KBB Uygulamaları 2025;13(2):73-77

Original Article / *Özgün Makale*

OPEN ACCESS

The impact of different local anesthetic methods on pain scores for intratympanic injections

Farklı lokal anestezik yöntemlerinin intratimpanik enjeksiyonlarda ağrı skorları üzerindeki etkisi

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ABSTRACT

Objectives: This study compared the effectiveness of different preparations in reducing pain.

Patients and Methods: The double-blind study was conducted between October 2023 and March 2024. Four different premedications (phenazone, lidocaine, Xylocaine, and physiological saline) were administered to patients to reduce pain. Twenty minutes after each procedure, the patient's pain levels were assessed using the Visual Analog Scale and Categorical Rating Scale-4. Patients were asked to select their preferred method of intratympanic injection at the end of all procedures.

Results: One patient was excluded due to a perforated eardrum. Thirty-eight patients (24 females, 14 males; mean age: 53.1±13.6 years; range, 27 to 76 years) were included in the study. The intratympanic injection of Xylocaine and physiological saline resulted in significantly less pain than lidocaine. Fifteen (39.5%) patients favored Xylocaine, while 14 (36.8%) patients chose physiological saline.

Conclusion: Xylocaine and physiological saline were more effective premedications than lidocaine and phenazone. Xylocaine, due to its deionized structure, was superior to lidocaine but did not provide greater efficacy compared to physiological saline. Further studies are needed to develop new agents, particularly deionized drops.

Keywords: Intratympanic injection, lidocaine, phenazone, Xylocaine.

ÖZ

Amaç: Bu çalışmada, ağrıyı azaltmada farklı preparatların etkinliği karşılaştırıldı.

Hastalar ve Yöntemler: Bu çift kör çalışma Ekim 2023 - Mart 2024 tarihleri arasında yürütüldü. Ağrıyı azaltmak için hastalara dört farklı premedikasyon (fenazon, lidokain, Xylocaine ve serum fizyolojik) uygulandı. Her işlemden 20 dakika sonra hastaların ağrı seviyeleri Görsel Analog Skala ve Kategorik Derecelendirme Ölçeği-4 kullanılarak değerlendirildi. Hastalardan tüm işlemlerin sonunda tercih ettikleri intratimpanik enjeksiyon yöntemini seçmeleri istendi.

Bulgular: Bir hasta kulak zarının delinmesi nedeniyle çalışma dışı bırakıldı. Çalışmaya 38 hasta (24 kadın, 14 erkek; ort. yaş: 53.1±13.6 yıl; dağılım, 27-76 yıl) dahil edildi. Xylocaine ve serum fizyolojiğin intratimpanik enjeksiyonu, lidokainden önemli ölçüde daha az ağrıya neden oldu. On beş (%39.5) hasta Xylocaine tercih ederken, 14 (%36.8) hasta serum fizyolojik seçti.

Sonuç: Ağrıyı azaltmada Xylocaine ve serum fizyolojik, lidokain ve fenazondan daha etkiliydi. Xylocaine deiyonize yapısı nedeniyle, lidokaine göre ağrıyı daha iyi azaltmakla birlikte serum fizyolojiğe göre daha iyi etkinlik sağlamadı. Özellikle deiyonize damlalar olmak üzere yeni ajanlar geliştirmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar sözcükler: İntratimpanik enjeksiyon, lidokain, fenazon, Xylocaine.

The utilization of intratympanic steroid injections has become increasingly prevalent as a primary or adjunctive therapy for sudden idiopathic hearing loss, Ménière's disease, and various inner ear disorders, including tinnitus.[1] The pioneering work by Silverstein et al.[2] in 1996 marked the inception of intratympanic steroid treatment for sudden sensorineural hearing loss, and subsequent studies have corroborated its efficacy.[1,2] This modality is generally well-tolerated by patients, obviates the need

Received: April 15, 2025
Accepted: June 16, 2025
Published online: June 26, 2025

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Doi: 10.5606/kbbu.2025.66933

Citation:
Tüzemen G, Tuna B. The impact of different local anesthetic methods on pain scores for intratympanic injections. KBB Uygulamaları 2025;13(2):73-77. doi: 10.5606/kbbu.2025.66933.

