Does multi-modal cervical physical therapy improve tinnitus in patients with cervicogenic somatic tinnitus?

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Abstract

Background: Tinnitus can be related to many different aetiologies such as hearing loss or a noise trauma, but it can also be related to the somatosensory system of the cervical spine, called cervicogenic somatic tinnitus (CST). Case studies suggest a positive effect of cervical spine treatment on tinnitus complaints in patients with CST, but no experimental studies are available.

Objective: To investigate the effect of a multimodal cervical physical therapy treatment on tinnitus complaints in patients with CST.

Design: Randomized controlled trial.

Patients: Patients with a combination of severe subjective tinnitus (Tinnitus Functional Index(TFI): 25–90 points) and neck complaints (Neck Bournemouth Questionnaire(NBQ)>14 points).

Intervention: All patients received cervical physical therapy for 6 weeks (12 sessions). Patients were randomized in an immediate-start therapy group(n = 19) and a 6-week delayed-start therapy group(n = 19).

Measurements: TFI and NBQ-scores were documented at baseline, after the wait-and-see period in the delayed-start group, after treatment and after 6 weeks follow-up. The Global Perceived Effect(GPE) was documented at all measuring moments, except at baseline.

Results: In all patients (n=38) TFI and NBQ-scores decreased significantly after treatment ($p=0.04$ and $p<0.001$). NBQ-scores remained significantly lower after follow-up($p=0.001$). Immediately after treatment, 53% (n=38) experienced substantial improvement of tinnitus. This effect was maintained in 24% of patients after follow-up at six weeks.

Conclusion: Cervical physical therapy can have a positive effect on subjective tinnitus complaints in patients with a combination of tinnitus and neck complaints. Larger studies, using more responsive outcome measures, are however necessary to prove this effect.

Trial registration: NCT02016313

Introduction

Tinnitus is the phantom sensation of sound in the absence of overt acoustic stimulation (Landgrebe et al. , 2012). It occurs in 10 to 15% of adults and is experienced as severely annoying by 1.6%(Baguley et al. , 2013). The degree of severity can be expressed in terms of health-related quality of life (Tinnitus Functional Index (TFI)) and in terms of tinnitus loudness, graded with the visual analogue scale (VAS), as there is no objective way to measure tinnitus (Henry et al. , 2013).

Tinnitus is mostly subjective, as only the patient experiences the tinnitus, and it is generally described as hissing, sizzling or ringing (Baguley, McFerran, 2013). In some patients, tinnitus has a pulsatile nature that, when synchronous with the heartbeat, is likely to be of vascular origin (Baguley, McFerran, 2013). Additionally, tinnitus can be constant or intermittent, located in one or both ears or centrally located in the head.

Typically, tinnitus is related to hearing loss or a noise trauma, where cochlear abnormalities are the initial source and neural changes in the central auditory system maintain the tinnitus (Baguley, McFerran, 2013).

One subtype of tinnitus is related to the somatic system of the cervical spine, called cervicogenic somatic tinnitus (CST). Several animal studies that have found connections between the cervical somatosensory system and cochlear nuclei (CN) offer a physiological explanation for CST (Pfaller and Arvidsson, 1988, Zhan X, 2006). Cervical somatosensory information is conveyed to the brain by afferent

fibres, the cell bodies of which are located in the dorsal root ganglia or the trigeminal ganglion. Some of these fibres also project to the central auditory system. This enables the somatosensory system to influence the auditory system by altering spontaneous rates or synchrony of firing among neurons in the CN, inferior colliculus or auditory cortex. In this way, the somatosensory system is able to alter the intensity and character of tinnitus (Shore et al. , 2007).

Previous research has shown that CST is present in 36 to 43% of the overall tinnitus population (Abel and Levine, 2004, Fabijanska A., 2014, Michiels, 2015, Ostermann K., 2014). Patients with CST mainly suffer from restricted cervical spine rotation (Michiels, 2015, Reisshauer et al. , 2006), pain provocation during combined extension, lateral flexion and rotation (Michiels, 2015) of the cervical spine or sensitive trigger points (Michiels, 2015, Reisshauer, Mathiske-Schmidt, 2006) in the presence of a score of greater than 14/70 on the Neck Bournemouth Questionnaire (NBQ) (Michiels, 2015).

Several studies have found positive effects of cervical spine treatments on CST, (Latifpour et al. , 2009, Sanchez and Rocha, 2011) but these studies often lack scientific quality due to very limited numbers of patients and lack of control groups and randomization. Therefore, the use of cervical spine treatment in tinnitus patients is still under dispute.

