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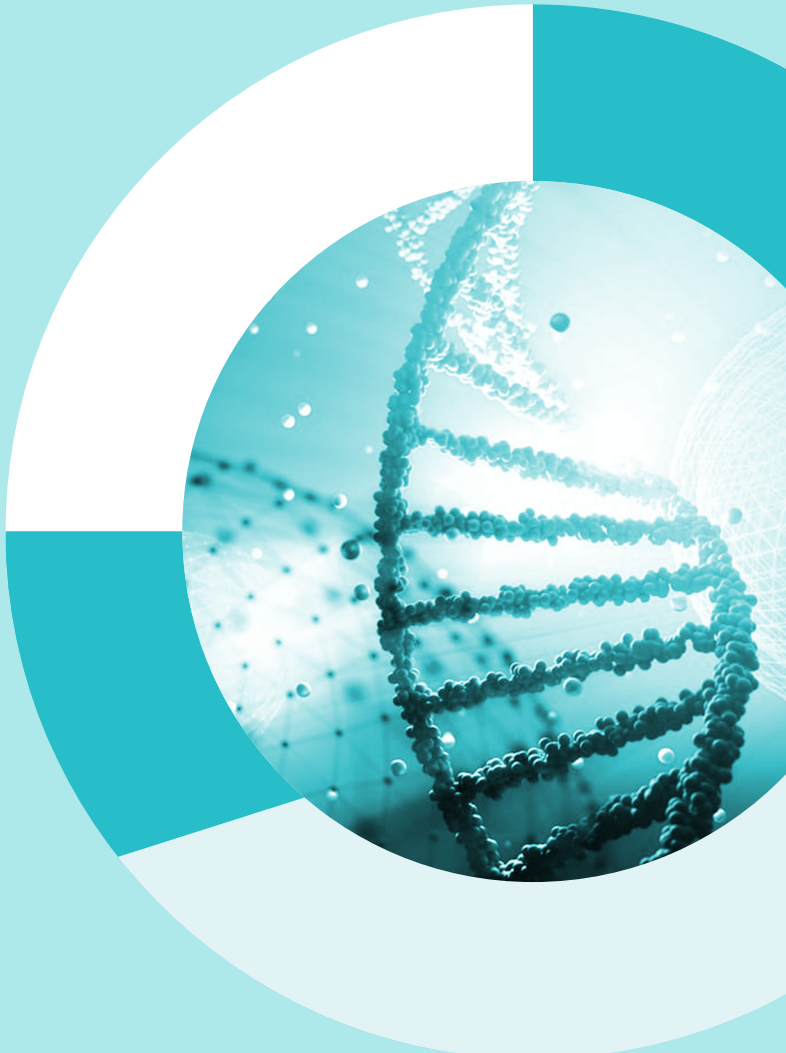

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CONTENTS

REVIEW

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Current Approaches in Pulp Capping: A Review

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Abstract

The aim of this review article was to evaluate the effects of different materials such as calcium hydroxide, mineral trioxide aggregate, bioceramics, biodentine, endosequence root repair material, light cured tricalcium silicate cement used for maintaining the vitality of the pulp in direct and indirect pulp capping.

Keywords: Pulp capping materials, MTA, calcium hydroxide, biodentine, bioceramics

INTRODUCTION

The purpose of pulp treatments after pulp perforation is to ensure that the pulp tissue recovers and maintains its vitality and functionality. Vital pulp treatment procedures involve the application of protective materials directly or indirectly on to the pulp after eliminating local irritants.[1,2] In vital pulp treatment techniques, the aim of the direct pulp capping is to place a medicament over the exposed pulp surface and stimulate reparative dentin formation and healing by inducing odontoblast-like cells.[3]

There are 3 vital factors for the success of vital pulp treatments:

1) Ensuring the control of infection by removing harmful elements from the environment,

2) Stimulation of pulp dentinogenic response by applying a biomaterial,

3) Preventing bacterial microleakages by forming a good plug/closure.[3]

Pulp capping: Vital pulp treatment is applied to teeth which have been traumatized (malocclusion, attrition, abrasion, erosion, mechanical trauma) or have deep caries lesions in order to maintain pulp vitality. The most applied vital pulp treatment procedure is pulp capping.[1]

