e-ISSN:2602-2079

Volume 9
Issue 8
2025

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

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Vol. 9 No. 8 (2025)

Published: 2025-08-29

Research Article

Hakan Yalım, Sidika Deniz Yalim, Aysenur Boztepe
132-134

Review

Effects of non-pharmacological approaches on anxiety, agitation and physiologic parameters in weaning from mechanical ventilation: A systematic review

Non-pharmacological approaches on weaning from MV

Kübra Şengör, İkbal Çavdar, Eda Polat
135-142

Case Report

The salvage of nipple-areola complex using dimethyl sulfoxide

Salvage of NAC by DMSO

Alper Ural, Harun Karaduman, Hala Halbony
143-145

Idiopathic (benign) intracranial hypertension-induced sudden hearing loss: A rare case

Idiopathic intracranial hypertension-induced sudden hearing loss

Meltem Akpınar, Elifnur Karatepe
146-148

J Surg Med. 2025;9(8):113-117.
https://doi.org/10.28982/josam.8204

JOSAM

Research article
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Is an intralesional approach a sufficient treatment for solid variant aneurysmal bone cysts in long bones? A case series

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Abstract

Background/Aim: The solid variant of aneurysmal bone cysts (SVABC) is a rare subtype, representing 3.4–7.5% of all aneurysmal bone cysts, which themselves account for 1.4% of benign skeletal tumors. This study evaluates the outcomes of four patients with SVABC in long bones (three femurs, one humerus), a condition rarely reported in the literature.

Methods: We conducted a retrospective case series analysis of patients who were definitively diagnosed with SVABC through histopathological examination following surgical intervention at our clinic. Inclusion criteria consisted of patients with radiologically identified bone lesions suspected to be SVABC and confirmed by postoperative pathology. Diagnostic workup included detailed imaging with MRI and CT to evaluate lesion morphology, vascularity, and cortical integrity. Surgical treatment involved intralesional curettage, structural allograft bone grafting, and internal osteofixation. Postoperative follow-up included regular clinical examinations and radiographic assessments at 1, 3, 6, and 12 months to monitor healing, detect recurrence, and evaluate functional recovery.

Results: Four patients met the inclusion criteria and underwent surgical management as described. All patients achieved radiological union and demonstrated significant functional improvement, with return to full weight-bearing and daily activity within six months. No postoperative complications, such as infection or hardware failure, were observed. Imaging at one-year follow-up showed no evidence of local recurrence or graft resorption. Functional assessments indicated full range of motion and absence of pain in all cases.

Conclusion: SVABC is a rare benign bone tumor that often mimics other aggressive lesions both radiologically and histologically. Despite its nonaggressive appearance, it requires accurate diagnosis and appropriate surgical management to prevent recurrence. Our findings suggest that thorough preoperative imaging, histopathological confirmation, and a combination of curettage with grafting and fixation can result in excellent clinical and radiological outcomes. SVABC should be considered in the differential diagnosis of solid-appearing bone lesions, particularly those with osteoblastic activity and giant cell–rich histology.

Keywords: aneurysmal bone cyst, solid variant of an aneurysmal bone cyst, long bone, allograft

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Ethics Committee Approval
The study was approved by the Non-Interventional Research Ethics Committee of Fırat University (approval number: 21.03.2025-33231). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2025 August 7

How to cite: Agar A, Key S. Is an intralesional approach a sufficient treatment for solid variant aneurysmal bone cysts in long bones? A case series. J Surg Med. 2025;9(8):113-117.

Introduction

Aneurysmal bone cysts (ABCs), first described by Jaffe and Lichtenstein in 1942, account for approximately 1.4% of benign skeletal tumors [1]. These rapidly growing, multicystic osteolytic lesions typically affect vertebrae, long bones, or flat bones [1,2]. The solid variant of ABC (SVABC) is even rarer, representing 3.4–7.5% of all ABCs, and often presents in the second decade of life [3,4].

Although benign, ABCs exhibit locally aggressive behavior in 20% of cases and are associated with clonal chromosomal abnormalities, such as the t(16;17) translocation, which activates the TRE17/USP6 oncogene in up to 69% of cases [5]. Their expansive growth can disrupt growth plates and cause pain, swelling, deformities, and pathologic fractures; depending on location, they may also lead to neurologic symptoms [4].

First described by Sanerkin et al. [6] in 1983, SVABC is often misdiagnosed as spindle cell tumors, particularly osteosarcoma, due to overlapping radiographic and histologic features [3,6]. While the pathophysiology of ABCs remains unclear, they are generally considered nonneoplastic reactive lesions linked to intraosseous vascular malformations, trauma, or other bone tumors [1,2,7].

Histologically, ABCs are characterized by blood-filled cystic cavities, osteoclastic giant cells, and fibromyxoid stroma. Radiographically, computed tomography (CT) and magnetic resonance imaging (MRI) reveal expansive osteolytic lesions with fluid-fluid levels, though SVABCs exhibit a more solid pattern with uniform contrast uptake, often resembling giant cell tumors or osteosarcomas [7,8]. Consequently, histopathological analysis remains the gold standard for diagnosis.

SVABCs present a diagnostic challenge due to their variable radiographic and histologic features, including spindle cell proliferation, osteoid formation, and scattered multinucleated giant cells [7]. While symptomatic ABCs are typically treated surgically, asymptomatic cases with minimal bone loss are often monitored [9]. This case series evaluates the outcomes of four patients (three femurs, one humerus) with SVABC in long bones, a condition rarely reported in the literature.

Materials and methods

This retrospective study was approved by the Non-Interventional Research Ethics Committee of Fırat University (approval number: 21.03.2025-33231). The study included patients treated at a tertiary university hospital between January 2020 and January 2024 who were diagnosed with SVABC in the long bones of the extremities.

Case selection

Patients were identified through a comprehensive search of the hospital's pathology database. Inclusion criteria were: (1) histopathologically confirmed diagnosis of SVABC, (2) lesion located in a long bone of the extremities, (3) availability of complete imaging studies including both plain radiography and MRI, and (4) treatment with intralesional curettage, allograft implantation, and osteofixation. Patients with incomplete clinical or imaging data, alternative diagnoses, or less than 11 months of follow-up were excluded. Four patients met these criteria and were included in the study.

Imaging evaluation

All patients underwent preoperative imaging that included standard anteroposterior and lateral radiographs and MRI. Imaging assessments evaluated lesion location (metaphyseal, diaphyseal, or epiphyseal), size (measured in three dimensions), and morphological characteristics such as cystic versus solid content, cortical thinning or breach, and associated soft tissue extension. MRI was also used to detect perilesional edema, fluid-fluid levels, internal hemorrhage, and enhancement patterns. Imaging findings were systematically documented and later correlated with histopathological results to enhance diagnostic accuracy.

Histopathological evaluation

Histological confirmation was essential for inclusion. Formalin-fixed, paraffin-embedded tissue samples were stained with hematoxylin and eosin and re-examined by experienced musculoskeletal pathologists. Diagnostic criteria for SVABC included: proliferation of spindle-shaped stromal cells, scattered multinucleated giant cells, hemorrhagic foci, hemosiderin deposition, fibrocollagenous matrix, and reactive osteoid formation. Absence of significant mitotic activity or cellular atypia helped distinguish SVABC from other giant cell–rich or fibro-osseous lesions. Imaging-pathology correlation was performed to reinforce diagnostic reliability.

Surgical technique

All patients underwent surgery under general anesthesia using a standardized three-step procedure:

1. Intralesional Curettage: A cortical window was created to access the lesion. Thorough curettage was performed using curettes and high-speed burrs to remove all gross tumor tissue.
2. Cavity Filling with Allograft: The resulting bone cavity was packed with structural cancellous allograft material to restore bone integrity and promote osteoconduction.
3. Osteofixation: Internal fixation was performed using titanium elastic nails or plate-screw systems based on the anatomical location and size of the defect. This step ensured mechanical stability and minimized fracture risk.

Postoperative follow-up

Patients were followed clinically and radiographically at regular intervals (1, 3, 6, and 12 months postoperatively). Clinical assessments focused on pain, joint mobility, weight-bearing capacity, and return to function. Radiographs were used to evaluate graft incorporation and bone healing and to detect any signs of recurrence. In selected cases, MRI was repeated at one year to confirm the absence of residual or recurrent lesion. Follow-up duration ranged from 11 to 14 months.

Results

This study evaluated four patients (three males and one female) with an average age of 9 years (range: 7–13 years) diagnosed with SVABC in long bones. Three patients were referred due to pathologic fractures, while one presented with shoulder pain and swelling. None had significant medical histories or systemic symptoms like fever or weight loss. Physical and systemic examinations revealed no additional abnormalities.

All patients underwent radiological evaluations, including direct radiographs and MRI (Table 1).

The patient in the first case had a 12-cm lytic lesion in the proximal humerus, showing cystic and solid areas with surrounding edema. Surgical treatment involved curettage, allograft filling, and stabilization with a titanium elastic nail. Histopathology confirmed a mesenchymal tumor with multinuclear giant cells and no mitotic activity. No recurrence was observed at the 11-month follow-up (Figure 1).

The second case had a lytic lesion in the distal femur showing cystic content, hemorrhage, and edema. The patient underwent curettage, allograft filling, and plate screw fixation. Histopathology revealed multinuclear giant cells and stromal cells. No complications or recurrence were noted at the 12-month follow-up (Figure 2).

The third patient had a cystic lesion in the distal femur with hemorrhage and edema. Preoperative biopsy suggested ABCs. Treatment included curettage, allograft filling, and plate screw fixation. Histopathology showed necrotic tissue, osteoclastic giant cells, and new bone formation. No recurrence had occurred by the 14-month follow-up (Figure 3).

The patient in the fourth case had a lytic lesion in the distal femur with cortical thinning, along with fracture. Biopsy confirmed multinuclear giant cells and stromal cells. Treatment involved curettage, allograft filling, and plate screw fixation. No complications or recurrence were reported at the 11-month follow-up (Figure 4).

In all cases, histopathology revealed multinuclear giant cells and stromal cells without mitotic activity. Surgical treatment was successful, with no recurrence or complications during follow-up periods ranging from 11 to 14 months (Table 1).

Figure 1: a: Radiography shows an enlarging lytic lesion with cortical lesions, b: MRI scan shows a tumor with fluid content, c: Intraoperative image shows a solid mass, d: Radiographic imaging in the 1st year of postoperative follow-up

Figure 2: a: Radiograph shows an enlarging lytic lesion with cortical lesions and pathological fracture (white arrow), b, c: MRI scan shows a tumor with fluid content (white arrow), d: Radiographic imaging in the 1st year of postoperative follow-up

Figure 3: a: Radiograph shows an enlarging lytic lesion with cortical lesions and pathological fracture (black arrow), b, c: MRI scan showing a fluid-containing tumor and pathological fracture (black arrow), d: Radiographic imaging in the 1st year of postoperative follow-up

Table 1: Summaries of general data of patients included in the study (age, gender, location, size, treatment, follow-up)

Case	Age/Sex	Location	Presentation	Radiologic Findings	Macroscopic view	Histopathology	Treatment	Follow-Up
1	9/M	Proximal humerus	Pain and swelling in the shoulder	Expansile lytic lesion (120 × 25 mm), cystic and solid areas, cortical thinning	4 × 4 × 3 cm, cream-brown, hard bone consistency, hemorrhagic areas	Mesenchymal tumor with multinuclear giant cells, no mitotic figures	Curettage, allograft filling, titanium elastic nail stabilization	No recurrence at 11 month
2	7/F	Distal femur	Pathologic fracture	Lytic lesion, cystic content, hemorrhage, edema, cortical loss	6.6 × 5.5 × 2.4 cm, brown hemorrhagic lesion, off-white hard areas	Multinuclear giant cells, stromal cells, no mitotic figures	Curettage, allograft filling, plate screw fixation	No recurrence at 12 month
3	13/M	Distal femur	Pathologic fracture	Expansile lytic lesion (74 × 40 mm), hemorrhage, edema, cystic content	6.2 × 4.9 × 2 cm, off-white to light brown, soft, irregular tissue with bleeding areas	Necrotic tissue, osteoclastic giant cells, new bone formation	Curettage, allograft filling, plate screw fixation	No recurrence at 14 month
4	7/M	Distal femur	Pathologic fracture	Lytic lesion, cortical thinning, cystic and nodular solid areas	5 × 4 × 3 cm, cream-brown, hard bone-like tissue	Multinuclear giant cells, stromal cells, no mitotic figures	Curettage, allograft filling, plate screw fixation	No recurrence at 11 month

Figure 4: a: Expanding lytic lesion with cortical lesions and pathological fracture on radiography, cortical destruction (white arrow), b, c: Tumor extension with fluid-containing tumor and pathological fracture on MRI scan (white arrow), d: Complete union and no recurrence on radiographic imaging in the 1st year of postoperative follow-up

Discussion

The craniofacial region and the small tubular bones of the hands and feet are the main locations for SVABC [1,6,10-12]. Sanerkin et al. [6] reported four instances of noncystic bone lesions— one cranial bone and three vertebrae—that histologically resembled solid regions of conventional ABCs were documented by.

Referring to these lesions as "solid ABCs," the authors of that study also proposed a tight histologic link between the condition and giant cell reparative granuloma, which typically affects the small tubular bones in the hands and feet as well as the jaw bones. Currently, it is believed that these lesions stem from similar, nonneoplastic reactive processes [10-12]. Because they can be mistaken for giant cell tumors, brown tumors of hyperparathyroidism, and osteosarcoma—all of which are frequently fibroblastic or low-grade subtypes—these reactive, nonneoplastic lesions have been a challenge for pathologists and treating surgeons [3].

It is uncommon for SVABC to occur in long bones. An uncommon instance of the disease manifesting as a giant cell reparative granuloma in the tibia's subperiosteal region was documented by Kenan et al. [13]. In 1994, Karabela-Bouropoulou et al. [14] reported a rare instance of solid ABC that included both femurs. In a 40-year retrospective review, Ilaslan et al. [7] documented 30 cases of SVABC in long bones. The most common location in these studies was the femur, which occurred in 10 cases; the ulna, tibia, humerus, fibula, and radius were implicated in 7, 7, 2, 2 and 2 cases, respectively. Consistent with the literature, in the present study, three of the four patients had lesions in the femur and one in the humerus.

The metaphysis and metadiaphysis are frequently affected in SVABC. Ilaslan et al. [7] reported juxta-articular involvement in only five cases. Men and women are almost equally affected, and the lesion is most common in the second and fifth decades of life. Yamamoto et al. [15] reported the oldest case, which affected the humerus of a 69-year-old woman, while Ilaslan et al. [7] reported the youngest, occurring in a 2-year-old patient.

Although three of the four patients in the present study presented with pathologic fractures, pathologic fractures from SVABC are not common in the literature [7]. The reason for this may be that this pathology is more common in skull bones and vertebrae than in long bones. While most of the SVABCs described in the literature are red to brown in color, fragile, soft, and have largely blood-filled cavities [16], Yamamoto et al. [15] reported a bronze to white color and hard tissues without cystic cavities. In the present study, the macroscopic images of the cases showed cream- to brown-colored hard tissue with foci of hemorrhage.

In the microscopic images of cases in the literature, tissues have been found to consist of fibroblasts, histiocytes, and numerous osteoclastic multinucleated giant cells on a collagenous ground with lymphocyte and plasma cell infiltration. Mitotic figures have been observed in places, but most studies have reported stromal cells devoid of nuclear atypia, absent aneurysmal sinuses, irregularly shaped woven bone, and osteoid deposition in the extracellular matrix in large areas, as well as some fibromyxoid areas [3,13,14,17-20].