Consequently, the aim of this study was to investigate the effect of a multi-modal cervical physical therapy program on subjective tinnitus complaints.

Methods

Study design

This study was designed as a delayed-start randomized controlled trial to evaluate the effectiveness of a standardized cervical physical therapy treatment on tinnitus in patients suffering from CST. The delayed-start design (D'Agostino, 2009) (Fig 1) allowed us to obtain data for a control group by creating a waiting list, since the use of a control group that receives no treatment at all, would not be ethical in a tertiary center population.

PLEASE INSERT FIGURE 1

At baseline, patients were randomly assigned, in a 1:1 ratio, to receive immediate treatment (immediate-start group) or to be placed on the waiting list (delayed-start group). In phase 1 (weeks 0 to 6), the immediate-start group received cervical physical therapy for 6 weeks; the delayed-start group received no cervical physical therapy during this phase. In phase 2 (weeks 6 to 12), the patients in the delayed-start group received cervical physical therapy for the next 6 weeks. The immediate-start group then entered a 6-week follow-up period. In phase 3 (weeks 12 to 18), the delayed-start group entered a 6-week follow-up period. The immediate-start group ended their participation in the study at the end of week 12.

Patients

Patients were recruited from the Antwerp University Hospital at the tertiary tinnitus clinic. During consult, patients were thoroughly examined by a multidisciplinary team to exclude any objective causes of tinnitus. Included in the study were patients suffering from severe chronic non-fluctuating subjective tinnitus that had been stable for at least three months combined with neck complaints. The severity of the tinnitus

was evaluated using the TFI (Meikle et al. , 2012). Severe tinnitus is defined as a score between 25 and 90 on the TFI(Meikle, Henry, 2012). Neck complaints were considered to be significant with a score of > 14 points on the NBQ (Bolton and Humphreys, 2002, De Hertogh et al. , 2007). Patients suffering from vertigo, objective tinnitus, subjective tinnitus with etiologies (such as hearing loss or Meniere's disease), severe depression (diagnosed by a psychologist), progressive middle ear pathology, intracranial pathology, traumatic cervical spine injury, tumors, cervical spine surgery or any cervical spine condition in which physical therapy treatment is contraindicated were excluded from the study. Patients were also excluded if they had received physical therapy treatment for the cervical spine in the past two months.

Intervention

The intervention consisted of multimodal physical therapy for the cervical spine and included, manual mobilizations, exercise therapy and home exercises. This multimodal physical therapy treatment was based on current evidence-based practice of cervical spine therapy (Gross et al. , 2004, Miller et al. , 2010). For the home exercises, a booklet established by Castien et al. (Castien et al. , 2009) was adjusted for the tinnitus patients, implementing exercises for the deep neck flexor muscles (Jull et al. , 2002) and self-mobilizing exercises (Reid et al. , 2008). Treatment was applied by a selected group of physical therapists, all of whom had obtained a master's degree in physical therapy and an additional master's degree in manual therapy. Prior to the start of the study, the research group organized a training session about the treatment protocol for all participating therapists. Patients included in the trial were referred for treatment to one of the trained therapists (guided referral). The treatment protocol provided 12 standardized cervical physical

therapy sessions during a 6-week treatment program. The therapists were free to adapt the mobilization techniques and exercises to the current situation of the patient. No manipulation techniques were allowed.

No changes were made to the patients' drug use during the study, but no additional treatments, such as neuromodulation were allowed.

Outcome measures

The primary outcome measure, the TFI (Meikle, Henry, 2012), assesses tinnitus annoyance in eight different domains: the unpleasantness of the tinnitus, reduced sense of control, cognitive interference, sleep disturbance, auditory difficulties attributed to the tinnitus, interference with relaxation, reduction in quality of life and emotional distress. The test-retest reliability of the TFI is good (r: 0.78). The convergent validity with the Tinnitus Handicap Inventory (r: 0.86) and visual analogue scale (VAS) (r: 0.75) is good, as well as the discriminant validity with the Beck Depression Inventory-Primary Care (r: 0.56) (Meikle, Henry, 2012). A reduction of 13 points is considered to be clinically relevant (Meikle, Henry, 2012).

Additionally, two secondary outcome measures, the NBQ (Bolton and Humphreys, 2002) and global perceived effect (GPE) were registered.