Indirect pulp capping: During indirect treatment procedures, it is necessary to avoid excessive approaches and secondary irritations which may endanger the vitality, function and health of the tooth. Pulp perforations which may occur during the cavity preparation, especially during the complete removal of deep caries, result in prolongation of the treatment and adversely affect the chance of recovery.[4]

Indirect pulp capping is a complex treatment method in teeth with deep carious lesions, in which the remaining dentin tissue is covered with a biocompatible material in order to prevent pulp exposure which may occur during mechanical trauma or caries removal. Indirect pulp treatment is applied in the presence of a deep caries lesion which is close to the pulp, when there is no pulp degeneration symptoms.[5] During the caries removal process, the affected dentin (firm but colored dentin) in the area adjacent to the pulp is not removed.[6] The tooth is then restored with a material which can prevent microleakages.[5]

Indications for Indirect Pulp Capping

There should be no spontaneous pain in the tooth. It may just be sensitive to cold. Radiographic examination should not reveal any apical pathology. There should be no pain on percussion and palpation. The vitality of the tooth should be determined by using an electrical pulp test.[6]

Expected Results in Indirect Pulp Capping Treatment

1. Neutralization: Hardening of acidic, infected, softened dentin with a decrease in caries microflora.

2. Protecting the pulp by reducing inflammation and improving blood circulation.

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3. Stimulation of fibroblasts, undifferentiated mesenchymal cells and odontoblasts.

4. Maintaining the vitality of the pulp.[4]

Direct Pulp Capping

The aim of this treatment in deep caries is to preserve the pulp tissue in a healthy way. In cases where the pulp has not lost its dentin stimulating factor and is not infected, perforated or injured by trauma or during cavity preparation, the process of stimulating the pulp-dentin complex and promoting the repair of dentin by covering it with a biocompatible chemical is called "Direct pulp capping". It is a form of treatment mostly applied to permanent teeth.[6]

Direct Pulp Capping Indications

There should be no spontaneous pain in the tooth. The tooth should respond normally to thermal tests and it has to be vital. The tooth should not be painful on percussion and palpation. No apical pathology should be seen on radiographic examination. The size of the exposure area should be as large as the needle tip (less than 0.5 mm in diameter). Exposure of the pulp should occur without trauma. If pulp exposure occurs due to trauma, treatment should be made in less than 24 hours after exposure and the exposed area should be less than 0.5 mm. Bleeding in the perforated area should be under control within 3-5 minutes. The exposed area should be uncontaminated and dry. Tissue damage in the tooth should be at a level which can be restored after vital pulp treatment and a hermetic seal should be provided in the cavity.[6]

History of Materials Used in Direct Pulp Capping

It was reported that the first pulp capping was performed by Pfaff in 1756 using "gold foil".[7,8] Since then, different kinds of materials have been recommended to be used in direct pulp capping. In 1930, Hermann reported that calcium hydroxide was an effective agent in repairing the exposed pulp surface. Long-term studies have pointed out some drawbacks of calcium hydroxide and it is being replaced by new materials at present.[6-8]

Properties of pulp capping materials:

The materials used in the treatment of direct and indirect pulp capping must have some common properties:

1. Stimulate reparative dentin and should be tissue friendly,

2. Should not irritate the pulp, the effect on the pulp should be superficial and the pulp should be able to maintain its vitality,

3. Bactericidal or bacteriostatic. They must have an antiseptic effect,

4. Show alkaline reaction,

5. Neutralize the acids due to caries,

6. pH of the materials should be equal to the pH of the pulp,

7. Be able to bond to dentin,

8. Be able to bond to the restorative material,

9. Must be able to withstand the forces during and after the restoration,

10. Must be sterile,

11. Should be radiopaque,

12. Should not allow bacteria to pass through into pulp,

13. Should not have any harmful effects on human body or in the surrounding area locally.[4,8]

Materials Used in Pulp Capping

Pastes Containing Calcium Hydroxide

Calcium hydroxide has been used in dentistry since the 1920s and is a strong base material with a high pH of 12.[9] It can dissolve in water in small amounts by releasing Ca^{2+} and OH^- ions. The high pH caused by the OH^- ions provides an excellent antimicrobial effect and prevents the penetration of bacteria into the pulp. In addition, high pH causes irritation in the pulp tissue and creates a superficial 3-layered necrosis area on the exposed pulp surface. It also stimulates the formation of mineralization against this necrotic area. It also provides calcium which will be a source of mineralization with the Ca^{2+} it contains.[9]

