



Original Article

A Pilot Study Using Intratympanic Methylprednisolone for Treatment of Persistent Posterior Canal Benign Paroxysmal Positional Vertigo

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OBJECTIVE: To assess the effect of intratympanic methylprednisolone (ITMP) in posterior canal benign paroxysmal positional vertigo (BPPV) that fails treatment involving repositioning maneuver in a case series.

MATERIALS and METHODS: Nine patients with persistent posterior canal BPPV after 6 or more repositioning maneuvers were treated by ITMP (two weekly doses of 0.3–0.4 mL at 40 mg/mL) before repeating the repositioning procedures.

RESULTS: Following ITMP treatment, 7 out of 9 patients were relieved of their symptoms and did not exhibit positional nystagmus after 1 or 2 repositioning maneuvers. The number of positional maneuvers performed before and after ITMP treatment in these 7 patients showed a statistically significant ($p=0.016$) reduction in the amount of repositioning treatments required. None of the 7 respondent patients showed any relapses during the follow-up period (follow-up range: 11–95 months).

CONCLUSION: Administering ITMP before resuming repositioning procedures can be a useful treatment for persistent BPPV of the posterior canal.

KEYWORDS: Benign paroxysmal positional vertigo, intratympanic injection, methylprednisolone

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a common vestibular disorder that affects nearly 40% patients with vertigo^[1]. It is characterized by spinning vertigo induced by changes in the head position. Posterior semicircular canal (PSC) BPPV is the most common clinical variant; however, BPPV of the lateral (LSC) and the anterior (ASC) canals are less commonly observed. Further, BPPV may be bilateral, and it may affect different canals simultaneously^[2–4]. It is generally accepted that cupulolithiasis, canalithiasis, or both are related to the cause of BPPV: canalithiasis is its most common form^[3,5]. Diagnosis is based on the features of the positional nystagmus provoked by the positioning tests, mainly the Dix–Hallpike test for PSC and ASC BPPV and the roll test for LSC BPPV. The characteristics of the nystagmus for each type of canal BPPV are described elsewhere^[5].

Particle repositioning maneuvers (PRM) are an effective treatment for BPPV with a 98% success rate after 3 maneuvers^[6,7]. However, a small subset of patients experience persistent positional symptoms and nystagmus even after repeated PRM^[8–10].

According to Horii^[11], intractable BPPV comprises 1) persistent BPPV (which continues despite appropriate physical therapy) and 2) recurrent BPPV (frequent relapses after the disappearance of the initial symptoms and nystagmus). A recent study^[9] found 12.5% incidence of persistent BPPV and 10% recurrent BPPV. This shows that intractable BPPV is not a rare condition, and it may occur more often than expected.

Schratzenstaller et al.^[12] studied 5 patients suffering from persistent BPPV with high-resolution three-dimensional magnetic resonance imaging (MRI) of the inner ear. They found structural changes, such as filling defects in the semicircular canals, in these patients that were not present in control groups. Other authors also found a high incidence of similar abnormal MRI images in patients with intractable BPPV^[11,13]. These filling defects may indicate a narrowing and/or an otoconial jam of the semicircular canal, and it may suggest that an inflammatory process of the membranous labyrinth could explain the failure of the repositioning maneuvers^[11–13].

Intratympanic (IT) steroids are often used to treat inner ear disorders such as sudden idiopathic sensorineural hearing loss, autoimmune hearing loss, and Ménière's disease [14]. Corticosteroids exert their effects in the inner ear after interacting with intracellular glucocorticoid receptors by producing metabolic and anti-inflammatory effects. It is also known that glucocorticoid receptors are widespread throughout the inner ear, including semicircular canal duct epithelial cells, where they facilitate cation absorption via sodium channels [15-17].

Thus, considering the possibility of an inflammatory process of the labyrinth or an imbalance of Na⁺ and Ca²⁺ in the endolymph could be related with the intractability of BPPV, we have carried out a pilot study to assess the effect of IT methylprednisolone (ITMP) in persistent posterior canal BPPV.

MATERIALS and METHODS

This prospective study included patients from 3 different hospitals. From January 2006 to March 2014, we diagnosed 187 patients affected from unilateral posterior canal BPPV. None of them had any symptoms or signs of central nervous system (CNS) disease. A complete otoneurological examination, including otoscopy, audiometry, head thrust test, spontaneous nystagmus recording, gaze-evoked nystagmus test, cover test, and Romberg and Fukuda tests, were performed in all the cases.