The NBQ (Bolton and Humphreys, 2002) consists of seven questions on the severity of the neck complaints and its interference with the patient's wellbeing and professional and daily activities. The test-retest reliability of the NBQ is moderate (ICC: 0.65). The construct validity is acceptable with both the Neck Disability Index (r: 0.50) and the Copenhagen Neck Functional Index (r: 0.44). The effect size was high

(Cohen's d: 1.67), which indicates that the NBQ is highly responsive to changes in cervical spine complaints. The clinically relevant change of the NBQ is a 12 points decrease(Bolton and Humphreys, 2002, Gay et al. , 2007).

The GPE consists of the patient's subjective opinion on changes in his or her tinnitus complaints after treatment or wait and see period. Figures for the GPE were obtained by asking whether or not (dichotomous) the patient experienced a substantial improvement of their tinnitus complaints following treatment. Patients who perceived substantial improvement were classified as 'improved'. All other patients were classified as 'not improved'. The test-retest reliability of the GPE was excellent (ICC: 0.90-0.99) in patients with musculoskeletal disorders, but the patients' current status strongly influenced the rating (Kamper et al. , 2010). Therefore, in our study we only compared the current status to baseline.

The TFI and NBQ were documented at baseline, after the 6-week wait-and-see period in the delayed-start group, immediately after the last treatment session (post-treatment) and after 6 weeks follow-up (follow-up) in both groups. The GPE was documented at all measuring moments, except at baseline.

To gain insight in the type of tinnitus and cervical spine dysfunction at baseline, we also investigated the tinnitus loudness, presence of hyperacusis, mobility and pain provocation of the cervical spine, pressure-tenderness of triggerpoints and provocation of tinnitus during cervical spine investigation.

The loudness of the tinnitus was rated using a visual analogue scale (VAS). The patient was asked to indicate the average loudness of his or her tinnitus on a 10 cm

horizontal line. On this line, the left end indicates ‘no tinnitus’ and the right end indicates ‘as loud as you can imagine’.

Hyperacusis was quantified and characterized using the Dutch version of the Hyperacusis questionnaire (HQ)(Meeus et al. , 2010) (based on (Khalfa et al. , 2002)). This questionnaire consists of 14 questions that are answered on a 4-point scale, ranging from ‘No’ (scoring 0 points), ‘Yes, a little’ (scoring 1 point), ‘Yes, quite a lot’ (scoring 2 points to ‘Yes, a lot’ (scoring 3 points)(Khalfa, Dubal, 2002). Scores on the HQ consequently range from 0 to 42 and the cut-off value for hyperaccusis is 28 points (Khalfa, Dubal, 2002).

The clinical examination of the cervical spine was performed by a master in physical therapy (MS) with an additional master’s degree in manual therapy and with 11 years of experience in musculoskeletal assessment and treatment. First, the left and right passive rotation movement of the cervical spine was investigated using the manual rotation test (De Hertogh, Vaes, 2007). Using this test, the quality of the passive rotation movement, on C0-C2 and C2-C7 levels, is rated based on three parameters: range of motion (hyper-/normal/hypomobility), end feel (hard/normal/soft/empty) and pain provocation (visual analogue scale VAS > 2 cm). The test was found positive, when for at least one movement, two out of three parameters are aberrant. Normal mobility at the C0-C2 segments was set at an estimated 45° rotation for subjects under 40 years of age, and an estimated 35° rotation for those older than 40 years. At the C2-7 segments, normal rotation was set at an estimated 25–30° rotation (De Hertogh, Vaes, 2007).

Second, the adapted Spurling test (AST), a segmental provocation test using a combination of cervical extension, lateral flexion and rotation, was used. This test was positive when at least on one segment, pain was provoked with a VAS > 2 cm

(De Hertogh, Vaes, 2007). Both tests have shown high sensitivity (77.8) and specificity (77.3) in discriminating patients with neck dysfunction from asymptomatic controls (De Hertogh, Vaes, 2007).

Thirdly, the tenderness of sixteen myofascial trigger points was tested by applying manual pressure. The following muscles were tested for the presence of sensitive trigger points: sternocleidomastoid, upper trapezius, levator scapulae and splenius capitis. A trigger point was identified as positive when the patient scored more than 2 cm on a VAS for pain. The test was positive when at least one trigger point was found positive. The locations of the trigger points were determined according to the findings of Teachey et al. in patients with tinnitus (Teachey et al. , 2012).

During all of the abovementioned clinical cervical spine tests, the patient was asked to report changes in tinnitus perception, to investigate the provocation of tinnitus due to neck movements.