The common disadvantages of calcium hydroxide are its weak dentine adhesion, mechanical instability (low mechanical resistance), dissolution in oral fluids over time (1-2 years), deterioration of its structure after acid etching, presence of multiple tunnels in repair dentin, increased inflammation in clinical use and its toxic effect on pulp cells. These adversely affect the long-term success of the treatment. The dissolution of calcium hydroxide over time causes microleakages in the restoration. Thus, bacteria can reach the pulp and pulp necrosis occurs.[6,10]

Zinc Oxide Eugenol Cements

Zinc oxide eugenol is a sedative and pain-relieving material that, when applied to dentin, reduces the metabolism of microorganisms and limits the diffusion of toxic products to the pulp, thereby eliminating the signs of pulpal inflammation. It is frequently used in dentin cavities due to its effectiveness against bacterial leakage.[11]

Additionally, Zander and Glass[12], suggested zinc oxide eugenol for use in direct pulp capping. However, chronic inflammation, failure of pulp healing and dentin bridge formation have been observed.[12]

Adhesive Systems

Theoretically, primers of self-adhesive systems decalcify the inorganic structure and simultaneously prevent the precipitation of dried demineralized dentin by infiltrating the collagen fibrils. Self-adhesive systems prevent microleakages between the restoration and the tooth. Studies report that the presence of bacteria in the pulpal healing, cavity walls or pulp chamber cause failures. If microleakages can be prevented and the presence of bacteria can be controlled, the pulp can heal on its own.[6,10]

Glass Ionomer and Resin Modified Glass Ionomer Cements

It is used in indirect pulp coatings due to its tight sealing (antimicrobial property), bonding and biocompatibility to dentin, and its fluoride release effect. Its main disadvantages are being cytotoxic to pulp tissues, poor physical properties, high solubility and slow hardening. Due to its cytotoxicity, it causes chronic inflammation and wide necrotic zones in the pulp.[6]

Polycarboxylate Cements

When this cement is used together with potassium nitrate (KNO_3), a desensitizing agent, it can be used as an effective liner or temporary cement in deep caries lesions. However, its antibacterial effect and dentin bridge formation is insufficient. It can chemically bond to tooth structures.[6]

Calcium Hydroxide

Soluble Calcium Hydroxide

In the past, calcium oxide powder was applied directly onto the pulp tissue and the formation of calcium hydroxide was observed as a result of the contact of the powder with the pulpal fluid. However, this practice does not continue today. One study which was carried out by Eleazer et al.[13], has shown that an infectious response develops in the pulp with the direct application of calcium hydroxide powder. Komabayashi et al.[7] stated that, instead of calcium hydroxide powder, paste forms of calcium hydroxide powder maybe used for pulp capping. Some disadvantages of soluble calcium hydroxide have been reported such as; incomplete hardening, resorption over time, and porosities in the newly formed dentin which may cause microleakages.[7]

Calcium Hydroxide Cement

Due to the disadvantages of soluble calcium hydroxide [$Ca(OH)_2$] described above, cement-type calcium hydroxide was developed and has been frequently used in clinical practice since the 1960s. The trade name of the most popular cement is Dycal. It consists of a catalyst and a base mixed in a ratio of 1:1.[7]

However, one study showed that $Ca(OH)_2$ cannot be fully bonded to dentin, dissolves over time, and many tunnel defects were observed in the dentin bridge formed close to the material.[14]

In another study using canine teeth, mineral trioxide aggregate (MTA) was found to be more successful in terms of dentin bridge formation. There are dentin tubules in the dentin bridge formed under the MTA, but these tubules do not have continuity, their ends are blocked and closed to bacterial passage. However, the tubular dentin bridge formed under calcium hydroxide is continuous with the existing lateral dentinal tubules. In addition, in that study, inflammation and bacterial infiltration were not observed when MTA was applied, while both chronic inflammation in the coronal pulp and gram-positive cocci were detected in 4 samples in the calcium hydroxide group.[15]