The diagnosis of posterior canal BPPV was made by Dix-Hallpike test, showing a mixed vertical and torsional nystagmus beating toward the undermost ear, with appropriate latency and duration, and the direction of the nystagmus reversed on resuming the upright position. In every patient, the roll test and head hyperextension test were also performed in order to rule out lateral or superior canal BPPV.

Patients with BPPV were treated by Epley or Semont maneuvers. We carried out only one of those maneuvers in every session. Each session, weekly programmed, began with a Dix-Hallpike test; if it was positive for the same posterior canal, a new therapeutic maneuver was carried out. After each treatment, we recommended not lying on the affected side and avoiding brisk movements.

Both procedures, i.e., diagnostic tests and treatment maneuvers, were performed under video-oculographic control (VO425b, Interacoustics, Denmark).

We defined persistent BPPV when the same posterior canal was still affected after at least 6 maneuvers.

MRI was performed on each patient in order to rule out a CNS disorder. The repositioning treatment was stopped until the patient underwent MRI.

The study was approved by the Ethical Review Board for Compassionate Use of Drugs, requiring individualized endorsement. All the patients received detailed information about the risks of the procedure, and informed consent was obtained in all the cases.

The inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria for ITMP treatment in persistent posterior canal BPPV^a

Inclusion criteria:	Patients affected of Persistent BPPV of unilateral, posterior semicircular canal
	Absence of pathologic findings on MRI
	Absence of clinical signs suggesting CNS disease
Exclusion criteria:	Anterior, lateral or multiple canal involvement
	Presence of clinical signs of CNS disease
	Presence of abnormal otoscopic findings
	Existence of a previously treated BPPV episode
	Patients receiving systemic steroids for a concomitant disease

^aPersistent BPPV was defined if the patient experienced vertigo and positional nystagmus during Dix-Hallpike test in the same affected posterior semicircular canal after six repositioning maneuvers

Method

Since a spontaneous resolution could occur during the period while the patient was waiting to be examined by MRI, all the patients were re-evaluated for posterior canal BPPV persistence before proceeding to the IT treatment.

The intratympanic methyl-prednisolone injection was administered in the outpatient clinic under a binocular microscope. After local anesthesia was administered, tympanic puncture was performed by using a 24-gauge spinal needle, and 0.4-0.5 mL of a 40 mg/mL solution of methylprednisolone was infused into the middle ear. Patients were told to avoid swallowing and to keep their head at 30-40° to the healthy side for up to 30 min.

We performed 2 weekly ITMP empirical treatments. One patient (number 3) experienced local discomfort, which was attributed to the methylprednisolone solvent, and the second IT treatment was performed with a solution of 8 mg/mL dexamethasone.

All the subjects were instructed to avoid taking vestibular suppressant medications during the complete treatment.

Once the IT treatment was completed, the repositioning procedure was resumed by following the methodology described above. Success was defined as the absence of nystagmus and positional vertigo during the Dix-Hallpike tests. Every patient was first revisited in a month and every 6 months thereafter. In addition, patients were instructed to return to the clinic if they re-experienced BPPV symptoms.

Statistical Analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Inc.; Chicago, IL, USA). The non-parametric Wilcoxon test was used to compare the number of pre- and post-treatment maneuvers. Here, p<0.05 was considered to be statistically significant.

RESULTS

Nine (5 men, 4 women) out of the 187 patients with a diagnosis of unilateral posterior canal BPPV (4.8%) fulfilled the criteria of persistent BPPV and were selected for the study. The patients belonged to the age range between 50 and 69 years, with a mean age of 58 years.

Table 2. Clinical features of patients with posterior canal BPPV and combined treatment with ITMP followed by the outcomes of repositioning maneuvers

Patient	1	2	3	4	5	6	7	8	9
Age (Years)	55	52	63	69	50	52	59	56	67
Gender	M	M	M	M	F	F	M	F	F
Side	L	R	L	L	R	L	L	L	R
Etiology	I	I	AUVD	AUVD	T	I	I	I	MD
Head trust test	Normal	Normal	L +	L +	Normal	Normal	Normal	Normal	Normal
Time from onset to diagnosis (months)	1	5	3	4	2	4	7	120	3
Time from diagnosis to ITMP (months)	4	6	4	4	9	3	12	7	4
Product	MP	MP	MP/D	MP	MP	MP	MP	MP	MP
Number of maneuvers before ITMP	8	6	7	6	8	7	9	6	6
	6E	4E	6E	4E	5E	3E	5E	3E	3E
	2S	2S	1S	2S	2S	3S	2S	3S	3S
Number of maneuvers after ITMP	2	1E	2E	2	2E	1E	8	11	1E
	1E			1E			5E	6E	
	1S			1S			3S	5S	
Follow-up (months)	101	67	57	44	36	32	29	20	17
High-Resolution 3D -MRI	Left Crus comunis & lateral canal stenosis	NA	Normal (no stenosis)	NA	NA	NA	NA	NA	NA
Status	Cured	Cured	Cured	Cured	Cured	Cured	Not cured	Not cured	Cured
Recurrence	No	No	No	No	No	No	-	-	No