In the present study, sections of biopsy specimens showed fibroadipose and muscular tissues as well as almost necrotic tissue fragments with numerous osteoclastic giant cells and hemosiderin accumulation scattered in a loose swirling stroma composed of spindle cells. In between, areas of new bone

formation surrounded by activated osteoblasts were found. The sections showed a mesenchymal tumor with well-circumscribed, fibrocollagenized stroma. The tumor was composed of homogeneously distributed multinuclear giant cells and stromal cells without mitotic figures, similar in appearance to giant cell nuclei. Also, two of the four patients had osteosarcoma in differential diagnoses during histopathological examinations.

SVABC of long bones has an excellent prognosis. Following surgery, our patients' pathologic fractures healed. Following bone unions, marginal sclerosis occurred. We did not find any recurrence in the follow-up data. However, SVABC in the short tubular bones of the hands and feet has been found to have local recurrence rates of 33–50% [21,22].

Although radiological imaging and histopathological diagnosis of SVABC cases present various difficulties, long bone involvement is especially rare. As a treatment option for long bone involvement, aggressive curettage followed by allograft application and internal fixation were found to yield good results in terms of union and absence of recurrence. We therefore recommend the use of curettage followed by allograft application and internal fixation as a treatment option, especially for long bone SVABC presenting with pathological fractures.

The most important limitation of this study is its retrospective nature. The other limitations of our study include the limited number of cases and the lack of a homogeneous age distribution. While SVABC cases are rare, especially in the long bones, comprehensive studies of the management of SVABC should be conducted. In this way, a consensus on treatment can be reached and supported by long-term results.

Conclusion

SVABC is an uncommon form of benign ABC that often has a nonaggressive radiographic appearance. However, diagnostic challenges are exacerbated by perplexing imaging findings, such as intact internal architecture and significant contrast enhancement in MRI. SVABC also shares several histologic characteristics with other solid bone cancers. When a solid-appearing tumor with osteoblastic activity, fibroblastic proliferation, and the presence of giant cell tumor-like areas is observed on a bone tumor, it should be considered a differential diagnosis in histopathology because SVABC is frequently missed radiologically.

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J Surg Med. 2025;9(8):118-122.
https://doi.org/10.28982/josam.8201

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Research article
https://jsurgmed.com/

Comparison of multiparametric prostate MR imaging and Ga-68 PSMA PET-CT imaging in prostate cancer staging

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Ethics Committee Approval
The study was approved by the Health Sciences University Gulhane Scientific Research Ethics Committee on February 25, 2020 with the decision number 2020-87.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2025 August 8

Abstract

Background/Aim: Staging in prostate cancer is essential for determining the right treatment approach and its execution. This study assessed the staging effectiveness of multiparametric prostate magnetic resonance imaging (MpMRI) compared to prostate-specific membrane antigen (PSMA) positron emission tomography – computed tomography (PET-CT) and examined the preoperative information that they provide.
Methods: We collected data from patients diagnosed with prostate cancer who visited our clinic between June 2020 and November 2022. The results from MpMRI performed prior to biopsy were compared to those from PSMA PET-CT conducted after diagnosis, alongside the outcomes of pathological evaluations.
Results: There was no significant correlation between MpMRI and PSMA PET-CT findings and the final pathology results regarding extraprostatic extension. However, both imaging techniques showed a significant correlation with the final pathology in evaluating pelvic lymph-node metastasis and seminal vesicle invasion. In terms of lesion localization, no significant correlation was found between the final site of the pathological lesion and MpMRI, while a significant correlation was noted with PSMA PET-CT. Patients with positive surgical margins had significantly elevated serum PSA levels, size of the index lesion identified in MpMRI, and maximum standardized uptake values (SUV max) of PSMA.
Conclusion: Although both imaging methods offer important staging insights, further research is needed to clarify their respective limitations and benefits. In the future, these techniques may have additional roles in predicting surgical margin positivity before surgery.

Keywords: MRI, prostate cancer, PSMA, staging, surgical margin

How to cite: Sicimli C, Bedir S, Çınar A, Arda KN. Comparison of multiparametric prostate MR imaging and Ga-68 PSMA PET-CT imaging in prostate cancer staging. J Surg Med. 2025;9(8):118-122.

Introduction

A diagnosis of prostate cancer is confirmed by histopathological examination, which typically is performed after clinical suspicion arises based on the findings of a digital rectal examination and elevated serum levels of prostate-specific antigen (PSA). Imaging modalities alone are currently insufficient for definitive diagnosis, and confirmation requires biopsy and histology [1]. However, imaging plays a crucial role in guiding biopsies and staging the disease prior to treatment [2].

A wide range of imaging techniques are employed for staging purposes in prostate cancer. These include bone scintigraphy, multiparametric prostate magnetic resonance imaging (MpMRI), Ga-68 prostate-specific membrane antigen positron emission tomography/computed tomography (Ga-68 PSMA PET-CT), conventional CT, fluoride PET, and choline PET [3]. Among these, MpMRI and Ga-68 PSMA PET-CT have gained prominence due to their high-resolution anatomical and molecular imaging capabilities, respectively. The aim of this study was to evaluate the staging performance of MpMRI and Ga-68 PSMA PET-CT in assessing lymph-node involvement, tumor localization, extraprostatic extension, and seminal vesicle invasion. Additionally, the study compared the preoperative information that each modality provides to assess their potential clinical utility.

Materials and methods

Approval was obtained from the Ethics Committee of Health Sciences University Gülhane (February 25, 2020, decision number 2020/87). The study included patients diagnosed with prostate cancer at our urology clinic between June 2020 and November 2022. The inclusion criteria consisted of elevated PSA levels, suspicious findings from digital rectal examinations, and a confirmed histopathological diagnosis of prostate cancer. All patients underwent radical prostatectomy.

MpMRI was performed before the biopsy for staging, and Ga-68 PSMA PET-CT was conducted after the diagnosis. We recorded demographic information, serum levels of PSA, and biopsy results. Additionally, we compared data on lesion localization, extraprostatic spread, lymph node metastasis, and seminal vesicle invasion from imaging with the final pathology findings.

Imaging protocols

MpMRI was carried out on a 3-Tesla MRI machine with intravenous gadolinium contrast. The reporting followed the PIRADS v2.1 scoring system. Key parameters were documented, such as extraprostatic spread, seminal vesicle invasion, bladder neck invasion, lymph node involvement, and lesion size and location. Ga-68 PSMA PET-CT imaging took place 55–60 minutes after intravenous administration of 0.06 mCi/kg Ga-68 radiopharmaceutical. The scans covered the area from the vertex down to the mid-thigh.

Pathological examination

Radical prostatectomy specimens were analyzed for ISUP grade, tumor percentage, extraprostatic spread, lesion size and location, seminal vesicle invasion, lymph-node metastasis, and findings related to surgical margins.

Statistical analysis

Descriptive statistics were computed, and the distribution of variables was evaluated using the Kolmogorov–Smirnov test. An independent-sample *t*-test, Mann–Whitney U test, chi-squared test, and Fisher's exact test were applied as needed. Correlation analyses were conducted using the kappa test. All statistical analyses were performed using SPSS 28.0.

Table 1: Demographic data, clinical and pathological characteristics of patients

		Min-Max			Median	Mean±SD/n-%		
Age		46.0	-	75.0	65.0	63.9	±	6.6
Operation								
Robotic						37		68.5%
Open						16		29.6%
Laparoscopy						1		1.9%
PSA (ng/mL)		2.1	-	89.5	12.1	18.5	±	16.4
Prostate Volume (cc)		13.0	-	108.0	35.0	41.6	±	21.5
Biopsy ISUP Grade	**I**					7		13.0%
	II					21		38.9%
	III					10		18.5%
	IV					11		20.4%
	V					5		9.3%
Biopsy Tumor Side								
Left						15		27.8%
Right						8		14.8%
Bilateral						31		57.4%
Final Pathology ISUP Grade	**I**					4		7.4%
	II					18		33.3%
	III					10		18.5%
	IV					14		25.9%
	V					8		14.8%
Final Pathology Tumor Side								
Left						10		18.5%
Right						6		11.1%
Bilateral						38		70.4%
Final Pathology Tumor Percentage		1.3	-	85.0	20.0	24.6	±	18.6
Final Pathology Extra Prostatic Extension	Yes					27		50.0%
	No					27		50.0%
Final Pathology Seminal Vesicle Invasion								
Yes						12		22.2%
No						42		77.8%
Final Pathology Right Pelvic Lymph Node Metastasis	Yes					4		7.4%
	No					50		92.6%
Final Pathology Left Pelvic Lymph Node Metastasis	Yes					1		1.9%
	No					53		98.1%

Min: Minimum, Max: Maximum, SD: Standard Deviation

Results

A total of 54 patients in the study, and the mean age was 63.9 ± 6.6 years. The average preoperative PSA level was 18.5 ± 16.4 ng/mL. The majority of patients underwent robotic radical prostatectomy (68.5%), followed by an open procedure (29.6%). Demographic, clinical, and pathological characteristics are detailed in Table 1.

The mean index lesion size in MpMRI was 15.5 ± 10.1 mm. PIRADS 4 and 5 lesions comprised the majority (83.3%), and lesions were most commonly bilateral (27.8%). MRI indicated extraprostatic spread in 14.8%, seminal vesicle invasion in 11%, and perivesical/perirectal invasion in 13% of the participants. PET-CT revealed similar findings, with extraprostatic spread in 18.5%, seminal vesicle invasion in 9.3%, and perivesical/perirectal invasion in 11.1% of the participants. Lymph-node involvement was observed on the right (16.7%) and left (14.8%). The mean maximum standardized uptake value (SUV max) in Ga-68 PSMA PET-CT was 10.9 ± 9.4. The PSMA uptake was bilateral in 40.7% and absent in 13% of patients.

Correlation analyses

Extraprostatic spread: No significant correlation was found between the final pathology and MpMRI (κ=0.074, *P*=0.444) or PSMA PET-CT (κ=–0.074, *P*=0.484).

Seminal vesicle invasion: MpMRI (κ=0.348, *P*=0.005) and PSMA PET-CT (κ=0.391, *P*=0.001) both showed significant correlation with pathology (Table 2).

Table 2: Seminal vesicle invasion kappa analysis

		Final Pathology Seminal Vesicle Invasion		Sensitivity	Positive Prediction	Specificity	Negative Prediction	Kappa	*P*-value
		(+)	(-)						
MRI Seminal Vesicle Invasion	(+)	**4**	2	33.3%	66.7%	95.2%	83.3%	0.348	***0.005***
	(-)	8	**40**						
PSMA Seminal Vesicle Invasion	(+)	**4**	1	33.3%	80.0%	97.6%	83.7%	0.391	***0.001***
	(-)	8	**41**						

Lymph node metastasis:

- **Right pelvic nodes:** There was significant correlation for MpMRI (κ=0.460, *P*=0.001) and PSMA PET-CT (κ=0.400, *P*=0.001).
- **Left pelvic nodes:** There was strong correlation for MpMRI (κ=0.658, *P*<0.001) and PSMA PET-CT (κ=0.196, *P*=0.016).

Lesion localization: There was no significant correlation for MpMRI (κ=0.137, *P*=0.056), but PSMA PET-CT showed significant concordance (κ=0.163, *P*=0.040) (Table 3).

Table 3: Tumor localization kappa compliance analysis

		Final Pathology Tumor Localization			Compliance Rate	Stats
		Left	Right	Bilateral		
MRI Lesion Localization	Left	***6***	0	12	55.3%	Kappa=0.137 *P*=0.056
	Right	0	***4***	13		
	Bilateral	3	1	***11***		
	No Lesion	1	1	2		
PSMA Involvement Side	Left	***7***	1	7	65.8%	Kappa=0.163 ***P=0.040***
	Right	0	***1***	9		
	Bilateral	3	2	***17***		
	No Involvement	0	2	5		

Surgical margins: There was no significant difference in age, surgical type, or prostate volume between groups (*P*>0.05). However, patients with positive surgical margins had:

- Higher PSA levels (*P*=0.013) (Figure 1)
- Larger index lesions in MRI (*P*=0.021) (Figure 2)
- Higher SUV max of PSMA (*P*=0.008) (Figure 3)

The distribution of PSMA involvement was not significantly different (*P*>0.05).

Figure 1: Serum PSA level averages in groups with positive and negative surgical margins

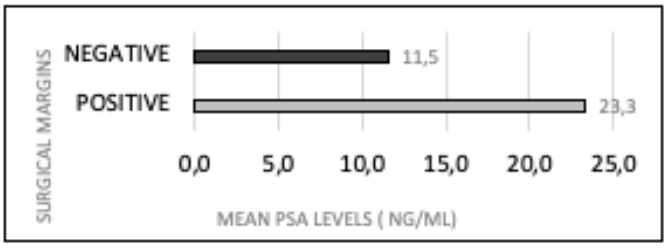


Figure 2: Mean index lesion size in MR imaging in groups with positive and negative surgical margins

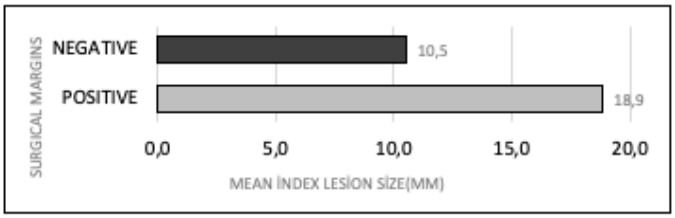
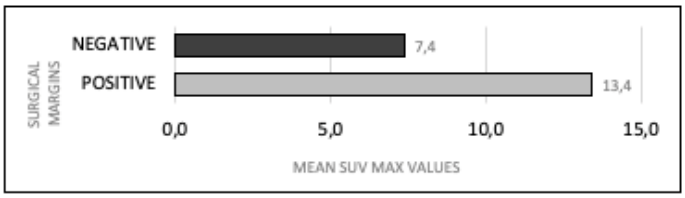


Figure 3: Mean SUV max values in groups with positive and negative surgical margins



Discussion

Accurate staging after a diagnosis of prostate cancer is vital for determining the appropriate treatment strategy. Local staging plays a key role in differentiating between localized and locally advanced disease. Recent publications highlight MpMRI as a highly recommended imaging modality for local staging. The European Association of Urology's prostate-cancer guidelines suggest that MpMRI should be conducted prior to biopsy for patients with elevated serum PSA levels [4]. Furthermore, MpMRI provides crucial anatomical information for treatment planning after diagnosis. Imaging findings such as broad tumor contact, asymmetric capsular bulging, obliteration of the rectoprostatic angle, and neurovascular bundle asymmetry are associated with extracapsular extension [5].

In a meta-analysis by de Rooij et al. [6], the sensitivity and specificity of MpMRI for detecting extracapsular extension were reported as 57% and 91%, respectively. For seminal vesicle invasion, the sensitivity was 58%, and the specificity was 96%. In our study, MpMRI demonstrated a sensitivity of 18.5% and specificity of 88.9% for extracapsular extension. However, no significant correlation with final pathology was found.

A multicenter study by Soeterik et al. [7] compared the accuracy of digital rectal examination and MRI in detecting extracapsular disease. They reported a sensitivity of 51% and specificity of 82% for MRI. The variability in MRI performance

has been attributed to differences in image-acquisition protocols and inter-reader interpretation [8]. Yılmaz et al. [9] compared Ga-68 PSMA PET-CT with MpMRI for local staging. The reported sensitivity and specificity of PSMA PET-CT for extracapsular extension were 30% and 85.7%, respectively, while for seminal vesicle invasion, they were 75% and 90%.

In our study, PSMA PET-CT showed a sensitivity of 14.8% and specificity of 77.8% for extracapsular extension, and there was no significant correlation with pathology. Although both modalities lacked statistical correlation with the final pathology, MpMRI outperformed PSMA PET-CT in sensitivity and specificity. The relatively low resolution of PET-CT may account for its reduced accuracy in evaluating extracapsular disease.

Seminal vesicle invasion staged as T3b is suggested in MpMRI by a low T2 signal within the seminal vesicles and in PSMA PET-CT by increased uptake at that level. In our findings, MpMRI and PSMA PET-CT both demonstrated moderate sensitivity (33.3%) and high specificity (95.2% and 97.6%, respectively), and each correlated significantly with the final pathology. Despite lower sensitivity compared to previous reports, both modalities provided valuable information that aligned with literature findings.