A similar study performed on maxillary third molars showed that after direct capping using calcium hydroxide, mild inflammation rich in lymphocytes and mild hyperemia were observed under the dentin bridge. While these findings were not observed in the MTA group in the same study, a thicker dentin bridge formation was observed under the MTA. According to the results of that study, it was reported that MTA has superior properties compared to calcium hydroxide.[16]

In another study in which different materials were evaluated in terms of their antibacterial properties in direct pulp capping, researchers reported that the MTA group had the highest bacterial inhibition in terms of *S. mutans*, but Dycal showed the highest antibacterial property in 3 different bacterial types. The researchers reported that the antibacterial property of calcium hydroxide is related to its ability to release hydroxyl ions.[17] The success of calcium hydroxide, which has been accepted as the "gold standard" for many years, especially as a direct capping material, is well known.[18] Today, the gold standard has changed and MTA is used more than calcium hydroxide in clinical studies.[19]

Mineral Trioxide Aggregate

MTA was developed as a bioactive material in the early 1990s and was aimed to be used as a retrograde filling material. It was first mentioned in the dental literature in 1993.[20,21] The main MTA, ProRoot grey MTA (Dentsply), was introduced in 1998. It contains 75% type 1 Portland Cement, 20% Bismuth Oxide and 5% calcium sulfate dehydrate.[7] The main component of MTA is Portland cement. However, unlike Portland cement, MTA also contains bismuth oxide. In addition, the particles in MTA are smaller and more uniformly shaped. MTA contains less heavy toxic metals and has a longer working time.[20]

The mechanism of action of MTA is similar to that of calcium hydroxide. Calcium hydroxide appears as a by-product of the hydration of MTA as a result of its contact with the pulp tissue and causes necrosis. When MTA powder is mixed with water during application, calcium silicate powders in the powder hydrate to form hydrated calcium silicate gel and calcium hydroxide. Accordingly, MTA can be considered as a calcium hydroxide releasing material and it is expected to have all the properties described for calcium hydroxide.[7]

Biocompatibility, good sealing ability, bioactivity and triggering the formation of mineralized tissue are said to be the advantages of MTA.[7,20] Pulp tissue has a natural tissue repair ability which can form reparative dentin. The healing of pulp tissue occurs as a result of the arrival of stem/progenitor cells to the damaged area and differentiation into odontoblast-like cells after proliferation. Reparative dentin often ends with a fibrodentin matrix composed of a tubular and/or irregular cuboidal cells.[20] In addition, it has been observed that the reparative dentinogenesis resulting from MTA application is more pronounced and consistent compared to calcium hydroxide.[21] While MTA was used only in a gray color until 2002, a new version was introduced [white MTA (WMTA)] to meet patients' aesthetic expectations. MTA is now classified into two different categories as either traditional gray MTA or WMTA. The main differences are the amounts of Al_2O_3, MgO and FeO.[21] In addition to all these, WMTA does not contain iron.[22]

Bioceramics

Bioceramics are biocompatible ceramic compounds. They are compatible with various chemicals. Bioceramics exhibit excellent biocompatibility due to their biological properties similar to hydroxyapatite. Bioceramics have the ability to induce a regenerative response by forming different compounds during hydration. Bioceramics consist of a porous powder containing 1-3 nm nanocrystals and this property prevents bacterial adhesion.[23] The reason why bioceramics are widely used in dentistry and biomedicine is that they are more inert than metals. Over the past two decades, interest has turned to bioceramic materials. Biomaterials can form close bonds with hard tissues as well as induce physiological function. Bioceramics are now used in the living body for different purposes. They can be divided into two as "bioinert" or "bioactive" ceramics, depending on their interaction with tissues. Oxides, such as alumina or carbon compounds, are inert bioceramics as they experience little or no chemical change when in prolonged contact with a physiological environment.[24]