for hospitalization, and can be employed as a primary, adjunctive, or salvage therapy in an outpatient setting. Furthermore, it offers a cost-effective alternative to systemic steroid administration.[3] However, drawbacks encompass injection-related pain, potential hearing deterioration, tympanic membrane perforation, otitis media, and vertigo in comparison to systemic steroid therapy.[1] Intratympanic steroid administration may be performed via direct injection without anesthesia or with the aid of local anesthetics such as lidocaine spray, lidocaine injection, topical phenol, pantocaine, or an analgesic cream (contains 25 mg lidocaine and 25 mg prilocaine in 1 g of cream).[4]

Upon review of the clinical trials, it has been recommended to incorporate a combination of topical drugs serving as a local analgesic and anti-inflammatory treatment with effective action and good tolerability for all age groups in the combined therapy of acute preperforative otitis media. The commonly utilized ear drops contain the nonopioid analgesic antipyretic drug phenazone and lidocaine. Phenazone, a nonsteroidal anti-inflammatory drug, exhibits an anti-inflammatory effect typical for nonselective cyclooxygenase inhibitors, while lidocaine manifests a local analgesic effect.[5]

Drugs containing phenazone and lidocaine have not been used so far due to the indication of minimizing the pain that occurs during intratympanic injection. We used phenazone, lidocaine, and Xylocaine (AstraZeneca, Cambridge, UK) to reduce pain; additionally, physiological saline was used to examine the placebo effect. This study aimed to compare the effectiveness and superiority of these four preparations to reduce pain.

PATIENTS AND METHODS

This double blind study encompassed patients who presented with sudden hearing loss or tinnitus to the Ministry of Health, Bursa City Hospital between October 2023 and March 2024. Sudden hearing loss and tinnitus were characterized by sensorineural impairment developing over a period of three days or less. Additionally, individuals experiencing refractory idiopathic tinnitus persisting for at least four weeks and showing no response to oral medical intervention were administered intratympanic steroid injections. Exclusion criteria encompassed patients who recently used painkillers or oral steroids and those who underwent ear surgery, suffered from chronic otitis media, exhibited Eustachian tube dysfunction, diagnosed with retrocochlear pathology, or received combined intratympanic and systemic steroid treatment for sudden idiopathic hearing loss. Patients who required more than four intratympanic injections were excluded from the study due to the investigation of four local anesthetic agents. Written informed consent was obtained from the participants. The study protocol was approved by the Ministry of Health, Turkish Medicines and Medical Devices Agency, Observational Studies Ethics Committee (Date: 23.08.2023, No: 22-AKD-130). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient assessment included a comprehensive medical history review, otoscopic examination, audiological testing, and magnetic resonance imaging to preclude the presence of a retrocochlear lesion. Pain, a subjective outcome influenced by numerous variables, was evaluated through self-reporting and deemed the most reliable approach to pain measurement.[6] Therefore, pain was evaluated with the Visual Analog Scale (VAS) and Categorical Rating Scale (CRS)-4.

Injections were administered in the outpatient department of otolaryngology by an experienced otorhinolaryngology surgeon. Before intratympanic injection, local anesthetic premedication was administered in a double-blind manner with agents prepared in numbered dropper bottles labeled 1 to 4. Both the agent we used for intratympanic injection and the topical drops were warmed in the palm of the hand for at least 5 min to approximate body temperature. The patient was instructed to assume a supine position, with the head turned at a 45° angle towards the unaffected ear. Five drops of these agents were instilled into the external auditory canal before each intratympanic injection in numerical order. These agents were as follows: lidocaine, Xylocaine, phenazone, and physiological saline. Lidocaine droppers contained 10 mg/mL lidocaine hydrochloride (Jetokain Simplex; Adeka İlaç ve Kimyasal Ürünler San. ve Tic. A.Ş., İstanbul, Türkiye). The Xylocaine spray contained 10% lidocaine in a dropper bottle. Phenazone droppers contained 11.38 mg/mL lidocaine hydrochloride + 45.52/mg/mL phenazone (PASSEAR; World Medicine, İstanbul, Türkiye). Physiological saline droppers contained 0.9% sodium chloride (Biofleks; Osel İlaç San. ve Tic. A.Ş., İstanbul, Türkiye) to demonstrate the placebo effect.