Lymph-node status was evaluated separately for right and left pelvic nodes. MpMRI revealed significant correlation with the final pathology for right-sided nodes with 50% sensitivity and 96% specificity. PSMA PET-CT also showed significant correlation with higher sensitivity (75%) but lower positive predictive value (PPV) (33.3%). For the left side, both modalities achieved 100% sensitivity. MpMRI had higher specificity (98.1%) compared to PSMA PET-CT (86.8%), and there was significant correlation for both.

These findings are supported by earlier studies. Budiharto et al. [10] reported a diffusion-weighted MRI sensitivity of 18.8% and specificity of 97.6%. A 2018 systematic review cited PSMA PET-CT sensitivities of up to 99% with specificities exceeding 90% [11]. Wu et al. found that PSMA PET-CT was superior to MpMRI for detecting lymph-node metastases in intermediate- and high-risk patients [12]. In our study, both methods correlated significantly with the final pathology, although MpMRI's resolution limitations in wider-field imaging may restrict its nodal staging utility. In contrast, the whole-body imaging capacity of PSMA PET-CT enhances its role in systemic staging.

Preoperative lesion localization is critical for nerve-sparing surgery. Lesions were classified as right-sided, left-sided, or bilateral. Both index and secondary lesions were included in the evaluation. MpMRI did not correlate significantly with the final pathology, while PSMA PET-CT did. In a study by Zamboglou et al. [13], PSMA PET-CT showed higher sensitivity and specificity (75% and 87%) than MpMRI (70% and 82%) in tumor-volume detection.

A significant association was observed between positive surgical margins and larger index-lesion size (mean 18.9 mm), higher PSA levels, and elevated SUV max. Tamada et al. [15] linked extracapsular extension and tumors at the base or apex with increased risk of positive margins. In our study, however, no direct correlation was found between extracapsular extension or tumor localization and margin status. Nonetheless, imaging characteristics of larger tumors may support preoperative planning decisions. Patients with extracapsular extension, seminal vesicle invasion (pT3b), ISUP grade >2, or positive surgical margins face increased risk of progression, with up to 50% risk at five years [16]. Preoperative identification of high-risk features may aid in optimizing treatment and improving outcomes.

The clinical implications of our findings are particularly relevant for surgical planning and treatment selection. Although MpMRI is limited in detecting extracapsular extension, it provides detailed anatomical guidance that is critical for nerve-sparing techniques. Ga-68 PSMA PET-CT offers broader systemic staging value, especially in identifying nodal involvement. When used together, these imaging tools can provide information for tailored surgical approaches, support decisions on wider excision or intraoperative frozen section use, and guide discussions about adjuvant therapy.

Limitations

A major limitation of our study is the absence of blinding for radiologists and surgeons. The image readers had access to clinical data, and surgeons were aware of the imaging results during surgery. This lack of blinding could have introduced interpretation and procedural bias. Radiologists may have been influenced by clinical expectations, which could have potentially affected the objectivity of the reported findings. Similarly, surgical decision-making could have been subconsciously shaped by the imaging results, particularly in margin control. This limitation may have impacted the generalizability of our findings and highlights the need for blinded assessments in future prospective trials.

Conclusion

Prostate cancer remains a major public health concern due to its high prevalence and the potential morbidity associated with its treatment. Accurate preoperative staging is critical for distinguishing between patients who require immediate intervention and those eligible for active surveillance, as well as for guiding surgical strategies. Our findings highlight the complementary strengths of MpMRI and Ga-68 PSMA PET-CT in this setting. While PSMA PET-CT demonstrated high sensitivity and specificity for lymph-node staging and seminal vesicle invasion, MpMRI provided detailed anatomical information that is valuable for lesion characterization and local staging.Importantly, we identified significant associations between positive surgical margins and factors such as index lesion size, PSA levels, and SUV max values. This suggests that these imaging parameters could support preoperative risk stratification and surgical planning. These findings are consistent with the literature and support the integration of both modalities into personalized treatment algorithms. As the clinical applications of advanced imaging continue to expand, future prospective and blinded studies are warranted to further clarify their roles and optimize their use in staging, treatment selection, and long-term outcome prediction for the management of prostate cancer.

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J Surg Med. 2025;9(8):123-127.
https://doi.org/10.28982/josam.7950

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Research article
https://jsurgmed.com/

Determination of the adrenomedullin gene variations in patients with coronary artery disease

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Ethics Committee Approval
The study was approved by the Manisa Celal Bayar University Faculty of Medicine Local Ethics Committee, dated July 2, 2014 and numbered 20478486261.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
This study was supported financially by the Scientific Research Projects Coordination Unit of Manisa Celal Bayar University (project no. 2014-116).

Published
2025 August 5

Abstract

Background/Aim: Coronary artery disease is characterized by atherosclerosis in the vessel wall. The protein encoded by the adrenomedullin (ADM; OMIM No. 103275) gene is a preprohormone, post-translationally modified to form two biologically active peptides. These peptides are involved in a myriad of functions including vasodilation, bronchodilation, regulation of hormone secretion, growth modulation, promotion of angiogenesis, and antimicrobial activity. This study was designed to explore the correlation between the development of atherosclerosis and variations in the *ADM* gene.
Methods: The study analyzed 62 cases with atheromatous plaques and 46 cases without such plaques. Genomic DNA was extracted from peripheral blood. Variations in the *ADM* gene were determined by Sanger sequencing.
Results: In this study, four different variants were found in the *ADM* gene, including c.-2140T>C (rs3814700), c.248+91T>G (rs545190978), c.150C>G (rs5005), and c.261C>T (rs767028428 C>T). The allele frequencies of these ADM gene polymorphisms in patients were as follows: T at 93% and C at 7% for rs3814700 (T>C); T at 99.2% and G at 0.08% for rs545190978 (T>G); C at 99.2% and G at 0.08% for rs5005 (C>G); and C at 99.2% and T at 0.08% for rs767028428 (C>T).
Conclusion: It was found that there was no significant difference in allele frequencies and genotypes of these polymorphic regions between the patients and the control group.

Keywords: coronary artery disease, atherosclerosis, vasodilation, *ADM* gene

How to cite: Geniş EÇ, Batır MB, Gerik-Çelebi HB, Çam FS. Determination of the adrenomedullin gene variations in patients with coronary artery disease. J Surg Med. 2025;9(8):123-127.

Introduction

Coronary artery disease (CAD) is a progressive and systemic inflammatory disease, where atherosclerosis with occlusive plaque formation is the underlying cause. This includes pathologies affecting the coronary arteries that supply blood to the heart. In developed countries, CAD is a leading cause of death. An important event in atherosclerosis is the formation of an atheroma or occlusive atheromatous plaque due to lipid accumulation and intimal thickening [1,2]. The role of several enzymes in the cardiovascular system and atherosclerotic plaque formation is considered protective against the disease. Adrenomedullin (ADM) with properties such as vasodilation, natriuresis, anti-apoptosis, and nitric oxide stimulation is believed to inhibit atherosclerosis by suppressing vascular smooth muscle cell proliferation. It has significant effects concerning vascular pathologies [3]. ADM is a peptide synthesized by endothelial cells with a vasoprotective effect on the cardiovascular system. Differences in ADM plasma levels have been noted due to its vasoprotective effect in various cardiovascular diseases [4]. High levels of ADM are found in atherosclerosis [5]. Consisting of 2,717 bases, the ADM gene is located on the p15.4 arm of chromosome 11. The ADM gene consists of four exons, three introns, and several TATA, CAAT, and GC regions in the 5 UTR regions that have bounds with five transcription factors [6]. Sequence changes in the ADM gene's promoter region are known to affect ADM and cause various pathologies [7]. Plasma ADM levels are associated with a single nucleotide polymorphism (SNP) in the ADM gene. Proadrenomedullin (proADM) was recognized as a novel biomarker reflecting vascular function [8]. ADM gene polymorphisms are thought to influence its expression, possibly leading to a genetic predisposition to various systemic diseases. Ong et al. reported that rs11042725 change was a risk factor for dysglycaemia, and other ADM gene sequence changes were predicted to carry the same risk [9]. In the study by Cheung et al., they correlated plasma ADM levels with IL-6 levels and linked the ADM gene rs4910118 polymorphism with lower adrenomedullin levels. The study proposed that ADM gene sequence variations could be utilized to predict cardiovascular risk [10]. It is hypothesized that functional polymorphisms of the ADM gene may make individuals susceptible to the development of atherosclerosis.

The objective of this study was to explore the correlation between gene sequence variations and the onset of atherosclerosis in ADM.

Materials and methods

Study population

Manisa Celal Bayar University Faculty of Medicine's Department of Cardiology included a total of 108 patients, over 40 years of age, with pre-diagnosis of CAD in a study. The study consisted of 62 patients with atheroma plaque and 46 patients who had normal angiography results. Each patient was analyzed for demographic characteristics and risk factors such as smoking, diabetes mellitus, dyslipidemia, hypertension, and family history of CAD. The Ethics Committee of the Manisa Celal Bayar University Faculty of Medicine approved this study on July 2, 2014, with the approval number 20478486261.

Determination of ADM gene changes

Genomic DNA isolation was conducted using an Invitrogen DNA isolation kit procedure with peripheral venous blood samples. Both patient and control DNAs were obtained following the appropriate protocol. The purity range and the quantities of DNA samples from the isolation were assessed using a NanoDrop device. Standard 50 µl PCR reactions were formed using PCR components, drawing from 30 ng/µl cases from the DNA samples. Two pairs of primer designs were created to augment the promoter and exonic regions of the ADM gene, and these designs were applied in the PCR studies (promoter region primers: F:5′-CTAGCTGTCCTTGACCTCCC-3′, R:5′-ATCGAATGTCCTGAAGCCCA-3′; exonic region primers: F1: 5′-GCTCGACTCTCTTTCTTCT-3′, R1:5′- GAAGTCCTTCGTCCCGGG-3′). Primer3Plus, an online software primer design program, was used for the primers [11]. The PCR was conducted in a 50 µl reaction which included 150 ng DNA, 10× PCR buffer, 2.5mM MgCl2, 20 µM dNTPs, forward primer (10 pmol/ µl), reverse primer (10 pmol/ µl), and 5U/ µl hot start Taq polymerase. Amplification conditions were as follows: initial activation at 94°C for 15 min, followed by 35 cycles of denaturation at 94°C for 45 s, annealing at 60°C for 45 s, extension at 72°C for 1 min and 45 s, and a final extension step at 72°C for 10 min. To assess the amplification products from the PCR, we conducted a 1.5% agarose gel electrophoresis alongside a 100 base pair (bp) DNA Ladder. Samples underwent sequencing if PCR product formation occurred. DNA purification preceded sequencing, following the appropriate protocol.

Sequence study and analysis

Purification was carried out using Exosap. The sequencing was conducted following the appropriate protocol. For the PCR sequence, 2 µl of the purified product was incorporated. Relevant primers (F and R primers) were also diluted and added. The primary dilution process involved adding 16 µl distilled water and 4 µl primer, priming with 1/10 primers to contribute 2 pmol. Following this, a mixture of 2 µl 5× buffer, 2 µl dNTP and ddNTP (dideoxynucleotide triphosphate), featuring BigDye to detect the study's DNA region using fluorescent nucleotides, and 2 µl dH_2O, prepared by adding a 6 µl mix, was introduced. The PCR program for the sequence entailed: heating for 10 s at 96°C, 5 s at 50°C, 4 min at 60°C, and repeating these steps 25 times before holding for 1 h at 4°C and indefinitely at 100°C. DNA sequencing pertains to determining the sequence of nucleotide bases (adenine, guanine, cytosine, and thymine) in a DNA molecule. The sequencing is aligned to a single primer direction but can be ordered separately from the two directions, forward and reverse primer.

Sequence evaluation

The resulting sequence data was analyzed using the MEGA5.1 sequencing program. This program aligns the sequences with each other. This comparison was carried out for 108 samples. As a result, the transformed regions (base) were determined, and repeated PCR was performed to confirm the sequence analysis and the sequence analysis was repeated. In

addition, new changes and sequence results for polymorphic regions were checked from graphs.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) was utilized for the statistical analysis of the study's results. Complementary statistical methods (mean, standard deviation) were employed to evaluate the data. Differences in frequencies and distributions between groups were assessed by the chi-squared test. Furthermore, allelic distributions and frequencies were evaluated using the chi-squared test, with percentages and p-values being calculated. Values of p <0.05 were deemed statistically significant. Additionally, the odds ratio method was used to compute the risk values for genotype-allele distribution frequency and disease risk factors.

Results

The study included a total of 108 individuals, consisting of 62 patients (32 males and 30 females) and 46 controls (24 males and 22 females). Both groups underwent an assessment for coronary risk factors. Significantly higher instances of hypertension, dyslipidemia, and family history were observed in the patient group compared to the control group. Table 1 presents the data collected relative to coronary risk factors.

Table 1: Percentages of risk factors forming the study group

Risk factors	Patient group (n=62)	Control group (n= 46)	OR (Odds Ratio) (95%CI)	*P*-value	Total (n=108)
DM	25	10	1.40 (1.03-1.91)	0.061	35
HT	39	18	1.51 (1.06-2.15)	0.019	57
DL	26	6	1.71 (1.28-2.91)	0.001	32
family history	20	6	1.50 (1.11-2.02)	0.024	26
smoking	15	11	1.00 (0.68-1.47)	135	16

DM: diabetes mellitus, HT: hypertension, DL: dyslipidemia

The research determined ADM genotypes amongst patients with coronary angiography atheroma plaques, and a separate control group without such plaques. The researchers observed the presence of *ADM* gene: NM_001124.3: c.-2140T>C variation (rs3814700) within the promoter region. Another variant, *ADM* gene: NM_001124.3: c.248+91T>G (rs545190978), was detected within the 5′UTR regions.

Similarly, the *ADM*: NM_001124.3: c.150C>G variation (rs5005) was identified within exon 3. This particular change also prompts a switch from the serine amino acid at position 50 to arginine. Lastly, the *ADM*: NM_001124.3: c.261C>A: p.(Ala87=) variant was found within exon 4, although this substitution does not alter the amino acid sequence (alanine to alanine).

Genotype and allele frequencies of case controls are summarized in Tables 2, 3, 4, and 5. The distribution of rs3814700 genotype frequencies in the patient group was 87.1% (54/62) for TT and 12.9% (8/62) for TC. In the control group, the distribution of genotypes was 93.5% (43/46) for TT and 6.5% (3/46) for TC. There were no significant differences in rs3814700 genotype frequencies when comparing the patient group and controls (*P*=0.278) as Table 2 shows. T and C allele frequencies of the rs3814700 polymorphism were 93% and 7% in the patient group, and 96% and 4% in the control group, respectively (*P*=0.764).

The distribution of rs5005 genotype frequencies in the patient group was 98.4% (61/62) for CC and 1.6% (1/62) for CG. In the control group, the distribution of genotypes was 100% (46/46) for CC, and 0% (0/46) for CG. There were no significant differences in the rs5005 genotype frequencies when comparing the patient group to the controls (*P*=0.386) (Table 5). The C and G allele frequencies of the rs5005 polymorphism were 99.2% and 0.08% in the patient group, and 100% and 0% in the control group, respectively. There were no significant differences in the rs5005 allele frequencies when comparing the patient group and the controls (*P*=0.387) (Table 3).

Similarly, the distribution of rs545190978 genotype frequencies in the patient group was 98.4% (61/62) for TT and 1.6% (1/62) for TG. Meanwhile, in the control group, the genotype distribution was 100% (46/46) for TT and 0% (0/46) for TG. The comparison of rs545190978 genotype frequencies between the patient and control groups did not reveal any significant differences (*P*=0.386). (Table 4). The T and G allele frequencies of rs545190978 polymorphism were 99.2% and 0.08% in the patient group, and 100% and 0% in the control group, respectively. There were no significant differences in rs545190978 allele frequencies between the patient and control groups (*P*=0.387) (Table 4).