Biodentine

Biodentine is a tricalcium silicate-based dentin restoration material obtained from Portland cement. Many silicate-based materials have been developed in order to eliminate the difficulties which may be experienced due to the long setting time of MTA. Among them, Biodentine is a material consisting of powder and liquid and it can be used instead of damaged dentin (Biodentine; Septodont, Saint Maur de Fosses, France). It has a reduced curing time (12 min), strengthened mechanical properties and ease of application (high viscosity). It is used as an alternative to MTA.[11,25,26] Biodentine is a calcium silicate-based bioactive material with the same usage areas as MTA. Since it has mechanical properties similar to dentin, it is a material which can be preferred in treatments which require the regeneration of the dentin-pulp complex. This material, which has a positive effect on vital pulp cells, induces tertiary dentin formation and provides reparative dentin production when it comes into direct contact with the vital pulp.[6,11,25] In a study carried out by Poggio et al.[27] in 2014, the biocompatibility of Biodentine was compared with pulp capping materials such as Dycal, MTA Angelus and ProRoot MTA. According to their study, Biodentine and MTA-based materials showed less cytotoxicity than Calcium Hydroxide-based materials, and it was reported that the Biodentine material may be the best pulp capping material among these materials.[27]

Endosequence Root Repair Material

This is a root canal filling material designed mainly for endodontic treatment. It contains calcium silicate, monobasic calcium phosphate, zirconium oxide, tantalum oxide, thickening agents and special fillers.[6] It is a stable and ready-to-use material, having high mechanical bond strength, high pH, radiopacity, and hydrophilic hardening properties.[28]

Light Cured Tricalcium Silicate Cement

This material, which is marketed as an alternative to light-cured calcium hydroxide-based pulp coating materials, contains 45% white mineral material (type 3 Portland cement), 10% white radiopaque material, 5% white hydrophilic thickening agent (fumed silica barium zirconate) and approximately 45% resin. The resin content consists of both hydrophobic monomers (UDMA, BisGMA, TriEDMA/TEGDMA) and hydrophilic monomers (HEMA, PEGDMA). Due to its resin content, this material has good physical properties. It can induce the formation of apatite crystals with its calcium fluoride content. Tricalcium silicate material is biocompatible and has properties which induce the differentiation of human pulp cells similar to calcium hydroxide.[6,29] In addition, it is formulated to reduce microleakages by providing good bonding to composites by using light-cured tricalcium silicate-based materials as linings under composite restorations.[30]

In the study conducted by Cengiz and Ulusoy[26] in 2016, the bond strengths of Theracal and Biodentine materials were compared with restorative materials and it was reported that the Theracal material achieved a stronger bond. Accordingly, the success of the capping treatment will be positively affected.[26]

In another study by Camilleri[31] in 2014, the setting reactions of Theracal and Biodentine materials were compared. It was determined that the calcium ion release resulting from the setting reaction is much higher in Biodentine.[31]

In another study, Biodentine and Theracal were compared and it was reported that Theracal could not produce calcium hydroxide, and it used the water necessary for its hydration by diffusion of the water in the environment. It is also thought that resin monomers may cause adverse reactions in the pulp.[32]

Calcium Phosphate

Calcium phosphate containing materials are biomedical materials with excellent biocompatibility and non-toxic properties because of their chemical compounds. Calcium phosphate cements are bioactive synthetic materials and the most frequently used ones are hydroxyapatite and tricalcium phosphates. These types are generally preferred because of their osteoconductivity, crystallographic structure and chemical structure similar to skeletal tissue.[33] Calcium phosphate cement is a self-curing bioactive material consisting of powder and liquid. Al-Sanabani et al.[34] said that it was developed by Brown and Chow in the 1980s. Calcium phosphate, which is a material superior to pure calcium hydroxide due to its self-curing feature, appropriate compressive strength and biocompatibility, has the potential to be used in direct or indirect pulp capping applications for dentin regeneration.[35] In one study, calcium hydroxide was compared with calcium phosphate for the potential of dentin bridge formation in the primary teeth of pigs. It was reported that calcium phosphate can form a more regular, faster and thicker dentin bridge compared to calcium hydroxide.[29]

However, as tricalcium phosphate could not completely prevent microleakages due to its porous structure, bacterial infiltration was encountered. For this reason, there are also researchers who recommend not to use it for pulp capping.[6]