Sample size

The sample size was calculated using Medcalc (Medcalc Software bvba.). This calculation was based on data of the primary outcome measure, obtained in a pilot study of 14 patients. Sample size calculation was performed for the clinically relevant change of 13 points in TFI score. The sample size was calculated for the study to have 80% power to reject the null hypothesis. The type I error probability, associated with this test, is 0.05. To achieve the 80% power, 17 patients are needed in each group. Taking into account a 15% dropout rate, 20 patients were included in each group.

Randomization procedure and blinding

After baseline measurements were recorded, patients were randomized into the immediate-start group or delayed-start group in a 1:1 ratio based on block-randomization with variable block lengths. A concealed randomization list was generated using random numbers in Microsoft Excel® software (version 14.3.5, 2010 © Microsoft Corporation). All questionnaires were filled out in the presence of a blinded investigator. Treating therapists were blinded at all times to whether a patient was included in the immediate-start or delayed-start group.

Ethical approval and consent

Ethical approval was obtained from the local ethics committee (reference number: B300201421113). Informed consent was obtained for all patients. The study was registered at ClinicalTrials.gov (NCT02016313).

Statistics

An intention-to-treat analysis was performed on the study cohort. Baseline comparability ($p > 0.05$) of both groups was analyzed using descriptive statistics, independent samples t-tests and chi-square tests.

The difference in changes from baseline of the TFI and NBQ between both groups was analyzed using a two-way repeated measures ANOVA. To analyze changes in tinnitus and neck complaints throughout the study in the entire study population, the evolution in time of the TFI and NBQ was calculated using a one-way repeated measures ANOVA. Additionally, differences between baseline, post-treatment and follow-up were calculated using paired samples t-tests. Differences in TFI and NBQ between the improved and not improved patients (on GPE) at baseline, after treatment and after follow-up were calculated using an independent samples t-test.

Results

Patients

In total, 40 patients were randomly assigned to the immediate-start or delayed-start groups in a period of one year. Two patients decided not to receive physical therapy after the randomization. An overview of the enrollment, allocation and follow-up can be found in Figure 2. None of the patients reported important adverse events or side effects due to the applied treatment.

PLEASE INSERT FIGURE 2

No significant differences were found at baseline between the immediate-start and delayed-start groups, except for the combination of manual rotation and AST (Table 1).

PLEASE INSERT TABLE 1

TFI responses to treatment

All patients (n = 38) suffered from severe tinnitus at baseline with an average TFI score of 49 (SD: 21). Immediately after treatment, the average TFI score decreased statistically significantly to 44 points (n = 38, SD: 22, p = 0.04) and increased to 47 points (n = 38, SD: 22) 6 weeks after the last treatment session.

Figure 3 shows the difference in evolution between the immediate-start and delayed-start group. This difference in evolution, however, was not statistically significant.

PLEASE INSERT FIGURE 3

NBQ responses to treatment

The average NBQ score at baseline was 33 points (n = 38, SD: 12). Immediately after treatment, the NBQ score decreased significantly to 16 points (n = 38, SD: 12, $p < 0.001$). This significant decrease was maintained 6 weeks after the last treatment session (n = 38, $p = 0.001$), although the average NBQ score slightly increased to 21 points (n = 38, SD: 15).

Figure 4 shows the evolution of NBQ scores over time between the immediate-start and delayed-start group. A significant difference between both groups was found 6 weeks after the baseline measurements ($p = 0.001$). All changes in NBQ were statistically and clinically significant.

PLEASE INSERT FIGURE 4

Global perceived effect

Six weeks after the baseline measurements, 58% of the patients in the immediate-start group (11 out of 19) experienced substantial improvement of the tinnitus compared to no improvement in the delayed-start group that had ended the wait-and-see period.

Immediately after treatment, 53% of the entire study population (20 out of 38) experienced substantial improvement of tinnitus compared to baseline. This effect was maintained 6 weeks after the last treatment session in 24% of the patients (9 out of 38).

Characteristics of improved patients

At baseline, no significant differences were documented in TFI or NBQ between the substantially improved and not improved patients.

Immediately after treatment, the subjectively improved patients (n = 20) reported an average decrease in TFI of 11.9 points (SD: 21.4), while the not improved patients (n = 9) reported an average increase of 0.7 points (SD: 4.8). After the follow-up period, the average TFI score decreased by 16.9 points (SD: 26.6) in the improved patients (n = 20) and increased by 2.4 points (SD: 8.3) in the not improved patients (n = 9) when compared to baseline. No significant differences in the decrease of NBQ scores were found between subjectively improved and not improved patients. The changes in TFI and NBQ scores are presented in Table 2.