The distribution of rs767028428 genotype frequencies in the patient group was 98.4% (61/62) for CC and 1.6% (1/62) for CT. In the control group, the genotype distribution was 100% (46/46) for CC and 0% (0/46) for CT. There were no significant differences in rs767028428 genotype frequencies between the patient and control groups (*P*=0.386) (Table 4). C and T allele frequencies of rs767028428 polymorphism were 99.2% and 0.08% in the patient group, and 100% and 0% in the control group respectively. There were also no significant differences in rs767028428 allele frequencies between the patient and control groups (*P*=0.387) (Table 4).

Table 2: ADM gene (rs3814700-promoter) polymorphism genotype frequencies

rs3814700	Patient group (62)	Control group (46)	OR (Odds Ratio) (95%CI)	*P*-value
Genotype frequency and distribution				
TT	54 (87.1%)	43 (93.5%)		
TC	8 (12.9%)	3 (6.5%)	0.76 (0.51-1.14)	**0.278**
Allele frequency and distribution				
T allele	116 (93%)	89 (96%)		
C allele	8 (7%)	3 (4%)	0.77 (0.53-1.13)	**0.291**

Table 3: ADM gene (rs5005-exon 3) polymorphism genotype frequencies

rs5005	Patient group (62)	Control group (46)	OR (Odds Ratio) (95%CI)	*P*-value
Genotype frequency and distribution				
CC	61 (98.4%)	46 (100%)		
CG	1 (1.6%)	0 (0%)	0.57 (0.48-0.67)	**0.386**
Allele frequency and distribution				
C allele	123 (99.2%)	92 (100%)		
G allele	1 (0.08%)	0 (0%)	0.57 (0.50-0.64)	**0.387**

Table 4: ADM gene (rs545190978-5'UTR) polymorphism genotype frequencies

rs545190978	Patient group (62)	Control group (46)	OR (Odds Ratio) (95%CI)	*P*-value
Genotype frequency and distribution				
TT	61 (98.4%)	46 (100%)		
TG	1 (1.6%)	0 (0%)	0.57 (0.48-0.67)	**0.386**
Allele frequency and distribution				
T allele	123 (99.2%)	92 (100%)		
G allele	1 (0.08%)	0 (0%)	0.57 (0.50-0.64)	**0.387**

Table 5: ADM gene (rs767028428-exon 4) polymorphism genotype frequencies

rs767028428	Patient group (62)	Control group (46)	OR (Odds Ratio) (95%CI)	*P*-value
Genotype frequency and distribution				
CC	61 (98.4%)	46 (100%)		
CT	1 (1.6%)	0 (0%)	0.57 (0.48-0.67)	**0.386**
Allele frequency and distribution				
C allele	123 (99.2%)	92 (100%)		
T allele	1 (0.08%)	0 (0%)	0.57 (0.50-0.64)	**0.387**

Discussion

The polymorphisms of the *ADM* gene may influence ADM expression and predispose individuals to various systemic diseases. Variations in the *ADM* gene are suggested to contribute to the development of atherosclerosis due to ADM's roles in processes such as inhibiting vascular smooth muscle cells and enabling vasodilation in vessels. A cohort study involving 1370 patients with acute coronary syndrome found adrenomedullin to be an accurate biomarker for predicting acute coronary syndrome and comorbid cardiovascular disease in patients with chronic kidney disease and preserved renal function [12]. Another study indicated that ADM expression is higher in patients with coronary heart disease [13].

The four different polymorphisms were detected in the promoter, 5'-untranslated region (5′UTR), exon 3, and exon 4 of the *ADM* gene. This study's findings suggest no statistically significant disparity between the patient and control groups in terms of allele and genotype frequencies and polymorphism regions. The *ADM* promoter region presented a higher frequency of the rs3814700 polymorphism in the patient group; however, no statistically significant outcomes were attained. The A>G change (rs3814700) at position 1984, previously reported, is associated with blood pressure, and plasma ADM levels are higher in healthy controls with the G allele [14]. The absence of plasma ADM levels in our study precludes the evaluation of this polymorphism's effect on ADM levels in individuals. The frequency of the polymorphism observed in this study compares to the prevalence of the polymorphism in the healthy European population. Given the insufficient number of cases and the unknown ethnic origin, we believe that the determination of the ADM rs3814700 polymorphism in healthy populations will yield more precise data on the actual polymorphism's frequency in our country.

The rs767028428 polymorphism, detected in the fourth exon of the *ADM* gene, is a synonymous mutation that does not alter the encoded protein. The current literature review reveals no publications on this polymorphism in relation to the *ADM* gene and atherosclerosis. According to the available database data, this polymorphism's clinical significance remains uncertain. Given our study's limited number of control cases, we believe that a larger sample size would provide more precise data on this polymorphism.

The rs5005 polymorphism, identified in exon 3 of the *ADM* gene, has been cited in the literature as a variant of uncertain clinical significance. The detected change is a non-synonymous change that results in the substitution of a small, polar amino acid for a large, basic amino acid at position 50 in the encoded protein. The effect of this change on protein folding remains unknown. Given this polymorphism's low prevalence in other populations and the fact that the patient group is the only one with a detected polymorphism, it is critical to evaluate the polymorphism in conjunction with ADM levels to determine its clinical significance and assess ADM expression in patients with this polymorphism.

In their 2023 study, Chang et al. [15] proposed that a long-acting adrenomedullin analog may prove beneficial in managing hypertension and preventing organ damage related to vascular ischemia in pre-eclampsia patients. The intramyocardial injection of Recombinant Adeno-Associated Viral Vector PR39/Adrenomedullin co-expression has been shown to increase angiogenesis and reduce apoptosis in a rat myocardial infarction model [16].

Limitations

As a result, in the present study, further analysis is needed in terms of the polymorphisms determined by the sequence analysis. To determine the role of adrenomedullin in the pathogenesis of atherosclerosis, ADM expression, and plasma levels should be evaluated simultaneously.

Conclusion

No significant differences were found in the allele and genotype frequencies of the ADM gene between the patient and control groups. A potential new gene therapy-based approach for clinical use is proposed.

Acknowledgments

All individuals participating in the study were informed about the study and an informed consent form was obtained. We thank all the individuals who took part in this study.

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J Surg Med. 2025;9(8):128-131.
https://doi.org/10.28982/josam.8285

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Research article
https://jsurgmed.com/

ThuLEP technique for managing benign prostatic hyperplasia: Intraoperative and postoperative complications in a series of 42 consecutive cases

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Ethics Committee Approval
This study was approved by the Ethics Committee of Atlas University Hospital (institution review board number, E-22686390-050.99-42447, received date: April 22, 2024).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2025 August 12

Abstract

Background/Aim: Data from the first series of 42 patients diagnosed with benign prostatic hyperplasia (BPH) who underwent Thulium laser prostate enucleation (ThuLEP) surgery at our clinic were retrospectively reviewed. The procedures were performed by a single physician with 10 years of endoscopic surgery experience. The purpose of this retrospective study was to add our results, which highlight potential complications during and after ThuLEP surgery, to the already reported ThuLEP results in the literature.
Methods: Data from 42 patients with BPH who underwent ThuLEP surgery at Atlas University Hospital between January 2020 and January 2024 were retrospectively analyzed. Patients with a high international prostate symptom score (IPSS>7), a low quality of life score (QoL<3), a prostate volume ≥ 50 cc according to urinary ultrasonography, a peak urine flow rate (Q_{max}) ≤ 15 ml/s on uroflowmetry, a total serum prostate-specific antigen (tPSA) <4 ng/mL, and a negative biopsy tPSA ≥ 4 ng/mL were included in the study. All patients underwent pre-operative evaluations that included urinalysis, urine culture, tPSA, uroflowmetry, IPSS, QoL, urinary ultrasonography, prostate volume, postvoid residual urine volume (PVR), and sexual function (IIEF). ThuLEP surgery was performed en bloc using the "Omega Sign" technique in all patients.
Results: Mean enucleation and morcellation times were 110±40 and 25±18 min, respectively. Mean resected prostate tissue weight was 40±25 g. Mean hospital stay and catheterization time were 40±12 and 36±10 h, respectively. Significant improvements were observed in post-operative IPSS, IIEF, QoL, Q_{max}, and PVR (P<0.05). Q_{max} increased, whereas PVR decreased. Post-operative hemoglobin values decreased initially (P<0.05) but returned to baseline at six months (P>0.05). Intra-operative complications included superficial bladder mucosal injury in two patients (4.76%), major capsular perforation in one patient (2.38%), and major perforation below the bladder neck between the five and seven o'clock positions in one patient (2.38%). Complications that developed in the first six months after surgery included urinary retention in one patient (2.38%), stress incontinence in two patients (4.76%), and urethral stricture in one patient (2.38%).
Conclusion: Due to the steep learning curve for surgeons, ThuLEP surgery can initially cause complications, which are manageable. Despite these complications, current reports support its safety and effectiveness across a variety of prostate sizes. The ThuLEP technique offers patients several advantages, such as shorter hospital stays, shorter catheterization times, and fewer complications.

Keywords: ThuLEP, benign prostatic enlargement, transurethral resection

How to cite: Ergün M, Sağır S, Hacıbey İ. ThuLEP technique for managing benign prostatic hyperplasia: Intraoperative and postoperative complications in a series of 42 consecutive cases. J Surg Med. 2025;9(8):128-131.

Introduction

Prostate enucleation surgery (PES) techniques have gained significant popularity among urologists as a common approach for managing benign prostatic hypertrophy (BPH). The main purpose of these endoscopic surgical techniques is to remove the prostate lobules from the surgical capsule using enucleation. In comparison to transurethral resection of the prostate (TURP), which is the established standard for BPH treatment, PES has become increasingly favored by urologists for its benefits that include shorter hospital stays, a reduction in complications, and effectiveness in managing large-volume prostates [1–3]. With advancements in laser technology, Holmium:YAG was initially used for ablation and later for complete enucleation in BPH treatment [1].

The fundamental principles of PES techniques and their emergence as the benchmark treatment for BPH were established primarily through holmium laser enucleation of the prostate (HoLEP) [1,2]. Thulium laser, which consists of a different type of energy, has a slightly shorter wavelength than holmium lasers. This type of system provides a continuous wave output that enhances vaporization while limiting the depth of penetration into prostate tissue. These characteristics, along with rapid advances in laser technologies, have brought minimally invasive surgical approaches to the forefront and are influencing current urological practice [3]. Compared to TURP and HoLEP, advantages of PES, such as better intra-operative bleeding control, a shorter learning curve, and similar results across prostate sizes, have been reported. However, it has been reported that complications occur at varying rates as surgeons gain experience.

The European Association of Urology (EAU) guidelines emphasize that ThuLEP offers a strong alternative to TURP and HoLEP for patients with moderate to severe lower urinary tract symptoms and has yielded clinical improvements in the short to medium term. Although randomized controlled trials on ThuLEP are limited, this technique is becoming more widely accepted as the preferred surgical option and a viable alternative to TURP and HoLEP.

The primary objective of our study was to review our results in light of the available evidence regarding thulium enucleation techniques. Our study aimed to inform urologists who had newly adopting the ThuLEP method about potential intra- and post-operative complications during the first six months and to discuss the early safety and efficacy results of the method in terms of the literature.

Materials and methods

Results from 42 patients who underwent ThuLEP surgical technique at Atlas University Hospital between January 2020 and January 2024 were retrospectively analyzed. The study was approved by the Ethics Committee of Atlas University Hospital (institutional review board number: E-22686390-050.99-42447; approval date: April 22, 2024). The study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Patients with a high international prostate symptom score (IPSS>7), a low quality of life score (QoL<3), a prostate volume ≥ 50 cc according to urinary ultrasonography, a peak urine flow rate (Q_{max}) ≤15 ml/s on uroflowmetry, a total serum prostate-specific antigen (tPSA) <4 ng/mL, and a negative tPSA ≥4 ng/mL on biopsy were included in the study. Exclusion criteria included patients with prostate cancer, neurogenic bladder dysfunction as detected by urodynamic testing, and those who had previously undergone lower urinary tract surgery (TURP).

All patients underwent pre-operative evaluations that included urinalysis, urine culture, tPSA, uroflowmetry, IPSS, QoL, urinary ultrasonography, prostate volume, postvoid residual urine volume (PVR), and sexual function scores (IIEF).

The ThuLEP procedure was performed by a single surgeon who had 10 years of extensive experience in endourological surgery, including endoscopic treatments, such as TURP, for BPH. Most patients underwent spinal anesthesia, while a few patients underwent general anesthesia when spinal anesthesia proved ineffective.

All surgical procedures were performed using the "Omega Sign" technique for en bloc prostate enucleation. Enucleation was performed using a Thulium:YAG laser using a 550 µm fiber (CyberTM 200W; Quanta System) in conjunction with a 26 Fr continuous-flow resectoscope. Power settings of the thulium laser were controlled at 60 W for the left pedal and 40 W for the right pedal. A Hawk Jaws tissue disruptor (Hawk, Minitech Co.) and a 26 Fr nephroscope were used to remove the enucleated prostate tissue.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows version 11.5.1 (SPSS Inc., Chicago, IL, USA). Paired-samples t-tests were applied to compare pre- and post-operative values in addition to 6-month follow-up values of functional and laboratory parameters. A *P*-value of <0.05 was considered statistically significant. Descriptive statistics are presented as mean±standard deviation and range

Results

Demographic and pre-operative clinical characteristics of the 42 study patients are shown in Table 1. The mean enucleation time was 110±40 min (range: 40–180 min), while the mean morcellation time was 25±18 min (range: 10–40 min). The mean weight of the enucleated prostate tissue was 40±25 g (range: 35–180 g).

When pre-operative data were compared with discharge and 6-month post-operative data, statistically significant improvements were observed in IPSS, IIEF, Q_{max}, PVR, and QoL scores (P<0.05). Changes in IPSS, IIEF, QoL, Q_{max}, PVR, tPSA levels, and hemoglobin (Hb) values are summarized in Table 2. The mean hospital stay was 40±12 h (range: 24–72 h), and the mean catheter removal time was 36±10 h (range: 24–168 h). Other peri-operative data are presented in Table 3. Although a significant decrease (P<0.05), in post-operative Hb levels was noted (no significant change in Hb was observed at six months (P>0.05). Complications that developed during surgery and in the first six months after surgery are summarized in Table 4. One patient with a perforation below the bladder neck underwent open prostatectomy due to uncontrolled bleeding and injury depth. A blood transfusion was performed only in this case, whereas the other patients did not require such transfusions. One patient

developed both urinary tract infection and urethral stricture while another patient developed both prostate capsule perforation and bladder mucosal damage.