Calcium-Rich Mixture (CEM)/New Endodontic Cement

Calcium-rich mixture (CEM) is a tooth-coloured water-based cement. It consists of calcium-containing compounds such as calcium oxide, calcium carbonate, calcium phosphate, calcium silicate, calcium sulfate, calcium hydroxide, and calcium chloride. These substances stimulate the formation of hard tissue and are not cytotoxic. Its antimicrobial and sealing properties are similar to calcium hydroxide. Although its chemical content is different from MTA, its clinical applications are similar. It is considered as an alternative to MTA as it hardens in a shorter time, is more fluid, has less film thickness, can be easily shaped and does not cause tooth discoloration.[11,36]

In a study comparing MTA and CEM, it was stated that CEM gave better pulpal results than MTA, although it was not statistically significant. The mean dentin bridge thickness of the CEM group was found to be higher than that of the MTA group, and the layer formed by odontoblast-like cells was observed more frequently in the CEM group. It was reported that the high content of the calcium compounds of this cement provides a rich pool of calcium and phosphorus ions. These elements are also used as part of the natural hydroxyapatite production of pulp cells.[37] In another similar study, after CEM and MTA applications, a thicker dentin bridge was formed under the CEM and less pulp inflammation was observed. More tubular formations were observed in the dentin tissue formed under CEM, but no statistically significant difference was found between the materials.[38] In another study in which MTA and CEM were compared, it was reported that CEM material could be a vital pulp treatment material as successful as MTA.[36]

Zarrabi et al.[38] examined MTA and new endodontic cement (NEC) in human dental pulp and reported that both materials were biocompatible and formed dentinal bridges. However, NEC formed a thicker dentinal bridge and caused less pulp inflammation compared with MTA.[38]

Growth Factors and Proteins

Growth Factors are natural polypeptide hormones. They regulate key cellular events in tissue repair, such as cell proliferation, chemotaxis, differentiation and matrix synthesis, by binding to their specific receptors. They are involved in mitogenesis, migration, matrix synthesis and remodulation during tissue repair.[33,39] Growth factors can act as signaling molecules which modulate cell behavior by mediating intracellular communication. Growth factors are polypeptides or proteins which bind to specific receptors on the surface of target cells. They can initiate the intracellular signaling cascade and behave in an autocrine or paracrine manner. This can send signals to the cell nucleus and stimulate the genetic structure which will change the behavior and activity of the cell.[33,40]

Enamel Matrix Protein (Emdogain-EMD)

Enamel matrix derivative (EMD) is a bioactive molecule, the major component of which is amelogenin. This is released from preameloblasts to enable the differentiation of odontoblasts in the dental papilla during odontogenesis. It is derived from developing pig teeth, which resemble human enamel protein. The main component of EMD is amelogenin.[41] It has been reported that EMD potentiates alkaline phosphatase (ALP) activity and the release of bone matrix proteins in osteoblasts. It has been stated that amelogenin and amelin proteins participate in the differentiation of odontoblasts and the subsequent dentin formation during dentinogenesis. EMD induces endothelial cells of pulp capillaries and odontoblasts to produce a hard tissue barrier on the exposed pulp. EMD-enhanced ALP activity and bone morphogenetic protein expression in osteoblasts and dentin matrix protein go first to the site to strengthen the condition of the injured pulp and the production of repair dentin. This material was found to be clinically resistant because it contains amelogenin and amelin, which are defined as auto-proteins by the body's defense system, and it has been reported that it does not show any allergic or immunological reactions during 10 years of use.[42]

When EMD gel is applied to the exposed pulp, it induces the formation of dentin-like hard tissue. However, it is reported that when applied alone, Emdogain gel is ineffective in the formation of hard tissue due to its dissolution in propylene glycol alginate gel and it cannot provide a leak-proof seal. When used in combination with MTA, the differentiation of pulp cells into odontoblast-like cells is faster than when MTA alone is used. Therefore, it is not recommended to be used alone.[6,11]