Ten minutes after instilling the drops, they were aspirated from the external ear canal using a microscope to prevent them from entering the middle ear during the intratympanic injection. Following the procedure, patients underwent intratympanic

administration of 0.5 mL of dexamethasone at a concentration of 4 mg/mL. Patients received a total of four injections twice a week (three to four days apart) over two weeks.[7] Dexamethasone was administered via intratympanic injection into the inferoposterior quadrant of the tympanic membrane using a 27-gauge Whitacre needle. Following the injection, patients were advised to maintain the same position for 20 min to facilitate maximal absorption of the medication through the round window. Patients were instructed to refrain from swallowing to prevent drug leakage through the Eustachian tube. Subsequently, patients were requested to report any perception of vertigo following each injection. Twenty minutes after each procedure, pain levels in patients were evaluated using the VAS and CRS-4. In addition, at the end of the fourth injection, patients were asked to choose their preferred method of intratympanic injection.

Statistical analysis

Data analysis was conducted using IBM SPSS version 29.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages, while numerical variables were presented as means ± standard deviations (SD). The Shapiro-Wilk test assessed normal distribution, and the Friedman and Wilcoxon tests compared pre- and postoperative data. A p-value <0.05 was considered statistically significant.

RESULTS

One patient's eardrum perforated after an injection due to an atrophic eardrum. This patient was excluded from this study. During the follow-up, it was observed that the eardrum perforation regressed spontaneously. Thus, the final analyses were conducted with 38 patients (24 females, 14 males; mean age: 53.1±13.6 years; range, 27 to 76 years).

Upon evaluating the CRS-4 and VAS scores of the patients, it was observed that the intratympanic injection following the application of Xylocaine and physiological saline resulted in significantly less pain than lidocaine (Tables 1, 2). Furthermore, when queried about their preference, 15 (39.5%) patients favored Xylocaine, while 14 (36.8%) patients chose physiological saline.

There were no instances of hemorrhage in the external auditory canal resulting from the injection, and no patients required pain relief medication following the intratympanic injection. Two patients experienced mild, transient vertigo; however, none reported hearing loss or infection.

Table 1
Means of the pain intensities of the two scales

	Lidocaine	Xylocaine	Phenazone	Physiological saline
Measures	Mean±SD	Mean±SD	Mean±SD	Mean±SD
VAS	4.71±2.6	3.03±2.5	3.58±2.9	3.13±2.5
CRS-4	2.82±0.8	2.34±0.9	2.42±1.0	2.32±0.9

SD: Standard deviation; VAS: Visual Analog Scale; CRS-4: Categorical rating scale-4.

Table 2
Comparison of pain scores between VAS and CRS-4 using the Wilcoxon signed-rank test

Pain score	CRS-4 (p)	VAS (p)
Lidocaine > Xylocaine	0.004	<0.001
Lidocaine > phenazone	0.044	0.012
Lidocaine > physiological saline	0.004	<0.001
Phenazone > Xylocaine	0.532	0.187
Physiological saline > Xylocaine (VAS) Physiological saline < Xylocaine (CRS-4)	0.955	0.724
Phenazone > physiological saline	0.425	0.093

VAS: Visual Analog Scale; CRS-4: Categorical rating scale.

DISCUSSION

The intratympanic injection is a treatment method utilized for various inner-ear conditions, including sudden idiopathic hearing loss, tinnitus, and Ménière's disease. There has been a noticeable increase in the use of intratympanic injections for other indications in recent years.[8] Patients may experience earache, caloric vertigo, dizziness, tympanic membrane perforation, hearing loss, or infection due to intratympanic injections. It is possible to prevent caloric vertigo and dizziness by adjusting the temperature of steroids to body temperature prior to injection. Permanent tympanic membrane perforation, infection, and hearing loss are rare. Pain can be alleviated by using thin needles.[9] Using the product at body temperature may offer additional benefits over cooled or room-temperature products. Therefore, it would be prudent for future trials to employ the investigational product at a standardized temperature to eliminate this potential data confounder.[10] We administered drops in the external auditory canal and used dexamethasone in the intratympanic injection after adjusting the patient's body temperature. This approach resulted in limiting the development of vertigo to only two patients.

