharyngeus and enhancing quality of life. More extensive studies with larger groups of participants

and longer monitoring periods are necessary to confirm its effectiveness and safety, guiding evidence-based recommendations and enhancing patient treatment.

INTRODUCTION:

Globus pharyngeus is characterised by feeling like there is a lump in the throat, even though there is no actual trouble swallowing or pain, and is usually relieved temporarily by eating. This issue, making up approximately 4% of referrals in otolaryngology, continues for a long time, proving difficult to control and often coming back, greatly affecting quality of life. The unclear roots of globus make it difficult to create standardised protocols for investigation and treatment.(Alshahrani and Almasabi 2024)

Amitriptyline (AMT), a tricyclic antidepressant, used to have restrictions due to side effects at high doses (up to 100 mg/d). Recent research shows that low-dose AMT has the potential to effectively treat functional gastrointestinal disorders with improved tolerability. Even with thorough research, there is limited evidence to support the advantages of low-dose AMT specifically for globus pharyngeus. Hence, verifying its effectiveness in this setting is a crucial area lacking in current medical knowledge and management choices for impacted individuals.

This study seeks to assess how effective the combination of amitriptyline and PPIs is in relieving symptoms of refractory globus pharyngeus compared to standard treatments. It also aims to evaluate the impact of this dual treatment on swallowing function and related symptoms like dysphagia, throat clearing, and feeling of something stuck in the throat.(You et al. 2013)

MATERIALS AND METHODS:

STUDY DESIGN:

The research utilised a prospective, randomised controlled trial (RCT) approach, recognized as the best method for assessing the effectiveness of treatments, guaranteeing robust and trustworthy evidence. This method consists of randomly distributing participants into various treatment groups to reduce bias, thus linking any observed effects specifically to the treatments administered and not to other variables. Through following RCT principles, the research upholds strong scientific rigour, which improves the credibility and dependability of its results. This method is essential for assessing the dual treatment of amitriptyline and PPIs for difficult-to-treat globus pharyngeus, allowing for a direct comparison with traditional therapies in a controlled setting. It enables researchers to gather data in a structured manner over a period of time, making it easier to evaluate the effectiveness of treatments and gaining important information about the efficiency of therapy in clinical environments.

SAMPLE SIZE:

Thirty individuals were assigned randomly to two treatment groups through the use of a simple randomization technique facilitated by computer-generated randomization. This technique reduces prejudice and ensures an even spread of participants across the treatment groups. This method guarantees that any variations in results seen among the groups are due to the treatments given, not the participants' existing traits. By employing computer-generated randomization, the research upholds methodological rigour and boosts the dependability of its results. This rigorous approach is crucial for assessing the effectiveness of treatments in clinical studies, like evaluating the effects of combining amitriptyline and PPI therapy on refractory globus pharyngeus symptoms. It enables a structured evaluation of results across different treatment groups, offering significant understanding into the efficacy of the interventions under investigation.

INCLUSION CRITERIA:

The research included adult participants 18 years and older with a diagnosis of refractory globus pharyngeus. Refractory globus pharyngeus is characterised by ongoing symptoms even after trying standard treatments like acid suppression therapy and behavioural interventions. Participants needed to be ready for a combined treatment including both amitriptyline and PPIs and able to give informed consent. The purpose of this inclusion criterion was to make

sure that participants were eager to test the experimental treatment and comprehended the possible advantages and drawbacks.

EXCLUSION CRITERIA:

Patients who had allergies, intolerance, or potential drug interactions with amitriptyline or PPIs were not included in the study. Moreover, participants with other important medical or mental health issues that might hinder the assessment of treatment results were not included in the research. The exclusion criteria were made to reduce safety risks and ensure that the study results accurately represent the effects of the combination therapy on refractory globus pharyngeus, without interference from other health issues.

TREATMENT REGIMEN:

Subjects were allocated at random to one of two groups: the first group received a combination of amitriptyline and pantoprazole, while the second group received pantoprazole alone. This research design enables a thorough comparison of the efficacy of combined therapy versus monotherapy in treating refractory globus pharyngeus. The study seeks to assess how each treatment regimen affects symptom reduction and overall patient outcomes through direct comparison.(Kortequee et al. 2013)

This method guarantees that any variances in symptom progress between the two groups are solely due to the inclusion of amitriptyline in the treatment plan. Randomly assigning participants reduces bias and guarantees that participant traits are evenly spread across treatment groups, which improves the trustworthiness and dependability of the study results. Including a group receiving only pantoprazole as a monotherapy acts as a control to compare the added benefit of including amitriptyline in the treatment protocol.(Chiba et al. 2013)

OUTCOME MEASURES:

This approach ensures that any differences in symptom improvement between the two groups are exclusively the result of including amitriptyline in the treatment regimen. Assigning participants randomly decreases bias and ensures that participant characteristics are evenly distributed among treatment groups, enhancing the reliability and credibility of the study findings. Having a group that is only given pantoprazole as a monotherapy serves as a reference point for evaluating the extra advantage of adding amitriptyline to the treatment plan.