In one study on miniature pig teeth, the success of calcium hydroxide and Emdogain materials in creating dentin bridges in direct pulp capping was compared. Hard tissue formation in teeth treated with Emdogain was reported to be 2 times greater than in calcium hydroxide for the 2 and 4 week results.[41]

Transforming Growth Factors

Transforming growth factor (TGFs) are a structurally and functionally related family isolated from healthy and neoplastic tissues. The two best-characterized types are TGF-alpha (α) and TGF-beta (β). TGF-β is a dimeric polypeptide linked by covalent bonds and has three different structures: TGF-β1, TGF-β2, TGF-β3, TGF-β4 is a multifunctional growth factor and it can be synthesized by many tissues, but bone and platelets are its main source. The three best-known iso-types of TGF-β in mammals, TGF-β1, TGF-β2, and TGF-β3, are reported to be involved in embryonic differentiation and development. It has been reported that the activity of TGF-β is observed in the dental papilla and stellate reticulum in odontogenesis in mammals.[40,43,44]

Bone Morphogenetic Proteins

In 1965, Marshall Urist determined that a demineralized bone matrix induces bone formation when placed subcutaneously. The ability to form a demineralized bone matrix has been attributed by Urist to a protein called "Bone Morphogenetic Protein."[45] It has been shown that bone morphogenetic proteins and recombinant human bone morphogenetic proteins stimulate osteodentin and subsequent tubular reparative dentin formation in pulp capping and amputation treatment in the absence of inflammation, but this success cannot be achieved in the presence of inflammation. In pulp capping, it has been reported that recombinant human proteins form repair dentin by protecting the pulp in a healthy way without wasting the deep pulp tissue.[45]

Insulin-Like Growth Factor

Insulin-like growth factors (IGF) belong to the family of single-chain serum proteins. They are important regulators of cell proliferation and cell differentiation in various cells (osteoblast, fibroblast). Two separate polypeptides belonging to this family have been identified: IGF-1 and IGF-2. IGF-1 and IGF-2 are growth factors which are biochemically and functionally similar to insulin. IGFs are synthesized by many tissues such as the liver, smooth muscle, and the placenta.[40] It has been reported that dentin bridge and tubular repair dentin formation, which completely covers the exposed pulp, has been observed in capping treatments with IGF-1.[44]

Propolis

It is an antimicrobial and anti-inflammatory agent consisting of resins collected by honey bees from cracks in trees and leaf buds. The most effective pharmacological component in propolis are flavonoids. Flavonoids are plant compounds with antioxidant, antibacterial, antifungal, antiviral and anti-inflammatory properties. Stimulation of TGF-β release and collagen synthesis of pulp cells are promising for their use in pulp coatings.[6,46]

Iloprost

Prostacyclin (PGI2) is a potent vasodilator which increases angiogenesis and cellular differentiation by stimulating the release of vascular endothelial growth factor (VEBF), and it is also involved in bone remodeling. An increase in bone mass was observed in animals whose PGI2 synthesis was triggered. Osteoblasts produce PGI2 in response to growth factors, and both osteoblasts and osteocytes release PGI2 in response to mechanical loading. In addition, PGI2 induces VEBF in a large number of cells. VEGF stimulation triggered by PGI2 also increases endothelial cell proliferation and angiogenesis. Iloprost is a long-acting PGI2 analog used in the treatment of pulmonary hypertension. Iloprost is also used clinically in order to prevent bone necrosis. It has been reported that circulating endothelial cells and their progenitors increase in patients receiving iloprost infusion.[11,47]

When the effect of iloprost on the blood flow of dental pulp was examined, there was no significant difference with $CaOH_2$ in the first 24 hours, however, it was reported that blood flow increased significantly in samples treated with iloprost within 72 hours. This increase is thought to be effective in maintaining pulp vitality and the formation of the dentin bridge.[47]

In an *in vivo* study with iloprost in rats, it was found to be successful in forming tertiary dentin. Although the material is a long-acting PGI2 analogue, it has a short half-life in the lungs. Therefore, it is important to adjust the amount to be applied.[47]