Lidocaine hydrochloride is a commonly used local anesthetic that takes effect quickly (peaking in 2 to 5 min) and lasts for 30 to 45 min.[11] However, due to its low lipid solubility, it is not easily absorbed through the intact eardrum.[12] Interestingly, studies have shown that in other conditions, such as napkin rash[11] and under occlusive dressings,[13] the drug is more readily absorbed by altered skin, which could explain why it is more effective when the eardrum is inflamed.[14] Bonain's solution consists of equal amounts of cocaine hydrochloride, menthol, and phenol. Phenol causes epithelial maceration of the tympanic membrane, which allows cocaine to have an analgesic effect.[15] Belhassen and Saliba[4] reported that intratympanic injection without local anesthesia was well tolerated by patients, similar to injections performed with an analgesic cream (contains 25 mg lidocaine and 25 mg prilocaine in 1 g of cream) or a lidocaine injection. A recent study found no significant difference in mean VAS scores at 5 min between patients who received intratympanic steroid injections without anesthesia and those who received lidocaine spray anesthesia.[16] Møller and Grøntved[17] conducted a study comparing the effectiveness of Xylocaine, lidocaine 4%, and lidocaine hydrochloride 5% against a placebo for minor therapeutic procedures on the tympanic membrane. They found that lidocaine hydrochloride showed no effect, while the effectiveness of the other two drugs appeared to depend on their ionization. The un-ionized drugs, lidocaine and Xylocaine, were effective, while the ionized lidocaine hydrochloride was ineffective. Their study demonstrated that Xylocaine 10 ($p=0.008$) and lidocaine 4% ($p=0.05$) were superior to the placebo and 5% lidocaine hydrochloride.

Local analgesic drops containing nonsteroidal anti-inflammatory drugs have been used to treat acute otitis media and external otitis. The drops are expected to be highly effective in both cases because the epithelium is macerated. A study by Adam et al.[18] reported that the active constituents procaine and phenazone, as well as the excipients, have documented safety profiles. The study demonstrated the drops' effectiveness in treating acute otitis media and external otitis; no side effects were reported. It is worth noting that the study did not use a placebo.[18] Hoberman et al.[19] used an agent containing phenazone, benzocaine, and glycerol and found that it provided additional pain relief to children with acute otitis media when administered alongside acetaminophen, with varying degrees of effectiveness within 30 min of drug administration. In this study, it was observed that there was no significant difference between the effectiveness of their agent and olive oil in treating acute otitis media in children.[19] François[20] conducted an evaluation of the efficacy and safety of ear drops containing phenazone and lidocaine hydrochloride for the treatment of congestive myringitis in a cohort of 18 infants and children aged 1 to 10 years. Their findings indicated the absence of adverse effects, leading to the conclusion that ear drops containing phenazone and lidocaine hydrochloride is an effective and safe treatment for painful congestive myringitis in infants and children.[20] Bolt et al.[14] conducted a double-blind, placebo-controlled study on pediatric patients with acute otitis media, comparing physiological saline and 2% lidocaine. They observed a significant reduction in pain among the patients who received lidocaine.[14]

The present study showed the effectiveness of Xylocaine and physiological saline as premedications rather than lidocaine and phenazone. A meta-analysis showed that giving a knee osteoarthritis patient an injection of normal saline (a placebo) can lead to a significant improvement in their reported condition after six months.[21] In our study, we found that the saline solution demonstrated efficacy similar to that of Xylocaine. We believe that the analgesic effect of the saline solution may be attributed to the maceration it can cause in the tympanic membrane.

However, further histopathological studies are needed to support this hypothesis.

In conclusion, we found that drops containing phenazone and lidocaine were ineffective compared to other premedications for patients with normal external ear canal and membrane structure. Xylocaine's deionized structure proved superior to lidocaine hydrochloride. However, it did not show superiority over physiological saline, indicating the need for further studies and the development of new agents, particularly in deionized drops.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Performed otolaryngological examination: G.T., B.T.; Wrote the first draft of the manuscript, and all authors commented on previous versions: G.T. All authors contributed to the study's conception and design. All authors read and approved the final manuscript.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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