STATISTICAL ANALYSIS:

The research utilised organised gathering of data using standardised forms, followed by thorough statistical analysis which incorporated techniques such as ANOVA and regression. This method enhanced the credibility of the study's findings. Findings were shown with average values and standard deviations (mean ± SD), where statistical significance was defined as $P < 0.05$. This approach made it easier to interpret and compare treatment results, guaranteeing transparent and precise reporting of the effectiveness of the interventions analysed.

RESULTS:

VARIABLE	AMT (Group n=16)	CONVENTIONAL GROUP (n=14)	P VALUE
GETS SCORE BASELINE	5.44±1.63	5.71±1.38	0.623
3 DAYS	3.69±1,14	5.64±1.28	0.000
10 DAYS	2±1.71	5.36±1.22	0.000
4 WEEKS	1.25±1.84	3.79±2.33	0.002

TREATMENT RESPONSE	12(75)	5(35.71)	0.004
PSQI	4.19±2.07	8.5±4.97	0.008

The main measure of effectiveness assessed the rate of effectiveness following 4 weeks of treatment. Findings indicated a notably greater response rate in the AMT group when compared with the Conventional group (75% vs. 35.7%, P = 0.004). Furthermore, the AMT group showed notable enhancements in GETS scores on days 3 and 10, as well as week 4, while the Conventional group did not (all $P < 0.01$). There was a significant decrease in GETS scores among the AMT group at days 3 and 10 and week 4 compared to baseline (all $P < 0.05$). In contrast, the Conventional group only showed a significant reduction after 4 weeks of treatment. Moreover, the AMT group showed a noteworthy enhancement in PSQI in comparison to the Conventional group (4.19 ± 2.07 vs 8.5 ± 4.97, P = 0.008), with significant enhancements observed when compared to the initial measurements. Nevertheless, there were no substantial discrepancies in PSQI from the beginning to after receiving Pantoprazole therapy ($P > 0.05$). The notable enhancement seen in PSQI scores indicates that low-dose AMT may have a key impact on improving sleep quality and overall health in these patients. This shows how effective AMT is at improving the quality of sleep in patients with globus pharyngeus.

DISCUSSION:

Low-dose AMT has demonstrated potential in easing symptoms of globus pharyngeus and enhancing both sleep quality and overall quality of life. Yet, more extensive research with bigger study groups and lengthier observation periods is needed to confirm these initial results. Thorough research is crucial to achieve a complete understanding of how effective and safe low-dose AMT is in treating globus pharyngeus. Expanding study cohorts and prolonging follow-up durations are crucial for obtaining a better understanding of the treatment's advantages and possible constraints.(O'Hara et al. 2021)

This method aims to improve both clinical practice and enhance patient management strategies. In-depth analysis of the effectiveness and safety of low-dose AMT is essential to develop evidence-based recommendations and improve patient care. Extended monitoring allows scientists to evaluate the ongoing effectiveness and longevity of the treatment, giving critical information about its appropriateness as a potential treatment choice. By carefully recording information and consistently observing, researchers can provide valuable knowledge about the safety and effectiveness of treatment in real-life clinical environments.(Editore 2014)

LIMITATIONS:

This study has specific constraints. Firstly, in our clinic we saw many patients with globus symptoms and normal exams, but our study only focused on a small sample from this population. Additional restrictions, such as just starting PPI treatment or being diagnosed with moderate to severe anxiety or depression, reduced the pool of eligible cases for the study even further. Also, the length of time that the medication was given in our research may not have been enough; usually, in medical facilities, AMT is recommended for a usual timeframe of 4 to 12 weeks.

Furthermore, our evaluation only considered the immediate reaction to PPI medication and did not investigate how individuals may react to extended PPI therapy lasting over 3 months. These restrictions together limit the ability to apply the results of our study to a wider population and gain a complete understanding of treatment outcomes. Future research should focus on larger sample sizes and longer observation periods to gain a better understanding of the effectiveness and suitability of these treatments for globus pharyngeus.