PLEASE INSERT TABLE 2

Discussion

The aim of this study was to investigate the effect of a standardized cervical physical therapy program on tinnitus complaints. The applied physical therapy treatment was a noninvasive, approachable and easily available treatment option. The tinnitus population is currently unknown territory for most physical therapists, but should gain more interest, given the high prevalence rates of somatic tinnitus. Taking into account that tinnitus has a prevalence of 15% among the adult population and that approximately 40% of these tinnitus patients suffer from somatic tinnitus (due to somatosensory changes of the cervical spine (called CST) or temporomandibular area), the somatic tinnitus population is a rather large group. To date however, a lot of patients with CST are not referred for physical therapy because of lack of evidence of physical therapy for CST complaints. We assume that more evidence will result in better referral of these patients, who are now often left without treatment. Future studies, investigating prognostic factors, will also contribute to the referral of those patients that are most likely to benefit from physical therapy treatment.

In our study, 53% of the patients (n = 38) perceived substantial improvement of tinnitus immediately after a 6-week treatment period. This effect was maintained after the follow-up period in 24% of the patients (n = 38). This success rate is high, given the chronicity and the therapy resistance of the tinnitus complaints in our tertiary referral center population. Despite the difference in outcome measures, our results match the results of a study performed by Bakker (Bakker, 2012) that found a significant decrease of tinnitus after 12 sessions of physical therapy in 62.9% of the patients. This effect was not maintained in any of the patients after follow-up.

Despite the relatively high success rate, our study could not prove a statistically significant difference in TFI scores between the immediate-start (n = 19) and delayed-start groups (n = 19) at week 6 of the study. At this point, we expected the patients in the immediate-start group to experience the effects of the treatment while the delayed-start group had not received treatment yet. Small differences in TFI scores between both groups were found, but due to large standard deviations, these differences were not statistically significant.

It is possible that the TFI is not responsive enough to identify changes in tinnitus at 6 weeks. Meikle et al. (Meikle, Henry, 2012) used a time interval of 3 months to identify the effect sizes of the TFI. In our study, the average TFI decrease in the improved group was 11.9 points, which is similar to the 13-point reduction Meikle et al. (Meikle, Henry, 2012) suggested to be clinically important. The standard deviations, however, were very large in our study as well as in that of Meikle et al. (Meikle, Henry, 2012), making it hard to identify statistically significant differences between groups. Similar

concerns regarding the responsiveness of the TFI were recently proposed by Fackrell et al.(Fackrell et al. , 2015).

The NBQ scores showed significant and clinically relevant improvement on the cervical spine complaints immediately after treatment as well as after follow-up. Despite the significant decrease of NBQ scores between baseline and follow-up, a slight increase of NBQ scores can be seen during the follow-up period. In cervical spine treatment studies of other populations, the effect of the treatment on the VAS for pain remained about the same post-treatment and after a 6-week follow-up period (Reid, Rivett, 2008, Reid et al. , 2014).

Various factors may have caused the increase of neck complaints in our study. First, the treatment period of 6 weeks might have been too short for a population with a chronic disorder. In this case, the cervical spine dysfunction may not have disappeared completely, causing a quick reoccurrence after the treatment period. Second, patients might have stopped the home exercises after the last treatment session. These exercises are meant to prevent the reoccurrence of cervical spine dysfunction and need to be continued on a regular basis. Therefore, we suggest the use of more physical therapy sessions over a longer treatment period. For example, 18 sessions spread out over a 12-week treatment period or the use of a home exercise program.

Patients were included in this study based on the diagnostic criteria for CST (Sanchez and Rocha, 2011). According to these criteria, the diagnosis of CST is assumed when at least one of the following criteria is present: (1) evident history of head or neck trauma; (2) tinnitus association with some manipulation of the teeth,

jaw, or cervical spine; (3) recurrent pain episodes in head, neck, or shoulder girdle; (4) temporal coincidence of appearance or increase of both pain and tinnitus; (5) increase of tinnitus during inadequate postures during rest, walking, working, or sleeping; and (6) intense bruxism periods during the day or night. After exclusion of other causes of tinnitus, the criterion ‘recurrent pain episodes in head, neck or shoulder girdle’ was used as the main criterion for inclusion, as patients without recurrent pain episodes are not likely to benefit from a cervical spine treatment. The other diagnostic criteria were also questioned during medical history taking. The combination of cervical spine complaints and tinnitus as a diagnostic criterion for CST is however not ideal, since tinnitus and cervical spine complaints can also occur independently. This statement is supported by the fact that the cervical spine complaints (measured using NBQ) significantly and clinically relevantly decreased after cervical physical therapy treatment in all patients, including those who did not perceive a change in tinnitus complaints.

