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Modern Perspectives on the Role of L-Type Calcium Channel Blocker for Hearing Preservation in Sensorineural Hearing Loss: A Systematic Review of Recent Randomized Clinical Trials

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Abstract

***Background*:** Globally, an estimated 1.57 billion individuals experienced some degree of hearing loss, with 403.3 million cases classified as moderate to severe. Several L-type calcium channel blockers (CCBs) have demonstrated protective effects against various types of sensorineural hearing loss (SNHL). This systematic review aims to synthesize recent findings on the efficacy of L-type CCBs in preserving hearing function in SNHL and highlight research gaps for future exploration.

Methods and Results: A thorough search of the literature was conducted using several databases, including PubMed Central, Google Scholar, ClinicalTrials.gov, and EBSCOHost, for relevant literature from January 2000 to January 2024. Of the 578 studies screened, 4 RCTs met the criteria. In animal studies, L-type CCBs demonstrated reduced hearing threshold shifts and hair cell preservation under noise and ototoxic stress. In humans, nimodipine showed limited, non-significant benefits in surgical patients. Efficacy varied with SNHL etiology, and inconsistencies were noted due to differences in dosage, delivery, and study bias.

Conclusion: L-type calcium channel blockers may protect against sensorineural hearing loss under specific conditions, calcium overload. However, inconsistencies in findings and high risks of bias across studies make it difficult to draw firm conclusions for clinical application. Rigorous, well-designed research is needed to clarify when CCBs may be beneficial.(**International Journal of Biomedicine. 2025;15(1):90-94.**)

Keywords: calcium channel blockers • sensorineural hearing loss • noise-induced hearing loss

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Abbreviations

ABR, auditory brainstem response; **CCBs,** calcium channel blockers; **NIHL**, noise-induced hearing loss; **RCT**, randomized controlled trial; **SNHL**, sensorineural hearing loss; **VGCC**, voltage-gated calcium channels.

Introduction

Globally, an estimated 1.57 billion individuals experienced some degree of hearing loss, with 403.3 million cases classified as moderate to severe.[1] By 2050, that number is projected to increase by 56.1% to 2.45 billion.[2] Among those numbers, sensorineural hearing loss (SNHL) is the most prevalent form.[3] Many etiologies have been identified, namely heredity, ototoxicity, noise trauma, aging, and idiopathy.[3] While no preventive treatments exist for hereditary causes, many studies aim to identify preventive measures for other acquired etiologies.

Calcium channel blockers (CCBs), also known as calcium channel antagonists, have been widely approved and used for the treatment of cardiovascular conditions, such as hypertension and coronary heart disease, as well as certain off-label indications, such as subarachnoid hemorrhage. Calcium channel blockers work primarily by inhibiting L-type voltage-gated calcium channels (VGCC) located in vascular smooth muscle and cardiac muscle.[4] Observational studies in animal

models have also identified VGCCs in inner ear structures integral to hearing, including the organ of Corti, stria vascularis, spiral ligament, spiral limbus, and spiral ganglion neurons.[5]

Several L-type CCBs have demonstrated protective effects against various types of SNHL. In cases of noise-induced hearing loss (NIHL), dihydropyridine CCBs, such as nifedipine and nimodipine, have been shown to mitigate excessive intracellular Ca^{2+} influx, which can lead to cellular injury and death. Additionally, newer-generation CCBs, like lercanidipine, have demonstrated antioxidative properties that reduce production of reactive oxygen species, thus supporting hair cell survival.[6] Meanwhile, non-dihydropyridine CCBs, such as verapamil and diltiazem, have shown efficacy in protecting against SNHL with ototoxicity as an underlying cause.[7]

While there is a growing body of research on the effects of CCBs on SNHL, only a limited number of randomized controlled trials (RCTs) in both human and animal models have specifically examined their protective role. Thus, this systematic review aims to consolidate existing findings and highlight areas where further investigation could clarify the potential role of L-type CCBs in hearing preservation for populations with SNHL.

Methods

Literature Search and Criteria Screening

A thorough search of the literature was conducted using several databases, including PubMed Central, Google Scholar, ClinicalTrials.gov, and EBSCOHost, for relevant literature from January 2000 to January 2024. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines were followed in conducting this research.