M: male; F: female; L: left; R: right; idiopathic: AUVD Acute Unilateral Vestibular Deficit; T: posttraumatic; MD: Ménière's disease; MP: methyl-prednisolone; D: dexamethasone; E: epley maneuver; S: semont maneuver; NA: not available

BPPV was idiopathic in 5 cases, subsequent to an acute unilateral vestibular deficit in 3 patients, and secondary to Ménière's disease in 1 case. The remaining patient developed the posterior canal BPPV after suffering a head trauma.

There were no major complications during ITMP treatment.

Seven out of the 9 patients (78 %) were relieved of their BPPV signs and symptoms after the IT treatment. Four patients required 2 maneuvers after ITMP, and 3 patients were cured after a single maneuver. The comparison between the number of positional maneuvers performed before and after IT treatment in the 7 patients with complete resolution of the BPPV showed a statistically significant ($p=0.016$) reduction in the number of repositioning treatments required.

The 2 remaining patients persisted intractable, and we were unable to resolve the BPPV, even after repeated maneuvers following the IT treatment. Both patients refused surgical treatment (posterior canal occlusion).

None of the 7 cured patients experienced a recurrence during the follow-up period. The median follow-up period after IT treatment was 44 months (range: 17–101 months).

The main clinical features of the 9 patients and the outcome after ITMP treatment are summarized in Table 2.

DISCUSSION

Our results show that intractable posterior canal BPPV is about 5% in tertiary referral hospitals, and these patients may benefit from ITMP therapy.

In the series by Choi et al.^[9], persistent BPPV represents 12.5% of all the BPPV patients. Recently, Babac et al.^[8] have estimated a 6.5% treatment failure in BPPV patients.

Benign Paroxysmal Positional Vertigo is considered a benign disease, as it is usually self-limited or it responds well to physical maneuvers in most cases^[6,7]. However, when 5 or 6 maneuvers are ineffective and once typical features of the nystagmus are observed, these patients should be assessed by a specific neuro-radiological study to rule out CNS conditions^[9]. After CNS involvement has been ruled out, the persistence of positional vertigo symptoms should lead us to consider morpho-structural alterations of the labyrinth as well as metabolic and functional labyrinth conditions that facilitate the formation and maintenance of canaliths^[8,12,13].

Modern imaging techniques are able to directly display the bone and membranous structures of the labyrinth. In particular, the use of three-dimensional high-resolution MRI protocols enables us to see the internal structure of the cochlea, vestibule, and semicircular canals. Studies based on this technique have shown that patients with persistent BPPV had a higher incidence of abnormal MRI images (stenosis and canal filling defects) than normal controls^[11–13]. These anomalies might correspond to really ductal narrowness or to plugs of otoconial debris^[11,12]. Preliminary reports about these labyrinth abnormalities led us to consider the use of steroids because of their anti-inflammatory effect since glucocorticoid receptors are prevalent throughout the inner ear, including the vestibular structures (such as maculae of the utricle and saccule, otoconial membrane, the semicircular canal crista, semicircular canal duct epithelium, and extramacular epithelium of the saccule)^[15,18]. If the BPPV persistence had an inflammatory origin, the steroids can assist in improving the success of the maneuvers.

We were only able to study any possible canal stenosis in 2 out of the 9 patients, as the remaining 7 patients were referred to radiological units in which these high-resolution techniques were not available. Out of these 2 patients, 1 did not exhibit these abnormalities on high-resolution three-dimensional MRI and the other patient exhibited not only crus communis stenosis but the patient's horizontal semicircular canal was also affected. Horii et al. [11] described that no exact correlation exists between the affected canals diagnosed by MRI and the involved canals according to the nystagmus. We can speculate that a more extensive labyrinth disease, beyond the particular canal affected, can lead to chronic, persistent BPPV. To this extent, it has been shown that the other variety of intractable BPPV, i.e., recurrent BPPV, can affect any of the three canals in both the labyrinths. This suggests that some patients suffering from BPPV do not have a particular problem with one of their ears, but they have a pathological condition involving their vestibular organs [19]. Besides, BPPV affecting several canals, either bilaterally or on the same side, is not rare and it has been reported in percentages ranking from 4 to 21% [2-5]. This also leads to considering BPPV as the result of an extensive labyrinthine disease, more complicated than the problem of a specific canal.