Table 1: Baseline characteristics of patients and pre-operative data

n=42	Mean, SD (range)
Age (years)	63.9±6.2 (50 –79)
BMI	26.7±5.8 (19.5–31.1)
Prostate volume (cm^3)	60±35 (50-230)
PSA (ng/mL)	4.7±3.9 (0.8–15.0)
PVR (mL)	153±80 (0–300)
Qmax	8.3±2.7 (5.1–13.8)
IPSS	20.4±3.6 (17–30)
IIEF	16.6±5.8 (15–26)
QoL score	3.9±1.5 (3–5)
Hb level (g/dL)	13.8±1.9 (11.4–17.5)

BMI: Body Mass Index, PSA: prostate-specific antigen, Q_{max}: maximum urine flow rate, IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, QoL: Quality of Life, PVR: Post Voiding Residual Volume, Hb: Hemoglobin, SD: standard deviation

Table 2: Pre- and post-operative follow-up findings from the patients

Variables Mean, SD (range)	Preoperative	Postoperative	6-month follow-up	*P*-value (Pre-op vs Post-op)	*P*-value (Pre-op vs 6-Month)
IPSS score	20.4±3.6 (17–30)	4.2±2.2 (1–9)	3.8±2.5 (0–10)	0.021	0.020
IIEF score	16.6±5.8 (15–26)	-	20.2±6.4 (18–29)	-	0.038
QoL score	3.9±1.5 (3–5)	-	1.8±0.6 (0–3)	-	0.041
PSA (ng/mL)	4.7±3.9 (0.8–15)	1.1±2.3 (0.1–4.9)	1.3±2.4 (0.1–5.2)	0.018	0.020
Qmax (mL/sn)	8.3±2.7 (5.1–13.8)	29.3±10.6 (21.6–48)	30.5±11 (22–50)	0.015	0.013
PVR (mL)	153±80 (0–300)	20±8 (0–30)	25±10 (0–35)	0.018	0.020
Hb level (g/dL)	13.8±1.9 (11.4–17.5)	11.6±2.2 (8.3–15.7)	12.9±3.1 (10.4–16.8)	0.042	0.061

IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, QoL: Quality of Life, PSA: prostate-specific antigen, Q_{max}: maximum urine flow rate, PVR: Post voiding residual, Hb: hemoglobin

Table 3: Peri-operative data

n=42	Mean, SD (range)
Enucleation Time (min)	110±40 (40–180)
Morcellation Time (min)	25±18 (10–40)
Weight of Prostate Tissue Removed (g)	40±25 (35–180)
Hospital Stay Duration (h)	40±12 (24–72)
Catheter Withdrawal Time (h)	36±10 (24–168)

Table 4: Intraoperative and postoperative complications

Complications	n=42 (100%)	Assessment
Intra-operative		
Bladder mucosal injury	2 (4.76%)	72 h of catheterization
Prostate capsule perforation	1 (2.38%)	72 h of catheterization
Perforation at the sub-o'clock level of the bladder neck	1 (2.38%)	Open surgical repair
Post-operative (0–6 month)		
Urinary retention	1 (2.38%)	72 h of catheterization and NSAID
Stress incontinence	2 (4.76%)	Continence after 8 weeks
Urethral stricture	1 (2.38%)	Internal urethrotomy
Urinary tract infection	1 (2.38%)	Intravenous antibiotic therapy
Retrograde ejaculation	35 (83.33%)	-

NSAID: non-steroidal anti-inflammatory drug. Note: Urinary tract infection and urethral stricture occurred in one patient. Prostate capsule perforation and bladder mucosal injury occurred another patient.

Discussion

This retrospective analysis evaluated the clinical outcomes and complications in a series of 42 patients who underwent ThuLEP surgery for BPH by a single physician.

The surgical technical parameters of the study, namely mean enucleation time, morcellation time, hospital stay, and catheterization time, were found to be comparable with ThuLEP data in the literature [3,4].

The ThuLEP technique offers significant patient advantages over conventional TURP, particularly in terms of shorter hospital stays and urethral catheterization times. These advantages have been clearly documented in various comparative studies and demonstrate that ThuLEP surgery is a safe and effective treatment option, even for large-volume prostates [5,6].

Post-operative clinical evaluations revealed significant improvements in excretory parameters such as IPSS, QoL, Q_{max}, and PVR in addition to a significant increase in IIEF scores. These findings highlight the effectiveness of the surgical technique not only on symptoms but also on QoL and IIEF. While the impact of laser prostate enucleation surgery on sexual function is unclear in the literature, some studies have reported positive improvements in IIEF scores after surgery [7–12]. Our results are consistent with these findings.

Although the post-operative hemoglobin decrease was significant, only one patient required a blood transfusion. Based on both our clinical experience and results in the literature, blood loss is less compared to TURP and open prostatectomy (AP) [13].

Intra-operative complications were mostly limited to superficial bladder mucosa injuries and capsule perforations, except in one patient. Superficial bladder mucosa damage occurred during tissue morcellation in two patients. This complication was attributed to continuing morcellation without recognition of the decrease in that the irrigation fluid, which led to inadequate bladder filling. Therefore, morcellation with a full bladder and adequate irrigation fluid will help prevent further complications.

All of these occurred in the first 20 cases and coincided with the early learning curve. No such complications were observed in subsequent cases. We believe that the ThuLEP surgical technique is a learnable technique and that its safety increases with additional endoscopic surgical experience. This clinical experience is consistent with studies in the literature and demonstrates that surgeons can safely and effectively perform the ThuLEP technique after performing 15–20 supervised cases [14].

Post-operative complications, such as urinary tract infections, urinary retention, urethral strictures, and stress incontinence were observed at low rates and were transient. These findings were important in supporting the favorable safety profile of the ThuLEP technique. A review of studies in the literature reveals that these complications are generally minimal, self-limiting, and manageable with conservative approaches [15,16].

Stress incontinence has generally been shown to resolve spontaneously within 6–8 weeks post-operatively, whereas persistent incontinence is very rare [15]. In this respect, our results are consistent with those in the literature.

The most common post-operative complication in our series was retrograde ejaculation. This complication is a proven consequence of both endoscopic resection and laser enucleation techniques and is often a consideration for patients considering surgery [17]. Similar rates have been reported in previous studies, thereby supporting the consistency of our findings [18].

The guidelines for the surgical management of lower urinary tract symptoms related to BPH have recently been revised. The 2023 American Urological Association guidelines suggest that laser enucleation procedures can be considered a treatment option regardless of prostate size and are contingent upon the surgeon's level of experience [19].

Study limitations

This study has several limitations. Primarily, ThuLEP was not directly compared to standard TURP or other endoscopic laser surgical techniques. Additional limitations include the absence of a control group and a relatively small sample size.

Additionally, the retrospective study design, which was conducted in a single center and performed by a single surgeon in addition to possible selection bias, may be considered study limitations.

Conclusion

Our results support the safety, efficacy, and practicality of the ThuLEP technique for the surgical treatment of BPH. The technique yielded significant post-operative improvements as demonstrated by statistically significant changes in IPSS, Q_{max}, PVR, QoL, and IIEF scores. Intra- and post-operative complication rates were low and mostly mild or transient, thus supporting the technique's favorable safety profile. Notably, all intra-operative complications occurred within the first 20 cases and serve to highlight the steep but adaptable learning curve that is associated with the ThuLEP technique. With appropriate training and surgeon experience, ThuLEP can be safely performed and can be a strong alternative to conventional TURP or open prostatectomy, particularly for patients with large prostate volumes.

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J Surg Med. 2025;9(8):132-134.
https://doi.org/10.28982/josam.8130

JOSAM

Research article
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Review of pediatric burn patients in critical care at a tertiary facility

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Ethics Committee Approval
The study was approved by the Ethics Committee of Dr. Lutfi Kırdar Kartal Education and Research Hospital (Date: 2008, Number: 53).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2025 August 22

Abstract

Background/Aim: In Turkey, numerous individuals seek treatment every year for burn injuries due to socioeconomic conditions. This study aims to deliver insights into treatment strategies for pediatric burn patients in critical care settings in Turkey.
Methods: We retrospectively examined the medical records of 50 children, aged 0 to 14 years, treated in the Burn Intensive Care Unit. We analyzed the year of admission, age, gender, burn percentage, initial hematocrit and platelet levels, duration of stay in the critical care unit, and total hospital stay. We further assessed their mechanical ventilation duration, need for inotropic support, initial and 24-hour APACHE II scores, Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) score, and mortality rates.
Results: Children who succumbed had significantly higher GCSs, admission and 24-hour APACHE II scores, burn severity, and required mechanical ventilation and inotropic support. These factors were linked to mortality (P<0.01). Mortality showed no correlation with age, gender, hematocrit, platelet counts, critical care stay duration, or SOFA score.
Conclusion: Factors such as burn severity, need for mechanical ventilation and inotropic support, GCSs, and APACHE II scores in pediatric burn patients in critical care may be associated with mortality and influence their prognosis.

Keywords: burns, intensive care, coma, APACHE

Introduction

Burn injuries, caused by heat, electricity, or chemicals, pose serious health challenges by damaging the skin's protective layers and subcutaneous tissue [1,2]. Thousands seek burn treatment every year due to socioeconomic factors, with severe cases referred to specialized facilities.

The Glasgow Coma Scale (GCS) is a widely utilized neurological tool for assessing dysfunction and predicting mortality within two weeks post-injury, with lower scores indicating more severe damage [3].

Introduced in 1981, the APACHE scoring system evaluates disease severity through a combination of variables. Knaus et al. [4] developed an index to assess mortality risk based on APACHE II, allowing for the use of baseline disease coefficients.

The Sequential Organ Failure Assessment (SOFA) was created in 1994 during a European Society of Critical Care Medicine and Emergency Medicine conference. It applies to both septic and non-septic patients [5-7].

This study investigates factors such as high burn percentage, dehydration, fluid-electrolyte imbalance, and the critical need for early fluid therapy to reduce morbidity and complications in pediatric burn patients.

Materials and methods

We retrospectively assessed the medical records of 50 children, 30 males and 20 females, aged 0 to 14 years, treated in the Burn Intensive Care Unit of Dr. Lutfi Kırdar Kartal Education and Research Hospital from December 2008 to December 2010. The study was approved by the local ethics committee of Dr. Lutfi Kırdar Kartal Education and Research Hospital (Date: 2008, No: 53) and adhered to the 1964 Helsinki Declaration. Informed consent was obtained from the parents of hospitalized children in the burn unit. This retrospective study involving human participants was found to be in accordance with all ethical standards.

Three children were discharged after their initial admission but required readmission. Of these, two died during the second admission, and one was discharged. The second admissions were excluded from statistical data, while the first were included. We analyzed admission year, age, gender, burn percentage, initial hematocrit and platelet values, critical care and hospital stay duration. We further examined the mechanical ventilation duration, inotropic support need, initial and 24-hour APACHE II scores, Glasgow Coma Scale, SOFA score, and mortality rates.

Statistical Analysis

We used the Number Cruncher Statistical System (NCSS) 2007 & PASS 2008 Statistical Software (Utah, USA) for statistical analyses. Descriptive statistics (mean, standard deviation) assessed the data, and the Mann-Whitney U test compared quantitative data without normal distribution between the two groups. The chi-square test compared qualitative data with significance determined at *P*-value <0.05.

Results

The study included 50 children aged 2 months to 13 years, with an average age of 3.31±2.98 years. A significant number had burns covering 20-30% of the body. Mechanical ventilation was used for half of the children, averaging 4.80±6.93 days. Septic shock was the leading cause of death for 81.8% of the children (Table 1).

No significant age (*P*=0.981) and gender (*P*=0.676) differences existed between the deceased and surviving children. The burn surface area was significantly higher in deceased children (*P*=0.005). Mortality was higher in children needing mechanical ventilation (*P*=0.001). There was no significant difference in mechanical ventilation duration (*P*=0.001), critical care stay duration (*P*=0.869), hospital stay duration (*P*=0.001), SOFA scores (*P*=0.127), hematocrit levels (*P*=0.386), and platelet counts (*P*=0.090). Survivors had significantly higher GCS (*P*=0.022). Deceased children had significantly higher APACHE II scores (*P*=0.001).

Table 1: Distribution of demographic features.

		Minimum-Maximum	Mean (SD)
Age		0.17-13.0	3.31 (2.98)
		Number	**Percentage**
Gender	Female	20	40
	Male	30	60
Year of admission	2008	1	2
	2009	16	32
	2010	33	66
Burn percentage (%)	< 20%	3	6.1
	20-30%	17	34.7
	30-40%	10	20.4
	40-50%	8	16.3
	50-60%	7	14.3
	60-70%	3	6.1
	> 70%	1	2

SD: Standard deviation

Discussion

In our study, 60% of patients were male and 40% were female. The existing research shows similar male-to-female ratios [8,9]. Patients averaged 3.31±2.98 years, consistent with other studies [8,10,11]. Minor burns were less common, while severe burns were more frequent, likely due to the hospital's referral status, limited burn knowledge, and outpatient treatment for burns under 10% unless they involved the face or neck [12-14].

Our study's stay duration matches Soltani et al. [15], influenced by early burn detection, home occurrence, smaller burn areas, and quicker death in children with extensive burns. However, Ryan et al.'s [16] study in Canada reported an average hospital stay of 16 days.

In the present study, 22% of patients died; however, mortality rates were higher in other studies [10,11,17]. Children's burn treatment differs due to fluid-electrolyte balance changes and body proportions, with high mortality attributed to limited burn care units, large patient intake, and inadequate care [18].

The primary cause of death was septic shock, similar to other studies [18-20], which differed from Kobayashi et al. [21]. Septic shock deaths were due to patient referrals, insufficient fluid therapy, poor hygiene, understaffed units, and antibiotic-resistant bacteria.

No relationship between age and mortality was found, but burn surface area was significantly related to mortality [22]. Early thrombocytopenia and suppressed thrombocytosis were

linked to increased mortality, but our study found no significant relationship with thrombocyte values [23].

APACHE II scores were associated with illness severity, longer hospital stays, and increased mortality. In our research, both initial and 24-hour APACHE II scores were significantly linked to mortality [24].

Organ failure scoring during sepsis aids in evaluating prognosis and treatment efficacy. The SOFA score's simplicity and reliability support its use, but no significant relationship with mortality was found in our study [25].

Inotropic support during mechanical ventilation influenced the clinical course, and a five-point APACHE II score increase resulted in a 1.8-fold mortality increase [26]. A low Glasgow Coma Scale (GCS) was linked to mortality [27].

Study limitations include a small sample size, lack of national representation, and limited insights into mortality and morbidity causes.

We believe juvenile burn victims are more susceptible to sepsis and fluid-electrolyte imbalances due to impaired skin integrity. Pediatric burn management differs from adult treatment due to fluid-electrolyte balance and body proportions. Addressing these factors can reduce morbidity and complications.

Conclusion

We highlight the importance of fluid therapy in pediatric burn patients, enhancing infection prevention against sepsis, and educating families on burn prevention. Further research is needed to explore survival outcomes in pediatric burn patients.

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J Surg Med. 2025;9(8):135-142.
https://doi.org/10.28982/josam.8062

JOSAM

Review
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Effects of non-pharmacological approaches on anxiety, agitation and physiologic parameters in weaning from mechanical ventilation: A systematic review

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Ethics Committee Approval
Ethics committee approval is not required for this review article.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2025 August 6

Abstract

Background/Aim: Mechanical ventilator weaning refers to the incremental reduction of ventilatory support, facilitating a return to spontaneous breathing. It is essential that this process be carried out by skilled healthcare professionals equipped with both expertise and sound judgment to ensure it is performed at the optimal time and with the most appropriate methodologies. Such diligence is crucial in mitigating the morbidity and mortality associated with the protraction of mechanical ventilation (MV). The extant literature has explored the efficacy of various integrative, non-pharmacological interventions—including music therapy, guided imagery, reflexology, and aromatherapy—in managing the symptomatic burden experienced during both MV and its weaning phase. This study aims to systematically review the findings of investigations that assess the impact of these complementary therapeutic modalities employed by nurses on anxiety, agitation, and the physiological parameters of patients undergoing weaning from mechanical ventilation.

Methods: PubMed, CINAHL, Cochrane Library, Scopus, and Google Scholar databases were systematically searched using the key terms 'Mechanical ventilator weaning and complementary therapy or non-pharmacological approaches' and 'Mechanical ventilator weaning and/or music therapy, reflexology.' The search strategy was formulated based on the Patient-Intervention-Comparison-Outcome (PICO) framework: P—Adult intensive care patient cohort; I—Application of non-pharmacological approaches in the context of weaning from mechanical ventilation; C—Standard routine care; O—Outcomes related to anxiety, agitation, and physiological parameters. The 10 most pertinent studies, meeting predefined inclusion and exclusion criteria, were selected, encompassing a total of 750 participants. The predominant study design was the randomized controlled trial (RCT). The interventions examined across these studies primarily involved music and reflexology therapies.