The search phrases used in PubMed were as follows: "hearing loss, sensorineural"[MeSH Terms] or "hearing loss, noise-induced"[MeSH Terms] or "hearing loss, sudden"[MeSH Terms] or "deafness"[MeSH Terms] or "hearing loss"[MeSH Terms] or "hair cells, auditory"[MeSH Major Topic]) and "calcium channel blockers"[MeSH Terms].

Eligibility Criteria

The eligibility criteria for records included in the study were RCT conducted in humans or animals, focusing on outcomes relevant to SNHL within the past 24 years. Each author initially reviewed the titles and abstracts of the obtained search results. Subsequently, complete articles were obtained for further analysis if deemed necessary. The inclusion criteria were original articles, RCT conducted in humans or animals, full-text availability, and written in English or Bahasa Indonesia.

Risk of Bias

We used RoB 2 to evaluate the papers included in our systematic review. RoB 2 is organized into a fixed set of bias domains, concentrating on various elements of trial design, execution, and reporting. All the studies are RCTs. The upcoming Figure 2 will provide an overview of the sources of bias that have been discovered, providing important information on the strengths and limits of the reviewed studies.

Results

Following the application of the search strategy, four articles met the eligibility criteria for this systematic review and were selected for comprehensive analysis (Figure 1). All included studies were RCTs that evaluated the effects of L-type CCBs compared to either a placebo or an alternative intervention, with each trial using an L-type CCB as the intervention.

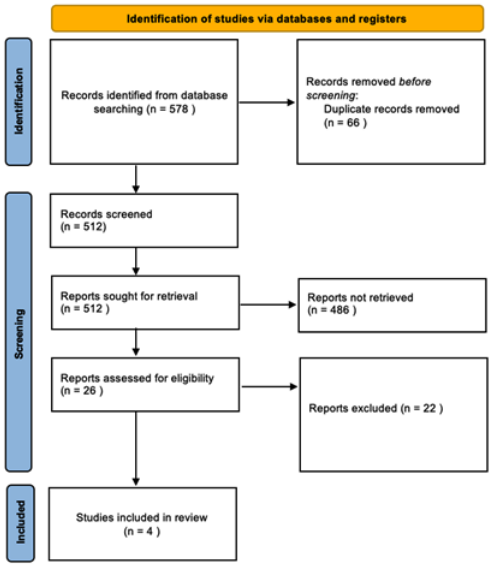

Figure 1. *PRISMA Flow Diagram.*

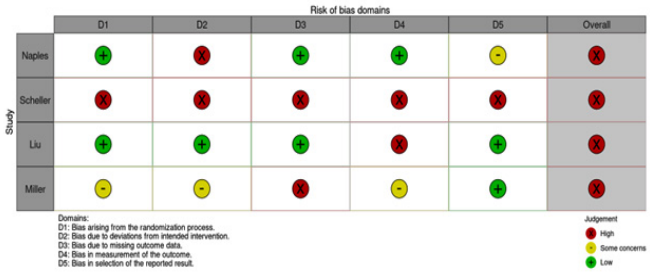

Figure 2. *Risk of bias summary: Author judgments about each risk of bias item for each included study.*

The Role of L-type CCBs on Hearing Preservation in SNHL

The data presented in Table 1 reveal considerable variation in the hearing assessment methods across studies, reflecting differing approaches to evaluating CCB efficacy on SNHL. Three studies used objective hearing evaluations. Naples et al.[7] and Miller et al.[8] utilized auditory brainstem response (ABR) testing, which measures the auditory brainstem's response to sound stimuli, whereas Liu et al.[9] used electrocochleography to record the cochlea's electrical potentials. In contrast, Scheller et al.[10] used subjective pure-tone audiometry with results categorized by the Gardner-Robertson scale.

Table 1.