During the last few years, many other factors involved with the intractability of BPPV have emerged. Potential risk factors associated with BPPV treatment failure are age over 50 years, secondary BPPV, head trauma, and the concurrency of comorbidities, such as diabetes, hypertension, and osteoarthritis.

Calcium metabolism seems to be involved in the susceptibility to BPPV. Thus, different studies have identified osteoporosis/osteopenia, estrogen deficiency, and low serum levels of vitamin D as potential risk factors for BPPV [21-25]. Otoconia are composed of calcium carbonate as calcite crystals and an organic core consisting predominantly of glycoproteins. The otoconia are in a dynamic state, and calcium and potassium are required to mineralize otoconia and to maintain any turnover in the otolith [26,27]. Two mechanisms have been proposed to explain the relationship between BPPV and abnormal calcium metabolism: 1) a disturbed internal structure of the otoconia or their interconnections and attachment to the gelatinous matrix and 2) a reduced capacity to dissolve the dislodged otoconia owing to increased concentration of free calcium in the endolymph, resulting from increased calcium resorption [28,29].

To this extent, both the cochlea and labyrinth were found to express crucial genes needed to constitute a Ca^{2+} absorption mechanism to maintain low levels of endolymphatic Ca^{2+} in order to sustain normal hearing and balance functions [30]. The Ca^{2+} absorptive system comprises an apical membrane entry pathway (TRPV5 and TRPV6 channels), a cytosolic Ca^{2+} buffer protein (calbindin-D9K and calbindin-D28K), and basolateral Ca^{2+} exit pathways (sodium-calcium exchangers -NCX-) and plasma membrane Ca^{2+} -ATPases (PMCA) [31]. Expression of these transporters can be regulated by the active form of vitamin D, i.e., 1,25-(OH)₂ vitamin D3 [30]. Further, it has been shown that some of these calcium transporters can be modulated by glucocorticoids [32].

The extent of molecular and biochemical processes reveal that glucocorticoids control is not well known. Glucocorticoids modulate the specific signaling mechanisms through the membrane glucocorti-

coid-binding sites. These effects are responsible for the decrease in intracellular Ca^{2+} in some tissues (such as hypothalamus neurons) and an increase in trans-epithelial sodium transport in extramacular saccular epithelium and semicircular canal duct epithelium [16,32,33].

In summary, glucocorticoids are able to modulate Ca^{2+} and Na^+ homeostasis of the labyrinth, and these ionic changes might assist in resolving persistent BPPV.

We select ITMP administration because it has been widely employed for treating inner ear processes such as Ménière's disease, autoimmune hearing loss, or sudden idiopathic sensorineural hearing loss [14]. Moreover, ITMP is well tolerated and safe, without the adverse effects of systemic steroids, and it increases the amount of steroids entering the inner ear when compared with systemic routes of administration [18,34].

Our study indicates that the combination of ITMP with repositioning maneuvers can resolve intractable BPPV. Choi et al. [9] recommended frequently repeated maneuvers for the management of intractable BPPV. It could be claimed that repeated maneuvers, rather than ITMP administration, have led to the resolution of BPPV, provided that 6 or more maneuvers were unable to resolve the BPPV after at least 3 months; however, after IT steroid administration, only 1 or 2 maneuvers were effective in eliminating BPPV signs and symptoms in 7 out of the 9 patients. It would be reasonable to attribute this success to the use of IT steroids.

It has been stated that BPPV patients requiring a large number of maneuvers have a particular tendency to relapse [19]. This may be linked to the concept of an underlying labyrinthine disease and the ionic factors mentioned above. In our series, none of the cured patients experienced a relapse during the follow-up period, which was over 17 months. Since 50% BPPV relapses usually take place during the first year after the successful repositioning manoeuvre, we might consider an additional possible benefit of the steroid treatment, i.e., preventing the development of BPPV recurrences.

A double-blind randomized controlled study should be performed to demonstrate the effectiveness of IT steroids in the treatment of persistent BPPV.

CONCLUSION

Intratympanic methyl-prednisolone, followed by repositioning treatment, can be a valuable aid in controlling persistent BPPV. A randomized clinical trial is needed to validate its efficacy.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethical Review Board for Compassionate Use of Drugs of the Hospital of Cabueñes.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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