Results: Most of the studies reviewed that the use of non-pharmacological interventions reduces patients' symptoms such as anxiety, agitation, and pain in patients. These methods also contribute to the stabilization of physiological parameters within normal ranges. Moreover, reflexology has been shown to expedite the weaning process from mechanical ventilation, thereby reducing the risk of prolonged mechanical ventilation, a significant challenge for patients and healthcare professionals.

Conclusion: Complementary therapy used in the process of mechanical ventilator weaning is an appropriate intervention to be used to manage patients' symptoms such as anxiety, agitation, and pain.

Keywords: ventilator weaning, music therapy, reflexology, nature, sound

How to cite: Şengör K, Çavdar İ, Polat E. Effects of non-pharmacological approaches on anxiety, agitation and physiologic parameters in weaning from mechanical ventilation: A systematic review. J Surg Med. 2025;9(8):135-142.

Introduction

Mechanical ventilation (MV), which is a life-saving intervention in cases of respiratory failure, cardiovascular surgery, septic shock, pneumonia, and chest and head traumas, is the maintenance of breathing with the help of an artificial ventilator device when the patient cannot perform respiratory function on his own. Approximately one million people in the United States require mechanical ventilation every year, and this requirement is thought to increase over time [1-3].

Weaning is the gradual withdrawal of ventilatory support that promotes a return to spontaneous breathing. In other words, the respiratory function is removed from the machine and performed independently by the patient. This process may last for a single day, several weeks, or several months. Many complications, such as infection, respiratory muscle and tracheal damage, barotrauma, and oxygen toxicity, may develop in intensive care unit patients due to prolonged ventilation [2,4,5].

Currently, the focus is on improving the ventilator weaning processes and reducing the duration of MV to reduce morbidity and mortality rates associated with mechanical ventilation. For effective weaning of patients from MV, weaning should be performed at the right time and with the proper method by an adequate and knowledgeable healthcare professional [1,6].

In addition to the risks associated with prolonged mechanical ventilation, premature weaning from MV poses significant health threats. Repeated intubation, increased mortality and morbidity, prolonged length of stay in intensive care, and MV may occur because of early weaning [7,8]. The decision for separation should be made by providing individualized care to the patient (especially regarding the method of separation) under the guidance of evidence-based practices. While evaluating patients before separation, checklists and protocols developed for the subject should be applied. The first fundamental component of weaning protocols involves using checklists that enumerate objective criteria, facilitating the daily assessment of a patient's readiness for weaning. The second component consists of algorithms designed to guide spontaneous breathing trials with various techniques in stages [9,10].

At the beginning of weaning, the patient was weaned from MV for 5-10 minutes, which could be increased to 30 min depending on patient tolerance. Patients are usually ready for extubation after two or more successful weaning attempts. Healthcare professionals (physicians, nurses, and respiratory therapists) are responsible for providing continuous support by evaluating patients' respiratory efforts during the weaning process. It has been stated that the success of the weaning process increases when nurses are more active, and it is recommended that they take an active role in this process [2].

MV and weaning from MV cause a range of uncomfortable symptoms, such as pain, agitation, sleep deprivation, and anxiety. Unmanaged anxiety stimulates the sympathetic nervous system, causing hyperventilation and respiratory muscle fatigue and resulting in failed weaning attempts [11,12].

Many pharmacological and non-pharmacological techniques manage symptoms observed during mechanical ventilation (MV) and the weaning process. Traditional management strategies primarily rely on antipsychotic, sedative, and analgesic drugs. However, the overuse of these pharmacological agents can lead to various adverse effects, including hemodynamic disturbances, respiratory depression, ileus, prolonged MV, delirium, intestinal dysfunction, and post-traumatic stress disorder (PTSD) [2,13]. Sedation, though commonly used, often addresses only the symptomatic relief of anxiety without targeting the underlying stressors.

Non-pharmacological interventions present valuable alternatives, including music therapy, guided imagery, reflexology, aromatherapy, massage, nature sounds, and animal-assisted therapy. These approaches have demonstrated efficacy in managing anxiety among ICU patients by attenuating stress stimuli and fostering relaxation through synchronizing physiological rhythms, such as respiration and heart rate [14,15]. Compared to pharmacological methods, non-pharmacological interventions are cost-effective, easy to implement, non-invasive, and can support nurses in managing their time more efficiently.

Despite these advantages, there is a need for further research to better understand the impact of non-pharmacological interventions on the MV weaning process. The current evidence base is limited, and a comprehensive examination of these techniques' effectiveness is necessary to optimize clinical practice. This systematic review aims to assess the efficacy of complementary treatment methods, specifically music therapy and reflexology, used by nurses during the weaning of intensive care patients from mechanical ventilation.

Materials and methods

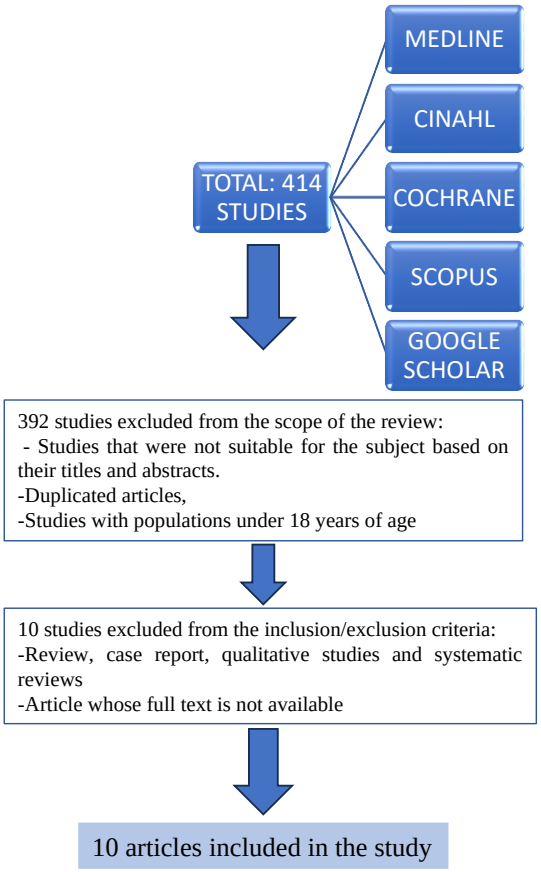
The PRISMA 2020 checklist was used to plan and prepare the research report [17-19]. The literature search, article selection, data extraction, and evaluation of research quality were conducted independently by one researcher and subsequently reviewed by two additional researchers to mitigate the risk of potential bias in our study.

Literature review

This systematic review was conducted to examine the results of studies (randomized controlled trials, case controls, and pilot studies) on complementary treatment methods (music therapy and reflexology) during weaning from mechanical ventilation between January 2010 and June 2023. The MEDLINE, CINAHL, Cochrane Library, Scopus, and Google Scholar search engines were used to determine the sample. Databases were searched using the key terms "weaning from mechanical ventilation and complementary treatment or non-pharmacologic approaches." Within the scope of the publications examined, the searches were also detailed as "weaning from mechanical ventilation and music therapy" and "weaning from mechanical ventilation and reflexology" within the scope of complementary methods applied by nurses. First, the titles and abstracts of the articles were examined. Articles repeated in databases and those conducted in neonatal or pediatric intensive care were excluded. Of the 22 articles determined following the inclusion criteria, those whose full text could not be accessed were excluded. The remaining 10 articles were randomized controlled trials, non-randomized controlled trials, pilot, and randomized prospective trials published in Turkish or English (Figure 1). The literature search was conducted between October 20, 2022, and December

31, 2022, and updated on May 02, 2023, to include the latest publications during the publication process.

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart



Inclusion and exclusion criteria

The Patient/Intervention/Comparison / Outcome / Research Design (PICOS) model was used to formulate the research questions.

P (Population): Adult intensive care patient group

I (Interventions): Use of non-pharmacological approaches for weaning from mechanical ventilation

C (Comparators): Routine maintenance

O (Outcomes): Anxiety, agitation, physiological parameters

S (Study Designs): 6 Randomized Controlled Trials, one non-randomized controlled trial, two pilot studies, and one prospective randomized crossover study.

The selection criteria for research under the PICOS were as follows:

The inclusion criteria were as follows: (1) articles with a sample of adult patients in intensive care, (2) articles published in the field of nursing between 2010 and 2023, and (3) articles for which the full text was available.

The exclusion criteria were as follows: (1) review, validity reliability, case reports, case reports, letters to the editor, and qualitative study design; and (2) articles whose language of publication was not Turkish or English.

Research question

1. Are non-pharmacological approaches used during weaning from ventilators effective for anxiety, stress, and pain levels?
2. What is the effect of non-pharmacological approaches used in the process of weaning from the mechanical ventilator on physiological parameters?

Data extraction, analysis, and quality assessment

As this study is a systematic review, it did not require ethical approval. Systematic reviews analyze previously published data and do not involve direct interactions with human participants. A Data Extraction Form prepared by the investigators was used to identify the characteristics of the included studies when collecting evidence in the current systematic review. Data were collected, including author, year of publication, research aim, intervention, sample size, research designs, evaluation methods, findings, and results. To assess the methodological quality and risk of bias of the studies included in the systematic review, checklists provided by the Joanna Briggs Institute (JBI) were utilized. The Experimental and Quasi-Experimental Research Checklist, validated for Turkish, was employed in this context. The quality assessment consists of 10 items, with each item evaluated as “yes,” “no,” “unclear,” or “not applicable.” A high score on the checklist indicates high methodological quality, although there is no specific cut-off score (Nahcivan & Seçginli, [20]; Hür et al. [21]). The studies reviewed exhibited varying JBI quality scores. Although the majority of studies provided detailed accounts of randomization and blinding processes, several studies were found to have insufficient or absent reporting on these critical methodological aspects. In further support of this, limitations in sample sizes and data deficiencies constrained the generalizability of the results. Consequently, a focus was placed on including studies with a JBI quality score of 6 or higher.

A narrative synthesis method was employed to analyze the data. This approach can combine quantitative and qualitative studies, especially when the results of the experimental studies in a systematic review are too different to be analyzed in a meta-analysis. Given the variability in the outcomes measured across the studies reviewed in this analysis, the findings were presented using the narrative synthesis method.

Results

In this study, ten research articles examining complementary treatment methods that can be applied by nurses during the weaning process from mechanical ventilation were analyzed. The characteristics of the studies are presented in Table 1 under the headings of ‘author/authors (year), aim, intervention, study design and levels of evidence, evaluation method, findings, and conclusions. The studies included in this review employed various designs, predominantly randomized controlled trials, with some pilot studies and non-randomized controlled trials. The variability in study designs and sample sizes may contribute to the heterogeneity of the results. For instance, smaller sample sizes and differing intervention protocols could impact the observed efficacy of the treatments.

The studies included were published between 2010 and 2023. The design type of the studies included in the review was mostly randomized controlled trials (n=6). Two other studies were pilot studies; one was a controlled study without randomization, and the other was a prospective randomized crossover study. The results of the studies analyzed revealed that nurses applied music therapy and reflexology methods during weaning from MV. Our study included 10 studies in which six music and four reflexology therapies were tested.

Table 1: Characteristics of studies using complementary treatment approaches in weaning from mechanical ventilation (n=10)

No	Author(s)	Objective	Int.	Study Design and Levels of Evidence	Sample Size	Evaluation Method	Results	Conclusion
1	Hunter et al. [11]	To determine the effect of music therapy on patients' anxiety levels during the weaning process to evaluate patient/nurse satisfaction with MV weaning trials.	Music	Pilot study The sample received 45-60 minutes of music therapy 3 times a week for 45-60 minutes prior to the allocation trials.	93	Anxiety-related physiological parameters (heart rate and respiratory rate) were measured before and after each music therapy intervention. Satisfaction scale by the patient and the researcher after the separation trials	Patient and nurse satisfaction with the intervention high - Heart and respiratory rates remained within normal values from the beginning to the end of the music therapy. -Investigator assessment of anxiety showed that the patient appeared less anxious after the intervention	Applying music therapy may be effective in mechanical ventilation weaning in patients hospitalized in intensive care units.
2	Aghaie et al. [12]	To examine the effect of nature-based sound therapy on agitation and anxiety during weaning from mechanical ventilation in patients with coronary artery bypass graft.	Nature-Based Music	Randomized Controlled The experimental group closed their eyes for 30 minutes with nature-based sound therapy, such as wind and water flow in a river. -In the control group, the process of wearing headphones and closing their eyes without music for 30 minutes	120	Anxiety: FAS Agitation: RASS Hemodynamic values of the patients in both groups were measured at 20-minute intervals throughout the procedure, immediately after the procedure, and 20 and 30 minutes after extubation. Anxiety and agitation levels were evaluated with simultaneous scales.	The experimental group had significantly lower levels of anxiety and agitation than the control group. The patients' mean systolic and diastolic arterial blood pressure, heart, and respiratory rates in the experimental and control groups showed significant differences (P=0.04).	Nature-based sound therapy may provide an effective method to reduce potential negative hemodynamic responses due to anxiety and agitation during weaning from mechanical ventilation in patients with coronary artery bypass graft.
3	Liang et al. [21]	To examine the effect of patient-selected music interference during weaning from mechanical ventilation.	Music	Prospective randomized crossover The sample was observed for 6 days (3 days with music and 3 days without music). Patients were randomized to the intervention. Music is left to each patient's own choice.	31	On the days the patient played music, physiologic parameters were monitored 30 and 90 minutes before the intervention. On the days when music was not played, it was observed for 90 minutes in the same period. Anxiety was measured with VAS immediately before the intervention and at 30-minute intervals throughout the intervention.	Comparisons between 3 music and 3 non-music days showed significant decreases in respiratory rate and VAS and a significant increase in separation times on music days (P<0.05).	Patient-preferred music playback during daily weaning trials is a simple, low-cost, and potentially beneficial intervention for patients on long-term mechanical ventilation.
4	Kurt and Celik [15]	To examine the effect of nature-based sound therapy on the weaning process from mechanical ventilation of patients hospitalized in the intensive care unit.	Nature-based Music	Randomized Controlled The experimental group closed their eyes for 30 minutes with nature-based sound therapy, such as wind and water flow in a river. -In the control group, the process of wearing headphones and closing their eyes for 30 minutes without music (quiet environment)	64	Pain: FPS Anxiety: MSFS, RASS Arterial blood pressure, heart rate, respiratory rate, oxygen saturation, pain, and anxiety levels were measured and recorded in both groups just before the music and at 10, 20, and 30 min after the separation.	The patients' mean systolic and diastolic arterial blood pressure, heart, and respiratory rates in the experimental and control groups showed significant differences (P=0.04). Pain, agitation, and anxiety levels of the experimental group were found to be lower than the control group.	Nature-based sound therapy applied in the process of weaning surgical patients hospitalized in the intensive care unit from mechanical ventilation support is effective in maintaining arterial blood pressure, heart rate, and respiratory rate within normal limits and reducing pain and anxiety.
5.	Park and Park. [8]	To examine the effects of two different music therapy methods (classical relaxation music versus preferred music intervention) on agitation and anxiety in patients weaned from mechanical ventilation.	Music	Pilot Study Sequence of interventions generated by randomization Half of the sample listened to the music they preferred for the first 30 minutes, followed by a 60-minute rest period and classical relaxation music for the next 30 minutes. - The other half of the sample listened to classical relaxation music for the first 30 minutes, followed by a 60-minute rest period, and then the music they preferred for the next 30 minutes with headphones.	6	Anxiety: STAI and VAS Agitation: RASS Patients in both groups were evaluated with scales before and after the intervention.	Patients' agitation and anxiety levels showed a significant decrease after both the preferred and classical relaxation music interventions. There was no significant difference between the preferred music and the effect of classical relaxation music.	Music interventions focused on patients' preferences or classical relaxation music to enhance relaxation may help reduce agitation and anxiety during the weaning process from mechanical ventilation.
6.	Yadak et al. [22]	To investigate the effect of listening to the Holy Quran in patients during weaning from mechanical ventilation.	Sound therapy/ non-pharmacological treatment	Randomized Controlled -The experimental group was made to listen to the Holy Quran with headphones for 30 minutes. -The control group was allowed to listen with headphones for 30 minutes.	55	Physiologic parameters, such as pulse rate, respiratory rate, systolic and diastolic blood pressures, oxygen saturation, exhaled carbon dioxide, and blood pressure, were measured 5 minutes before and 5 minutes during the application.	Physiologic and clinical parameters were compared between cases and controls, and no significant difference was found.	Listening to the Holy Quran has no negative effect on weaning patients from mechanical ventilation in the intensive care unit.