In TFI and NBQ scores, a similar decrease after treatment and increase after follow-up can be noted (figures 3 and 4). These findings can be considered proof of the somatosensory influence on the intensity and the character of tinnitus and can therefore contribute to the discussion on a causal relation between tinnitus and neck complaints.

To date, no information is available on the tinnitus subtype that benefits most from cervical spine treatment. Future research will have to concentrate on defining prognostic indicators, to recognize patients that are likely to improve after cervical

physical therapy. These prognostic indicators can then be used to include patients in future RCT's evaluating the effect of physical therapy on tinnitus complaints.

Conclusion

A multimodal cervical physical therapy treatment can have a positive effect on tinnitus complaints in some patients with a combination of tinnitus and neck complaints. Larger studies, using more responsive outcome measures, are however necessary to prove this effect. Additionally, future research should focus on identifying prognostic indicators that can predict this positive outcome.

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Characteristic	Immediate-start group	Delayed-start group	Total	p
Number of subjects	19	19	38	1.00
Age (SD)	46(14)	52(12)	50(13)	0.26
TFI (SD)	50(23)	51(18)	49(21)	0.91
NBQ (SD)	37(10)	32(12)	32(12)	0.15
VAS tinnitus	6(2)	5(2)	5(2)	0.55
Hyperacusis	20(9)	19(9)	19(9)	0.88
Manual rotation + AST	68%	37%	53%	0.05*
AST	74%	53%	63%	0.18
Trigger points	79%	84%	82%	0.68
Provocation of tinnitus	11%	11%	11%	1.00

Table 1: Demographic features of the immediate-start and delayed-start groups at baseline

* Significant difference between both groups

SD: standard deviation

TFI: Tinnitus Functional Index

NBQ: Neck Bournemouth Questionnaire

VAS: Visual analogue scale

AST: adapted Spurling test

	Post-treatment			Follow-up		
	Not improved	**Improved**	**p**	**Not improved**	**Improved**	**p**
Change in TFI	+0.67 (4.78)	-11.89 (21.43)	0.02*	+2.42 (8.28)	-16.89 (26.56)	0.001*
Change in NBQ	-15.19 (17.17)	-18.32 (15.03)	0.57	-13.07 (18.28)	-6.38 (24.63)	0.41

Table 2: Changes in TFI and NBQ in subjectively improved and not improved patients

* Significantly different between improved and not improved patients.