Results of included studies

Author, Year	Title	Intervention	Study Design, Duration, Number of Participants	Outcome
Naples,et al., 2020[7]	Intratympanic Diltiazem-Chitosan Hydrogel as an Otoprotectant Against Cisplatin-Induced Ototoxicity in a Mouse Model	Placebo vs. Intratympanic CGP-diltiazem 2 mg/kg	RCT on animal samples, 1 single injection, n=30	A single intratympanic injection of CPG-diltiazem following an IP injection of cisplatin 14 mg/kg resulted in a statistically significant reduction in ABR threshold shifts on all frequencies (8 kHz, 16 kHz, 24 kHz, 32 kHz, respectively) 7 days post-injection with fewer synapse loss in the apical turn of the cochlea. However, there were no significant differences in the number of OHCs from the CGP-saline group in any cochlear turn.
Scheller, et al, 2016[10]	Prophylactic nimodipine treatment for cochlear and facial nerve preservation after vestibular schwannoma surgery: a randomized multicenter Phase III trial	No prophylactic vs. Parenteral nimodipine of 1-2 mg/hour + HES 6%	RCT on human samples, 8 days, n=112	Patients in the treatment group had a 2 times lower risk (OR 0.49 [95% CI: 0.18-1.30], *P*=0.15) of their hearing getting worse to Gardner-Robertson Class IV or V after surgery than the control group. However, the result was not statistically significant.
Liu, et al., 2012[9]	Interaction of a calcium channel blocker with noise in cochlear function in guinea pig	Placebo vs. Cochlear perfusion of nifedipine (varying concentration) vs. Noise exposure + cochlear perfusion of nifedipine (varying concentration)	RCT on animal samples, 2 hours of continuous perfusion of placebo or nifedipine, n=80	Statistically significant lower increases in CAP threshold shift from pre-experiment to post-experiment value were observed in noise exposure + nifedipine 0.5 μM (+20±5.3 dB SPL) and noise exposure + nifedipine 3μM group (+21.5±4.7 dB SPL) compared to noise exposure without nifedipine (+43.5±6.3 dB SPL). On the contrary, nifedipine with the same concentrations (0.5 μM and 3 μM) without noise exposure showed a higher increase in CAP threshold shift (+28±3.5 dB SPL, *P*<0.05).
Miller, et al., 2003[8]	Mechanism of electrical stimulation-induced neuroprotection: effects of verapamil on protection of primary auditory afferents	Perilymph vs. Verapamil vs. Perilymph+Electrical stimulation vs. Verapamil+Electrical stimulation	RCT on animal samples, 36 days, number of participants not specified	Both perilymph + electrical stimulation (P/E) and verapamil + electrical stimulation (V/E) groups showed decreases from ABR baseline threshold to 39 days post-implantation (-14.3±21.5μA and -10.9±19.2μA, respectively). However, neither result was statistically significant. Furthermore, greater enhancement of SGC cell count and density was found in the P/E group relative to V/E (19.8±5.8% for density; 13.1±6.7% for count vs. 2.6±11.4% for density; 4.1±10.3% for count, *P*=0.02).

Naples et al.[7] found that a single intratympanic injection of CPG-diltiazem led to a statistically significant lower gain in ABR threshold on all frequencies seven days after the injection of the animal group that had been exposed to ototoxic agent cisplatin 14 mg/kg, with the lowest gain occurring at high frequencies of 24 kHz [7.78 dB SPL (±2.2 dB) *vs.* 28.0 dB SPL (±4.97 dB), *P*=0.006] and 32kHz [10 dB SPL (±3.8 dB) *vs.* 31.9 dB SPL (±4.82 dB), *P*=0.005].

Similarly, utilizing ABR measurements in an animal model, Miller et al.[8] assessed the effects of verapamil combined with chronic electrical stimulation. Over a 36-day period, Miller's study[8] observed decreases in ABR thresholds in the verapamil + electrical stimulation (V/E) group compared to the control groups, with ABR threshold reductions from baseline to 39 days post-implantation of -10.9±19.2μA (*P*=0.92), though the result was statistically insignificant.

In a study by Liu et al.,[9] statistically significant decreases in the threshold shift in the compound action potential from the pre-experiment to the post-experiment value were observed in the noise exposure + nifedipine 0.5μM (+20±5.3 dB SPL) and the noise exposure + nifedipine 3μM (+21.5±4.7 dB SPL) groups, compared to noise exposure without nifedipine (+43.5±6.3 dB SPL), *P*<0.0001].

Human studies reviewed provided mixed outcomes. Scheller et al.[10] used subjective hearing tests to evaluate L-type CCBs efficacy in human subjects undergoing surgery

for vestibular schwannoma. Results of the study indicated a twofold reduction in risk of worsened hearing outcomes, compared to controls (OR 0.49 [95% CI: 0.18-1.30]), though these findings were not statistically significant (P=0.15).