MV: Mechanical Ventilation, FAS: Face Anxiety Scale, RASS: Richmond Agitation-Sedation Scale, VAS: Visual Analog Scale, FPS: Facial Pain Scale, MSFS: Modified Smiley Face Scale, STAI: State-Trait Anxiety Inventory, ICU: Intensive Care Unit

Table 1: Characteristics of studies using complementary treatment approaches in weaning from mechanical ventilation (n=10)

No	Author	Objective	Int.	Study Design and Levels of Evidence	Sample Size	Evaluation Method	Results	Conclusion
7.	Ebadi et al. [24]	To investigate the efficacy of foot reflexology on physiologic parameters and mechanical ventilation weaning time in patients undergoing open heart surgery	Reflexology	Randomized Controlled 1 hour after admission to the ICU unit - Experimental Group: foot reflexology for 10 minutes on each foot for a total of 20 minutes -Control Group: Routine care -Placebo Group: Simple surface touch without pressure on the heels for 20 min	96	Physiologic parameters: pulse rate, respiratory rate, systolic and diastolic blood pressures, mean arterial pressure, percutaneous oxygen saturation, including monitoring of physiologic indicators. Measured 6 times (immediately after ICU admission, 1 hour after ICU admission, immediately after reflexology, 10 minutes after reflexology, immediately after extubation, and 60 minutes after extubation). Time to weaning from MV was measured. (The time interval between admission to ICU and extubation was considered the time to weaning from ventilation and was measured using a stopwatch).	The study groups did not differ significantly in terms of physiologic parameters (P>0.05). The length of MV weaning time in the experimental group was significantly shorter than in the placebo and control groups (P<0.05).	He demonstrated the efficacy of foot reflexology in shortening the MV weaning time.
8.	Kandemir and Öztekin. [25]	To determine the effects of reflexology on physiological parameters and MV weaning time	Reflexology	Non-randomized Controlled Trial -Experimental Group:20-30 min foot reflexology -Control Group-: Routine care	85	Physiologic parameters (pulse rate, respiratory rate, systolic and diastolic blood pressure, mean arterial pressure, and oxygen saturation) were monitored six times a day. Weaning times from mechanical ventilation were measured.	According to the values obtained before reflexology for the experimental and control groups, pulse rate (P=0.013) and diastolic blood pressure (P=0.021) were significantly higher in the experimental group 5 minutes before reflexology. Patients in the experimental group had lower oxygen saturation values 5 minutes after extubation (P=0.012). However, reflexology did not show a significant change in other physiological parameters, but the time to weaning from mechanical ventilation after reflexology was shorter in the experimental group (P=0.023)	Reflexology has no significant effect on physiologic parameters in patients receiving mechanical ventilation support. It is recommended that weaning from mechanical ventilation be shortened.
9.	Elsayed. [26]	To investigate the effect of foot reflexology on physiological indicators and mechanical ventilation weaning time in open heart surgery patients	Reflexology	Randomized Controlled 1 hour after admission to the ICU unit -Experiment Group: Foot reflexology on each foot for 15-20 minutes -Control Group: Routine care	80	Physiologic parameters: pulse rate, respiratory rate, systolic and diastolic blood pressures, mean arterial pressure, and percutaneous oxygen saturation were monitored. Measured 6 times (immediately after ICU admission, 1 hour after ICU admission, immediately after reflexology, 10 minutes after reflexology, immediately after extubation, and 60 minutes after extubation). MV weaning time was measured with the MV weaning time assessment tool.	There were statistically significant differences between the experimental and control groups regarding all physiologic indicators (P<0.05). Statistically significant differences were also noted in shortening the time to weaning from MV between both groups (P<0.05).	Foot reflexology is an effective method to stabilize physiological indicators and reduce ventilator dependency in patients undergoing open heart surgery.
10.	Allahbakhsian et al. [27]	To investigate the effects of foot reflexology on agitation and MV weaning time in male patients after cardiac surgery	Reflexology	Randomized Controlled(I) - Experiment Group: 30 minutes of foot reflexology massage. - Control Group: Routine care -Placebo Group: 30 minutes of simple surface touch without pressure on the heels	120	Agitation: Before the intervention (Time 1), immediately (Time 2), and 10 minutes after the intervention (Time 3) were assessed using the Richmond Agitation- Sedation Scale. MV weaning time was measured from full consciousness to endotracheal extubation.	Agitation was reduced in all groups from Time 1 to Time 3 (p<0.05); however, the experimental group showed a significantly higher reduction at Time 2 (P<0.001) and Time 3 (P<0.001). Furthermore, extubation time was significantly shorter in the experimental group (P<0.01).	Foot reflexology can be considered as a nursing intervention to facilitate the process of weaning from MV.

MV: Mechanical Ventilation, FAS: Face Anxiety Scale, RASS: Richmond Agitation-Sedation Scale, VAS: Visual Analog Scale, FPS: Facial Pain Scale, MSFS: Modified Smiley Face Scale, STAI: State-Trait Anxiety Inventory, ICU: Intensive Care Unit

Findings of studies applying music therapy

In studies examining the effect of music therapy, one group of patients was generally allowed to listen to music, while the other group was allowed to listen to headphones in bed [12,15,22]. Although the duration, frequency, and timing of music therapy varied between studies, music was applied to patients for at least 30 min a day in all studies. In the study conducted by Liang et al. [23], we attempted to determine the effect of the sample on the separation process by playing music for some days and not playing music for some days. The results indicate that while music therapy generally reduced agitation and anxiety, the effectiveness varied across studies. Differences in the duration, frequency, and type of music therapy and the sample sizes might account for this variability. Further analysis is needed to determine the optimal conditions under which music therapy is most effective.

In the studies in this review, music therapy was performed using nature-based sounds, classical relaxation music, and music genres preferred by patients. In the study conducted by Park and Park [8], the effect of the music therapy method was examined by comparing classical relaxation music with the music style preferred by patients leaving MV. While 206 patients underwent music therapy, the total sample size consisted of 318 patients.

In a few studies, the Richmond Agitation Sedation Scale (RASS), a 10-point scale with four agitation levels (combative, calm and alert, and non-arousable), was used as a measure of sedation efficacy. According to the results of the studies, agitation

and anxiety levels were found to be lower in the experimental groups compared to the control group [8,11,12,15,23]. In these studies, the anxiety levels of the patients were evaluated using the Facial Anxiety Scale and State Anxiety Scale, while pain levels were determined using tools such as the Visual Analog Scale, Facial Pain Scale, and Modified Smiley Scale.

Anxiety, pain, and agitation levels of the patients were evaluated before music therapy, at certain intervals during the procedure, and once or several times at different times after the procedure. Simultaneously, physiological parameters were monitored and recorded, such as arterial blood pressure, heart rate, respiratory rate, oxygen saturation, pulse rate, respiratory rate, and systolic and diastolic blood pressures. Evidence suggests that music can reduce physiological anxiety symptoms in patients receiving MV, such as respiratory rate, heart rate, and blood pressure. In several studies, music intervention groups significantly reduced respiratory and heart rates [8,11,12,15,23]. However, in a study conducted by Yadak et al. [22], no significant difference was found between the case and control groups regarding physiological and clinical parameters.

Reflexology research findings

Studies in which reflexology intervention was applied examined the effects of foot reflexology on physiological parameters and MV weaning time in patients after cardiac surgery. When the studies were examined, foot reflexology was applied to a group of patients for an average of 15 min on each foot, while routine care was provided to the patients in the control group. In the studies by Allahbakhhsian et al. [27] and Ebadi et al. [24], a control group was formed, and the results were compared by applying simple surface touch without applying pressure equal to the reflexology time. In this systematic review, the total number of patients who underwent reflexology was 156 and 155, respectively, and the sample size of the placebo group was 70. Similarly, reflexology was found to shorten the time to weaning from mechanical ventilation in several studies. However, the inconsistency in physiological parameter outcomes suggests that additional factors, such as the exact reflexology techniques used or variations in patient characteristics, may influence the results. It is noteworthy to consider these factors when interpreting the overall effectiveness of reflexology.

Measured physiological indicators that were regularly monitored included pulse rate, respiratory rate, systolic and diastolic blood pressures, mean arterial pressure, and percutaneous oxygen saturation. Physiological parameters were monitored and compared periodically after ICU admission, as well as before and after reflexology application. In a study by Allahbakhhsian et al. [28], in addition to physiological parameters, agitation levels in patients were measured using the Richmond Agitation-Sedation Scale, and the duration of MV weaning was examined. The duration of MV weaning was recorded in hours and days as the interval between ICU admission and extubation.

A common and robust finding of these studies is the shortening of the weaning time from mechanical ventilation following reflexology application, albeit the results of the monitored physiological parameters varied between the groups in the sample. The variability in methodological quality among the studies, including differences in randomization and blinding, as well as sample size limitations, highlights the need for cautious interpretation of the findings. Studies with higher methodological quality and larger sample sizes tend to provide more reliable results, but further research is necessary to confirm these findings across different settings and populations.

In a study by Ebadi et al. [24], the study groups did not differ significantly in terms of physiological parameters. In addition, Kandemir and Oztekin [25] found that the pulse rate (P=0.013) and diastolic blood pressure (P=0.021) of patients in the experimental group 5 min before reflexology were significantly higher than the values obtained before reflexology for the experimental and control groups. In conclusion, most research findings suggest that reflexology does not have a significant effect on physiological parameters in patients receiving mechanical ventilation support. However, Elsayed et al. [26] found a statistically significant decrease in pulse rate, respiratory rate, systolic and diastolic blood pressures, and mean arterial pressure in the foot reflexology group compared with the control group, while a statistically significant increase was found in percutaneous oxygen saturation.

Discussion

In this systematic review, evidence was presented to support the use of music therapy and reflexology in the management of symptoms such as anxiety, agitation, and pain that negatively affect adult intensive care patients during MV weaning. When the literature is examined, the findings of our study are supported by the findings of other studies that systematically examined the effect of music therapy in patients receiving MV support in intensive care [13,16,26]. However, this review focused on nursing research examining the effect of non-pharmacological methods on weaning from MV. Although there is a need to increase the number of studies on the process of weaning from MV, it is seen that the music therapy method examined in this review is an effective method in the process of mechanical ventilation weaning in patients hospitalized in intensive care.

The types of music utilized in the studies, as well as patient preferences and the duration, frequency, and methods of music therapy application, vary considerably. Consequently, there is no consensus or established standard protocol in the literature regarding the specific effects of music types, duration, frequency, or timing.

A review of the studies in the literature evaluating symptoms such as anxiety, agitation, and pain seen in the process of weaning from MV shows that most studies used assessment tools based on self-report or nurse observations. Some of these tools are the Visual Analog Scale (VAS-A), Facial Anxiety Scale (FAS), Spielberger State-Trait Anxiety Scale (STAI), and Richmond Agitation Sedation Scale (RASS). However, the fact that these tools are based on self-report and sedation is applied in most intensive care unit patients makes it difficult to evaluate their reliability.

Kurt and Celik [15] evaluated the pain symptoms in addition to anxiety and agitation different from other studies and concluded that it is an effective method in reducing the pain level. There is a need for further studies in which the subjective pain symptom is evaluated with different scales to strengthen this research finding.

Physiologic parameters such as respiratory rate, heart rate, and blood pressure change in symptoms that negatively affect patient comfort, such as pain and anxiety. These parameters are continuously and closely monitored in patients receiving MV support. Upon reviewing the literature, research findings indicate that music therapy significantly reduces respiratory rate, heart rate, and blood pressure in patients receiving mechanical ventilation support. The literature further reveals a consistent downward trend in heart rate during and after music intervention. In all the studies analyzed in this review, the physiological parameters of the patients in the intervention group were found to be lower than those in the control groups.

Reflexology, a non-invasive and easy-to-apply intervention, regulates autonomic nervous system activity and physiological responses through targeted massage, promoting relaxation by alleviating anxiety [29,30]. The common finding of the reflexology studies included in this review is the shortening of the duration of separation from mechanical ventilation after reflexology application. The mechanism of action of reflexology in shortening this time is not fully understood, and there is much debate on this issue. In addition to this, only a limited number of studies have been conducted on the effectiveness of foot reflexology in reducing the time to weaning from mechanical ventilation. Notably, the samples in these studies have been restricted exclusively to cardiac surgery patients.

Three of the four reflexology studies included in the review reported that reflexology had no significant effect on the physiological parameters of patients receiving mechanical ventilation support. In a study by Elsayed et al. [26], statistically significant differences were observed across all physiological indicators in the group receiving foot reflexology during the mechanical ventilation weaning period compared to the control group. Reflexology was reported to be an effective method for stabilizing physiological parameters and reducing ventilator dependence. Additionally, it was noted that applying reflexology to the foot, hand, and ear led to decreased heart rate, systolic and diastolic blood pressure, and respiratory rate in mechanically ventilated patients. The study concluded that, despite these findings, the available literature on reflexology remains limited, and further research with larger sample sizes and more robust study designs is necessary [31]. Reflexology studies revealed mixed results, which may be attributed to variability in study designs, including differences in randomization and blinding and differing participant characteristics such as age and health status. Additionally, the protocols for administering reflexology varied, with differences in treatment duration, frequency, and techniques. These inconsistencies could have influenced the varying degrees of effectiveness observed across studies.

Limitations

This systematic review included published studies whose full text was available and whose language of publication was English or Turkish. Abstracts and unpublished theses were not included in this review. Many studies had small sample sizes. There is a need for randomized clinical trials that are sufficiently powered to answer the questions posed and for consistent protocols to compare findings across studies.

Conclusion

The results of this study indicate that music therapy is a valuable intervention during mechanical ventilator weaning, effectively managing symptoms such as anxiety, agitation, and pain. This method helps maintain physiological parameters within normal ranges. Additionally, reflexology has been shown to reduce the duration of mechanical ventilation weaning, addressing the challenge of prolonged ventilation for both patients and healthcare professionals. Given these findings, future research should focus on expanding non-pharmacological methods like music therapy and reflexology in the weaning process. Studies should include a wider range of interventions, larger and more diverse sample sizes, and robust study designs to validate these methods. Developing standardized protocols and exploring these interventions' mechanisms and broader patient outcomes will also enhance their clinical application and effectiveness.

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https://doi.org/10.28982/josam.8098

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Case report
https://jsurgmed.com/

The salvage of nipple-areola complex using dimethyl sulfoxide

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2025 August 8

Abstract

Nipple-areolar complex (NAC) necrosis is one of the most perilous minor complications in breast surgery. It is more common following mastectomy and less common after reduction mammoplasty. In the case study presented below, we share our approach and experience in NAC salvage following superomedial pedicle reduction mammoplasty. The application of dimethyl sulfoxide (DMSO) notably improved perfusion and played a crucial role in the salvage of NAC.

Keywords: mammoplasty, breast reduction, nipple-areola complex, salvage

Introduction

Breast reduction surgery, one of the most frequently performed plastic surgery operations, not only increases self-esteem but also relieves the burden on women suffering from hypertrophic breasts [1]. Patients with hypertrophic breasts often complain of shoulder, neck, and back pain, excessive sweating, maceration, and mycosis developing in the inframammary fold, especially in the summertime [2]. Although various safe techniques have been described for the reduction of large breasts, numbness in the NAC area can still result, in addition to insufficient breastfeeding as well as necrosis and total loss. This paper describes the management of unilateral nipple-areola complex (NAC) ischemia following a reduction mammoplasty operation in a 33-year-old female patient – an issue that became apparent on the second postoperative day, and which was satisfactorily resolved using topical Dimethyl Sulfoxide (DMSO).