RECOMMENDATIONS:

Several suggestions for improving future research on globus pharyngeus result from the limitations of this study, aiming to increase its reliability. First, including a wider range of patients with globus symptoms and normal exams in the study's sample size would strengthen its relevance and wide scope. Also, by including criteria that involve patients

who have just started on PPI treatment or have been diagnosed with moderate to severe anxiety or depression, a more thorough understanding of treatment results among different types of patients would be achieved.

Additionally, prolonging the period of AMT intake beyond the usual 4-12 weeks and investigating the effects of extended PPI therapy (3 months or more) could provide valuable information on the long-term effectiveness of treatment. Making these changes would enhance the credibility of the research and provide useful information for improving treatment plans for globus pharyngeus in medical settings.(Imperiale et al. 2023)

CONCLUSION:

Additional in-depth study is necessary to accurately determine the efficacy and safety of using low-dose amitriptyline for the treatment of globus pharyngeus. This study needs to involve a wider variety of subjects and extend the duration of follow-up in order to collect thorough and dependable data. By increasing our comprehension of this method of treatment, we can create more specific treatment plans and guidelines based on evidence that are customised to each patient's specific needs.

In the end, carefully assessing globus pharyngeus will result in improved management techniques, leading to better results and enhanced quality of life for those affected. Increased research endeavours will not just confirm the possible advantages of low-dose amitriptyline, but also provide insight into its safety record during prolonged usage. Healthcare providers must use this thorough approach to confidently suggest and provide this treatment in clinical settings, so that patients can get the best possible care.

Furthermore, the knowledge acquired from strong research will guide upcoming research and clinical choices, encouraging ongoing enhancements in the treatment of globus pharyngeus and potentially helping a larger group of patients facing this difficult condition.

REFERENCES:

1. You LQ, Liu J, Jia L, Jiang SM, Wang GQ. Effect of low-dose amitriptyline on globus pharyngeus and its side effects. World J Gastroenterol. 2013 Nov 14;19(42):7455-60. doi: 10.3748/wjg.v19.i42.7455. PMID: 24259978; PMCID: PMC3831229.
2. Kortequee S, Karkos PD, Atkinson H, Sethi N, Sylvester DC, Harar RS, Sood S, Issing WJ. Management of globus pharyngeus. Int J Otolaryngol. 2013;2013:946780. doi: 10.1155/2013/946780. Epub 2013 Jul 11. PMID: 23935629; PMCID: PMC3725834.
3. O'Hara J, Stocken DD, Watson GC, Fouweather T, McGlashan J, MacKenzie K, Carding P, Karagama Y, Wood R, Wilson JA. Use of proton pump inhibitors to treat persistent throat symptoms: multicentre, double blind, randomised, placebo controlled trial. BMJ. 2021 Jan 7;372:m4903. doi: 10.1136/bmj.m4903. PMID: 33414239; PMCID: PMC7789994.
4. TOPPITS: Trial Of Proton Pump Inhibitors in Throat Symptoms. Study protocol for a randomised controlled trial Gillian Watson1*, James O'Hara2 , Paul Carding3 , Jan Lecouturier4 , Deborah Stocken4 , Tony Fouweather4 and Janet Wilson2,4
5. Siau, Richard, Andrew Kinshuck, and Lisa Houghton. "The assessment and management of globus pharyngeus." *British Journal of Hospital Medicine* 82.3 (2021): 1-8.
6. Alshahrani, Abdulaziz S., and Faris Almasabi. "A new predictive scoring model for globus pharyngeus in patients with gastroesophageal reflux disease." *Saudi Journal of Gastroenterology* 30.3 (2024): 163.
7. Thejas, Saai Ram, Jangili Sharanya, and Ganganamoni Rajamohan. "Generalized anxiety causing globus pharyngeus: A prospective study." *MRIMS Journal of Health Sciences* 11.4 (2023): 223-228.
8. Järvenpää, Pia, et al. "Symptom relief and health-related quality of life in globus patients: a prospective study." *Logopedics Phoniatrics Vocology* 44.2 (2019): 67-72.
9. Bouchoucha, Michel, et al. "Clinical and psychological characteristics of patients with globus." *Clinics and Research in Hepatology and Gastroenterology* 43.5 (2019): 614-622.
10. Verma, Vinod, et al. "ASSESSMENT OF PSYCHOLOGICAL DISTRESS IN PATIENTS OF GLOBUS PHARYNGEUS: A CROSS-SECTIONAL STUDY FROM A TERTIARY CARE HOSPITAL OF EASTERN UTTAR PRADESH." *Int J Acad Med Pharm* 5.1 (2023): 704-707.