The Role of L-Type CCB on Hearing Cells Survival in SNHL

Three studies reported histological findings in animal models. Naples et al.[7] observed significantly less outer hair cell loss in animals treated with CGP-diltiazem, particularly in the apical regions of the cochlea, compared to untreated controls. Similarly, Liu et al.[9] found that nifedipine reduced hair cell loss in a NIHL model, suggesting a protective effect under conditions of Ca^{2+} overload. In contrast, Miller et al.[8] reported different cellular outcomes, noting that verapamil combined with electrical stimulation did not significantly improve spiral ganglion cell survival and may have even interfered with the protective effects of electrical stimulation.

Risk of Bias

The risk of bias summary was presented in Figure 2. All studies regarding the L-type CCBs on SNHL were at high risk of bias.

Discussion

Sensorineural hearing loss is a complex condition that impairs the auditory system and can be attributed to various factors, including aging, prolonged exposure to noises, and underlying medical conditions that affect the inner ear, such as vestibular schwannoma or associated neural pathways.[11] Understanding the mechanism underlying SNHL better could lead to new avenues for developing targeted interventions capable of addressing the underlying causes of the condition, improving outcomes and the quality of life for those who are impacted.[12]

Calcium channel blockers can act on the existing calcium channels within the inner ear to inhibit calcium influx, thereby eliminating a key factor for apoptosis and preserving essential inner ear structure and function.[7] These pharmacological agents have demonstrated the ability to mitigate intracellular calcium overload across diverse cell types, which can suppress the activation of calcium-dependent enzymes and transcription factors that drive the apoptotic cascade. Specifically, CCBs can block the VGCC that mediate calcium entry and activate the calcium pumps that extrude excess calcium from the cytoplasm.[13]

This class of drugs has been found to be effective in protecting inner ear cells from death in response to various insults, such as acoustic trauma, exposure to ototoxic medication, and other causes of acquired hearing impairment. Moreover, CCBs have also exhibited neuroprotective effects in other regions of the central nervous system, suggesting that this mechanism may be broadly applicable to preventing neurodegenerative conditions.[14]

Current available literature on the potential hearing-preserving effects of L-type CCBs in SNHL presents considerable variability. Differences in drug types, dosages, routes of administration, outcome measures, and underlying causes of SNHL all contribute to a nuanced picture. Despite this variability, both studies in animals by Liu et al.[9] and Naples et al.[7] align with the proposed mechanism by which CCBs mitigate SNHL, suggesting a protective role under conditions of calcium overload, as seen in noise or ototoxic-induced hearing loss.

However, results vary under stable conditions or with additional interventions. Liu et al.[9] also suggest that administering L-type CCBs is otherwise disruptive to the normal cellular calcium-dependent hearing process without noise exposure. Additionally, Miller et al.[8] reported that combining verapamil with electrical stimulation in an ototoxicity-induced SNHL model did not yield protection and even reduced spiral ganglion cell survival compared to stimulation alone, indicating that CCBs might interfere with calcium-driven neuroprotective mechanisms in some contexts.

While these animal studies suggest that CCBs can reduce threshold shifts in noise or ototoxic-induced SNHL models, this protective effect has yet to be consistently observed in clinical contexts. The study in human populations suggests that while L-type CCBs may have theoretical neuroprotective benefits, their effectiveness in clinical settings remains inconclusive. The results also imply that the conditions under which CCBs are beneficial may be highly specific, perhaps effective in contexts of calcium overload (in animal models of noise and ototoxic exposure).

Given the high risk of bias across studies, drawing firm conclusions about the role of L-type CCBs for SNHL in clinical practice remains challenging. Limitations, such as small sample sizes, lack of standardized pre- and post-intervention protocols, and ethical constraints in human research (e.g., the impracticality of exposing human subjects to high noise levels for experimental purposes), further complicate the evidence base. Rigorous, well-designed studies are essential to determine under what specific conditions, if any, these agents might reliably protect auditory function in human populations.

Additionally, it is worth investigating newer generations of CCBs, particularly those within the dihydropyridine class, which are thought to have antioxidant properties beyond calcium channel blocking. This antioxidant mechanism may provide an alternative pathway for safeguarding auditory cells against oxidative stress—a key factor in NIHL—and could lead to more effective hearing-protective therapies.[6]

In conclusion, L-type CCBs may protect against SNHL under specific conditions, calcium overload. However, inconsistencies in findings and high risks of bias across studies make it difficult to draw firm conclusions for clinical application. Rigorous, well-designed research is needed to clarify when CCBs may be beneficial.

Competing Interests

The authors declaresthat there are no competing interests.

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