How to cite: Ural A, Karaduman H, Halbony H. The salvage of nipple-areola complex using dimethyl sulfoxide. J Surg Med. 2025;9(8):143-145.

Case presentation

Our patient presented at our hospital's Plastic Surgery Clinic, complaining about her large, pendular breasts. Comprehensive information was provided to the patient, who then signed the informed consent form. The patient has previously given birth once and has also breastfed. She is an active smoker and was advised to quit smoking three weeks before the operation. Her body mass index (BMI) was 30.4. The patient's nipple position was 33 cm bilaterally (Figure 1), and we planned to relocate her nipples to a position 21 cm from the sternum's manubrium using a superomedial pedicle reduction mammoplasty.

On the first postoperative day, her physical examination and NAC circulation appeared healthy. However, on the second postoperative day, an ischemic appearance developed in the left nipple-areolar complex (Figure 2). We observed a diminished left NAC circulation, with the area appearing dusky and pale. The capillary refill test affirmed the impaired circulation. Further signs of compromised circulation, such as bullous formation and color change, were noted. Shortly after identifying the diminished circulation, all peri-areolar sutures were removed, and the pedicle was fully released to ensure there was no tension or kinking (Figure 3). Gauze soaked in DMSO (Botafarma, Ankara) was applied three times daily for 10 days. The patient was closely monitored during this period, with office examinations and evaluations of videos she sent via telemedicine both day and night. Enoxaparin of 6000 IU was also administered subcutaneously once daily for 1 week.

By the end of the week, both capillary refill time and NAC viability had noticeably improved. Staged delayed sutures were performed at our outpatient clinic. The lateral two-thirds of the area was sutured on the 10th postoperative day, with the remainder sutured in the second postoperative week. With diligent follow-up, the ischemic and congested appearance of the NAC had successfully resolved by the end of the second week (Figure 4). By the first postoperative month, NAC healing and aesthetic appearance had significantly improved (Figure 5). By the third postoperative month, the salvaged NAC and overall appearance of the breast tissue were reasonably acceptable, which the patient expressed satisfaction with (Figure 6). We advised tattooing the inferior border of the NAC for enhanced aesthetic outcomes, but the patient chose not to pursue this.

Figure 1: Preoperative photo of the patient

Figure 2: Impaired circulation, congested and dusky NAC

Figure 3: All the periareolar sutures were removed

Figure 4: NAC was salvaged successfully at the end of the second week

Figure 5: Healed NAC on postoperative 1st month

Figure 6: The salvaged NAC appearance was reasonably satisfying in the postoperative 3rd month.

Discussion

Reduction mammoplasty is associated with several risk factors, which can be categorized into major and minor complications. Major complications include thromboembolic events, surgical site infections, abscess formation, bleeding, and infected seromas. Conversely, minor complications encompass wound dehiscence, NAC necrosis, skin necrosis, hematoma, seroma, hypertrophic scarring, and keloid formation [3].

Xiong reported that NAC necrosis, at 5.56%, was the second most common complication of reduction mammoplasty, following wound dehiscence for superior and superomedial pedicles [4]. Risk factors correlated with an increased risk of NAC necrosis include a high BMI, resection weight of 650 g or more,

diabetes, a preoperative-postoperative SN-N distance (i.e., a pedicle length of over 10 cm), and smoking. Cessation of smoking more than four weeks before the operation may potentially reduce this risk [4]. In our case, the patient had four of these five mentioned risk factors. S. Polotto et al. found that partial NAC necrosis was the third most common minor complication, at 5.55%, however, their study primarily involved inferior pedicle and Thorek procedures [3].

DMSO, originally used as an organic solvent, was first discovered in the 19th century by the German chemical industry [5]. DMSO is a colorless liquid that has a highly polar group and two non-polar groups, enabling it to dissolve in both aqueous and non-aqueous solutions. DMSO was found to have local anti-inflammatory effects and was used in the treatment of cutaneous scleroderma, digital ischemia, keloids, and hypertrophic scars [5]. Over 50 years ago, DMSO was approved by the United States Food and Drug Administration for use in the treatment of interstitial cystitis [6]. Rand-Luby et al. demonstrated that the application of topical 60% DMSO to human mastectomy flaps decreased the ischemic area by approximately 63% [7]. The application of DMSO also reduces skin flap necrosis and improves the overall surgical flap outcomes [8]. The exact mechanism of action is not entirely known, but DMSO stimulates histamine release by mast cells and increases prostaglandin E1 production, inducing vasodilation. Furthermore, as a hydroxyl-inactivating compound, DMSO scavenges free radical species, reducing ischemia-reperfusion injury [7].

The topical application of DMSO is associated with side effects, most of which are tolerable to patients. These may include localized erythema, edema, itching, and a garlic-like odor in the breath [7]. Additionally, the oral use of DMSO can cause side effects, including nausea, vomiting, dizziness, constipation, and diarrhea. DMSO can amplify the effect of certain medications like blood thinners, steroids, and sedatives, possibly leading to serious health complications. In this particular case, initial venous congestion and stasis were attributed to patient characteristics and increased edema, which might have further led to an impairment of arterial circulation, resulting in this ischemia. To the best of our knowledge, the release of sutures coupled with the vasodilatory and anti-inflammatory benefits of DMSO were the key factors in salvaging the left NAC in this case.

Conclusion

In conclusion, this case demonstrates the safety and efficacy of DMSO in alleviating and treating NAC ischemia, as well as preventing necrosis following reduction mammoplasty. Based on the promising results from both this case and the literature, we believe DMSO can be safely used as a supplemental agent in similar situations, as it provides beneficial effects and enhances NAC circulation.

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J Surg Med. 2025;9(8):146-148.
https://doi.org/10.28982/josam.8099

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Case report
https://jsurgmed.com/

Idiopathic (benign) intracranial hypertension-induced sudden hearing loss: A rare case

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2025 August 11

Abstract

Sudden hearing loss (SHL) is a clinical condition characterized by the acute onset of sensorineural hearing loss. Although many etiological factors have been reported, it is primarily idiopathic. Idiopathic Intracranial Hypertension (IIH) is a syndrome that presents signs of increased intracranial pressure in the absence of any intracranial lesion, meningeal inflammation, or venous obstruction. In our case, a patient diagnosed with SHL presented with hearing loss and visual field constriction. An investigation into etiological factors identified IIH. Although rare, IIH can cause SHL. It is crucial to consider this possibility during the diagnostic process and carefully plan the treatment based on the potential etiology.

Keywords: sudden hearing loss, pseudotumor cerebri, ıdiopathic, benign ıntracranial hypertension, ıntracranial causes of sudden hearing loss, sensorineural hearing loss

Introduction

Idiopathic intracranial hypertension (IIH) is a syndrome that presents with symptoms and signs of increased intracranial pressure in the absence of intracranial mass lesions, meningeal inflammation, or venous obstruction [1,2]. The incidence of IIH is 0.9 per 100,000, with a higher prevalence amongst obese women of childbearing age. Sudden hearing loss (SHL) is characterized as a sensorineural hearing loss of a minimum of 30 dB at three consecutive frequencies occurring within 72 h. This condition requires prompt diagnosis and treatment [3,4].

In this case report, informed consent was obtained from the patient, with their information kept confidential.

Case presentation

A 56-year-old female patient presented at an outpatient clinic with complaints of hearing loss, tinnitus, and headaches in both ears that had begun 3 days prior. The patient had no history of systemic disease, trauma, or acute infections, except for hyperlipidemia and diabetes mellitus.

The otoscopic examination yielded normal results. The audiological evaluation revealed severe sensorineural hearing loss, with thresholds of 85/68 dB in the right ear and 86/69 dB in the left. The patient was diagnosed with sudden hearing loss (SHL) and began treatment with 1 mg/kg intravenous prednisolone. Informed consent was obtained. The patient continued her oral medications, which included metformin, gliclazide, and pitavastatin, for the management of diabetes mellitus and hyperlipidemia.

The patient was referred to neurology due to headaches. A mini-mental state examination was conducted, which came back normal and the patient was found to be alert and cooperative. Fundoscopy revealed visual field constriction and enlarged blind spots, thus leading to a referral to ophthalmology. An examination by the ophthalmologist showed visual field constriction in the left eye and swelling of the optic nerve. Thyroid function tests, B12, folate, sedimentation, and homocysteine levels were found to be within the normal range.

A radiological examination, which included contrast-enhanced temporal, cranial, and orbital MRI, was performed. No intracranial mass lesion or retrocochlear pathology was detected in the cranial and temporal contrast-enhanced MRI. The sagittal sections of the orbital MRI revealed increased tortuosity of the bilateral optic nerves. Cranial MR venography and Visual Evoked Potential (VEP) were conducted to confirm the increased intracranial pressure. The MR venography showed increased intracranial pressure, while VEP reported normal bilateral P100 latencies and amplitudes. These findings led to the conclusion that the sudden hearing loss and visual impairment in the right eye were caused by the increased intracranial pressure. The patient was subsequently transferred to the neurology department for further investigation and treatment of IIH. A lumbar puncture was carried out to reduce intracranial pressure and collect cerebrospinal fluid (CSF) for Anti-myelin Oligodendrocyte Glycoprotein IgG (MOG-IgG) testing. However, the patient continued to experience headaches, visual disturbances, and hearing loss, necessitating an adjustment in medical treatment to diazoxide 250 mg and topiramate 25 mg. The patient was then discharged.

A behind-the-ear hearing aid was prescribed for severe bilateral sensorineural hearing loss. However, even after three months of use, the patient-derived no benefit from the hearing aid, necessitating a cochlear implant procedure at our clinic.

Discussion

SHL is defined as sensorineural hearing loss of at least 30 dB across at least three consecutive frequencies, occurring within three days or less [4,5]. SHL affects both genders equally, primarily between the ages of 30–60, and accounts for 1% of all sensorineural hearing losses. The annual incidence of SHL is estimated to be between 5 and 20 cases per 100,000 people [6]. However, the actual incidence may be higher due to the low hospital admission rate associated with patients demonstrating a spontaneous recovery tendency. SHL is typically unilateral, affecting one ear in 90% of cases. In an estimated 80–90% of SHL cases, no identifiable cause can be found, and these cases are termed “idiopathic sudden hearing loss.” Recognizable causes of SHL include infections, neoplasms, vascular diseases, trauma, labyrinthine membrane ruptures, pharmacological toxicity, immunological disorders, and, rarely, neurological diseases [7].

Corticosteroids are the most commonly used drugs in the treatment of idiopathic SHL. Prednisolone is typically started with an oral dose of 1 mg/kg/day and gradually reduced [8]. If a cause is identified for SHL, treatment should be planned accordingly.

IIH is typically a self-limiting clinical condition. Although the etiology remains unknown, various mechanisms have been proposed. Reports suggest that the increase in intracranial pressure is a result of an escalation in cerebral blood flow, cerebral blood volume, and CSF production. This leads to compromised cerebral microcirculation and the development of intracellular or extracellular edema [9,10].

IIH is common in obese women of childbearing age, with a prevalence of 0.9 per 100,000 in the general population. The female/male ratio varies between 4.3/1 and 8/1. Female gender and obesity are major risk factors for IIH [9,10]. IIH has also been reported during pregnancy; menstrual disorders; antibiotic and contraceptive use; iron deficiency anemia; Behçet’s disease; systemic lupus erythematosus; protein C and S deficiency; antiphospholipid antibody syndrome; Addison’s disease; hypoparathyroidism; endocrine disorders (such as obesity); hypervitaminosis A (due to excessive liver consumption);the use of isotretinoin, synthetic growth hormone, and tetracycline; and steroid withdrawal [10].

Clinically, IIH manifests with symptoms such as headaches, visual loss, pulsatile tinnitus, and diplopia. Additional minor symptoms may include neck pain, paresthesia, arthralgia, and ataxia.

It is estimated that approximately 70% of IIH patients experience visual disturbances. Serial visual field testing holds significant importance in monitoring optic nerve function. Optic nerve compression resulting from increased CSF pressure can lead to visual disturbances [11]. Papilledema represents the most critical finding. Other than sixth cranial nerve palsy, neurological examination findings are typically normal.

The vestibulocochlear nerve, similar to the optic nerve, is also susceptible to compression, which explains the hearing and balance symptoms displayed by patients with IIH [11].

Unilateral tinnitus is one of the earliest symptoms reported by 70% of patients with IIH. Therefore, it is important to include IIH in the differential diagnosis for patients presenting with tinnitus. In IIH, tinnitus is believed to result from pressure exerted by brain structures on the venous sinuses, disrupting laminar blood flow and converting it into turbulent flow. This is perceived as pulsatile tinnitus in one or both ears [12].

A significant amount of literature has demonstrated that low-frequency hearing loss is more prevalent in patients with IIH. It is believed that the cause of hearing loss in IIH is due to the transmission of elevated intracranial pressure to the perilymph via the cochlear aqueduct. Rarely, IIH patients may also present with

symptoms typical of endolymphatic hydrops such as vertigo, hearing loss, tinnitus, and aural fullness. The cause of these symptoms correlates to the increase in fluid pressure (both endolymph and perilymph) in the inner ear, proportional to the increase in intracranial pressure. Notably, these symptoms tend to improve after the normalization of CSF pressure [13].

To accurately diagnose IIH, it is necessary to consider the patient's history, including medication use, carry out ophthalmological and neurological examinations, measure CSF pressure, utilize neuroimaging to confirm the presence of normal or small ventricles and establish that no mass lesion is causing increased intracranial pressure. Radiologically, normal or small ventricles, as well as normal CSF composition, are characteristic features of this condition.

The principal aim of medical treatment is to decrease intracranial pressure. Carbonic anhydrase inhibitors (CAIs), often employed for this purpose, reduce CSF pressure by lessening CSF secretion from the choroid plexus. This process requires carbonic anhydrase for CO_2 hydration in active CSF secretion. CAIs act by blocking the dehydration of carbonic acid into water and CO_2. There is not an ideal dosage, and it is adjusted according to the patient's symptoms and observations. Typically, treatment commences with a dosage of 0.5–1 g/day, which is progressively increased until the patient's symptoms improve and the dosage is tolerated [14].

Topiramate, a partial CAI, has gradually found use in the off-label treatment of IIH, either as an adjunct or an alternative to CAIs, owing to its headache-reducing and weight-loss effects. Alongside CAIs, furosemide may be incorporated in IIH treatment to leverage its diuretic properties. Furosemide (20–100 mg/day) can also diminish CSF secretion from the choroid plexus [14].

The role of corticosteroids in the treatment of IIH is controversial. While they are sometimes used in IIH treatment, both their usage and subsequent withdrawal can potentially exacerbate the disease. Surgical treatments are considered for IIH cases that are unresponsive to medical treatment. Options for surgical intervention in IIH include lumboperitoneal and ventriculoperitoneal shunt procedures, optic nerve sheath fenestration (ONSF), bariatric surgery, and venous sinus stenting [14].

The pathogenesis of IIH remains unclear. Reasons why the disease follows a benign course in some patients while displaying rapid progression in others are still unknown. At present, no definitive treatment for IIH exists. Despite surgical treatments being considered when medical interventions fail, the high rate of complications necessitates caution when considering these options. Current research is exploring the efficacy of treating venous sinus disease and endovascular stenting in the context of IIH.

Conclusion

In conclusion, the etiology of SHL, tinnitus, and accompanying left eye visual field reduction in this case was identified as IIH. Treatment was planned accordingly. The CSF pressure was reduced by lumbar puncture, and severe bilateral hearing loss was managed with cochlear implantation. The hearing thresholds improved from 85/68 dB to 86/69 dB in audiological testing. When dealing with cases of SHL, IIH should be taken into consideration. Treatment should be planned according to the identified etiology, as demonstrated in this case.

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