TFI: Tinnitus Functional Index

NBQ: Neck Bournemouth Questionnaire

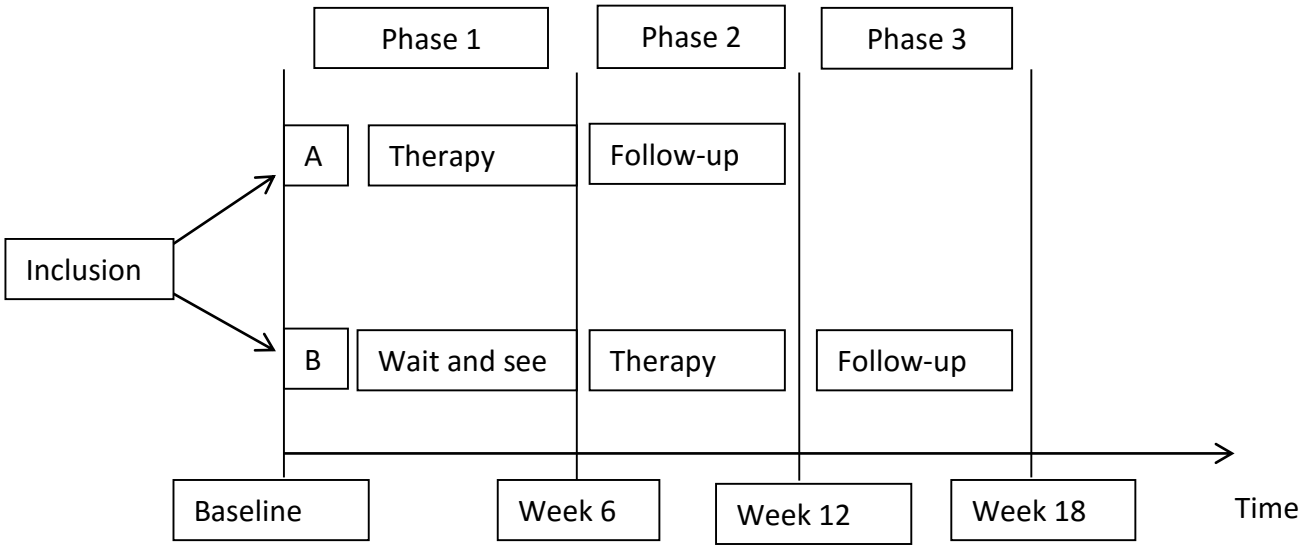

Figure 1: Delayed-start design

A: immediate-start group

B: delayed-start group

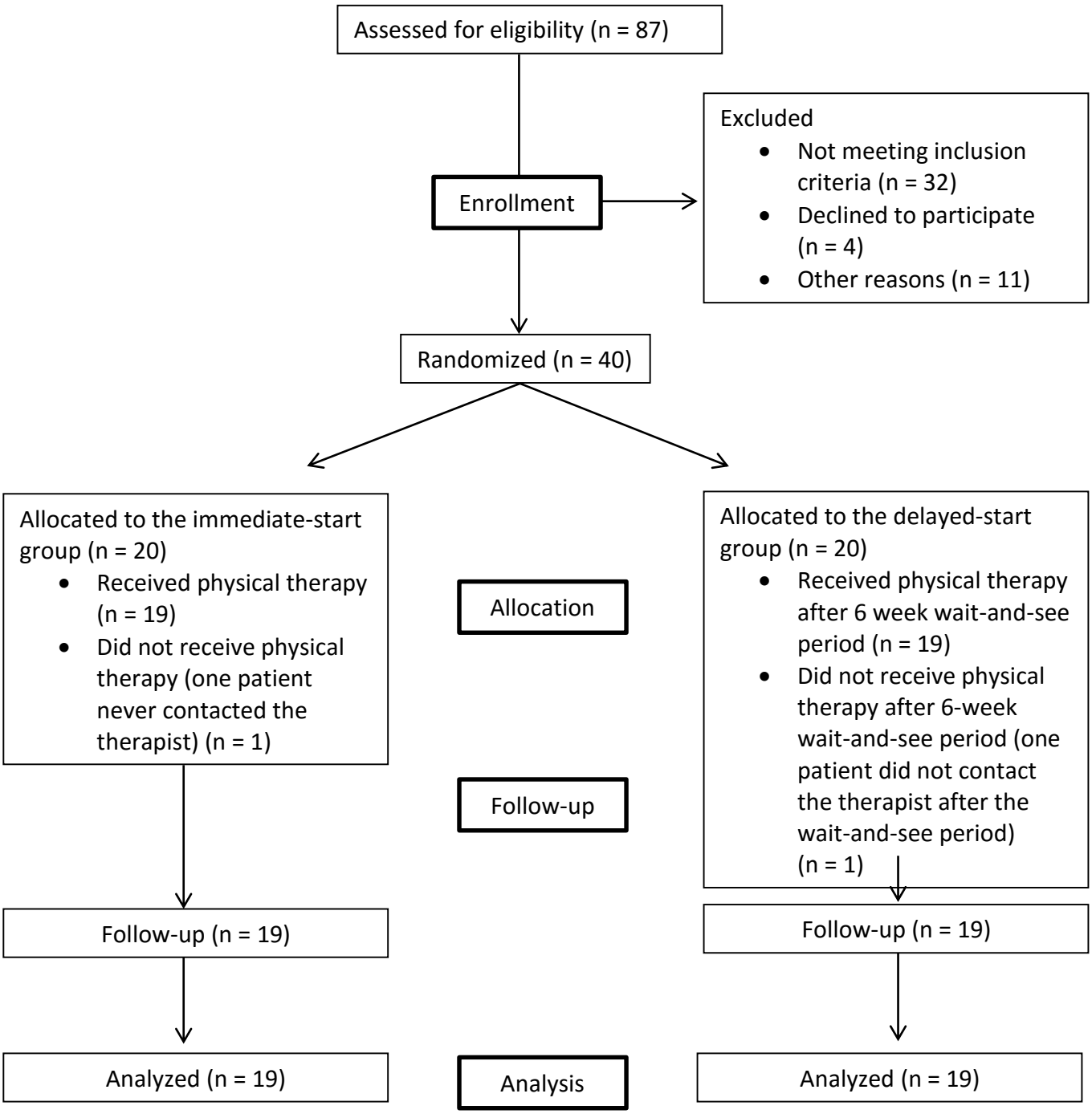

Figure 2: Flow chart of the participants' progression through the study

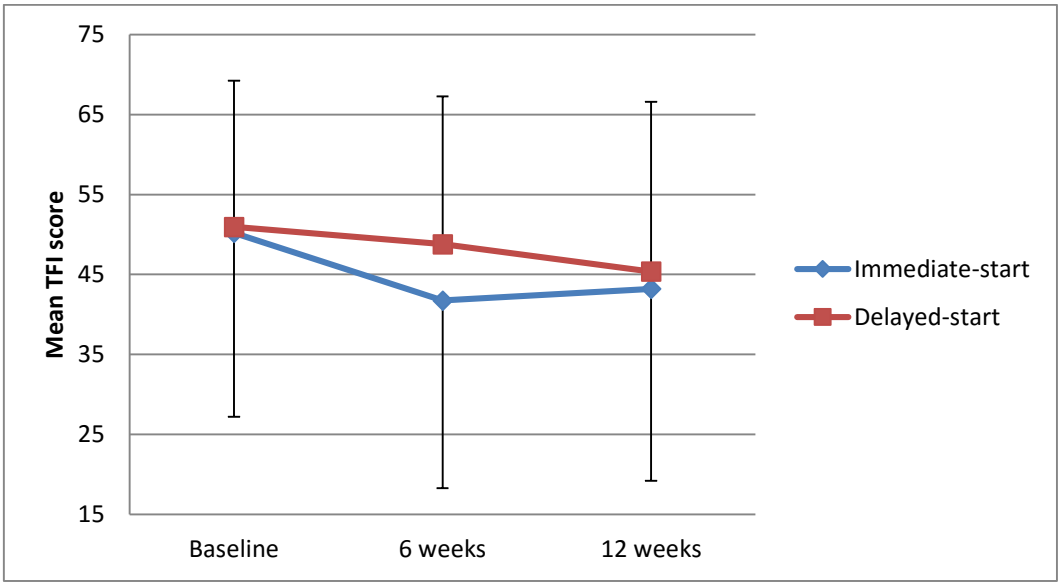

Figure 3: Evolution of the Tinnitus Functional Index (TFI) scores in the immediate-start and delayed-start groups

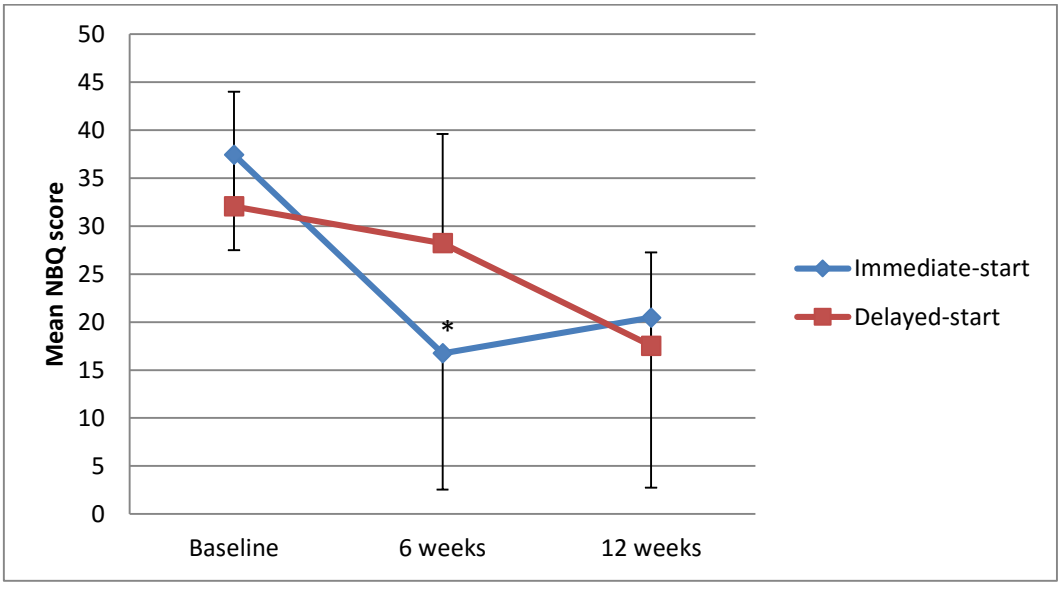

Figure 4: Evolution of the Neck Bournemouth Questionnaire (NBQ) in the immediate-start and delayed-start groups

* Significant difference between both groups