Laser Applications

Komabayashi et al.[48] said that, Melcer et al. first proposed the use of CO_2 lasers in direct pulp capping. They pointed out that laser applications improve the formation of tertiary dentin on the dentin surface and above all, provide sterilization. Melcer reported successful direct pulp capping with CO_2 lasers.[48] It was reported that low-intensity laser applications regulate the inflammatory response in injured tissues without causing side effects.[49] As a result of a clinical study in which direct pulp capping with CO_2 laser + $CaOH_2$ and only $CaOH_2$ were followed up for an extended period, vitality was reported as 93% in the laser treated group and 68% in the $CaOH_2$ group only. Researchers reported that laser applications in direct pulp capping can be recommended to increase success.[48]

Bleeding may begin again after the pulp capping material is placed in the exposed area. This can both cause microleakages by affecting the polymerization of adhesive systems and disrupt the sealing of pulp capping materials, leading to the presence of bacteria and bacterial invasion in the exposed area. Therefore, the use of lasers in pulp capping has come to the fore.[6]

High Frequency Radio Waves

The clinical success of direct pulp capping is closely related to achieving hemostasis in the pulp. When the pulp is exposed, providing hemostasis with a fast and reliable method as possible, this will increase clinical success. For this reason, high-frequency radio waves have found use in direct pulp capping. High frequency radio waves (HRW) creates coagulation in the soft tissue using 4 MHz radio signals.[11]

In the results of direct capping applications using HRW in mice, dentin bridge density increased as the intensity of the HRW application increased, but the dentin bridge formed in the most intense HRW group was more irregular and tunnel defected compared to the other 2 groups. As a result of this study, researchers reported that ensuring hemostasis reduces pulpal inflammation and triggers the formation of a better quality dentin bridge.[50]

CONCLUSION

According to the results of this literature review, it may be concluded that calcium phosphate can form a more regular, faster and thicker dentin bridge compared to calcium hydroxide. MTA, Biodentine, CEM and NEC may also be used safely in pulp capping in order to maintain pulp vitality and healing.

Future and long-term *in vivo* studies for pulp capping are necessary to investigate the clinical use of the promising materials and techniques, such as growth factors and proteins, propolis, laser applications and high frequency radio waves.

MAIN POINTS

- Pulp capping is a technique used in dental restorations to prevent the dental pulp from necrosis, after being exposed, or nearly exposed during a cavity preparation, from a traumatic injury, or by a deep cavity which reaches the center of the tooth causing pulp necrosis.
- Biodentine; a tricalcium silicate-based material, reported to be the best pulp capping material is discussed in this review.
- Light Cured Tricalcium Silicate Cement; TheraCal LC which provides a better bonding with dentin than Biodentine may be an alternative for pulp capping.
- Calcium-Rich Mixture (CEM) is considered as an alternative to MTA for pulp capping, as it hardens in a shorter time, is more fluid, has less film thickness, can be easily shaped and does not cause tooth discoloration.
- Today, MTA has taken its place in clinical studies as the gold standard compared to calcium hydroxide.

ETHICS

Authorship Contributions

Concept: Ş.A., N.U., Design: Ş.A., N.U., Data Collection and/or Processing: Ş.A., N.U., Analysis and/or Interpretation: Ş.A., N.U., Literature Search: Ş.A., N.U., Writing: Ş.A., N.U.

DISCLOSURES

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RESEARCH ARTICLE

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Comparison of Ultrasound-Guided Thoracic Paravertebral Block and Erector Spinae Plane Block for Postoperative Analgesia After Laparoscopic Cholecystectomy

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Abstract

BACKGROUND/AIMS: Many block methods have been applied for postoperative analgesia after laparoscopic cholecystectomy (LC). We aimed to compare the effectiveness and reliability of thoracic paravertebral block (TPVB) and erector spinae plane block (ESPB) performed with ultrasonography in elective LC cases on postoperative analgesia.

MATERIALS AND METHODS: This study was carried out as a randomized double-blinded prospective study. We divided 102 patients who would undergo elective LC into 2 groups (TPVB; group 1, and ESPB; group 2) using a website (www.randomizer.org) with 51 patients each. We applied the blocks unilaterally with 20 mL of 0.25% bupivacaine at the T-8 level under the guidance of ultrasound. Postoperative visual analog scale scores, additional analgesic requirements up to the 24th hour, the duration of block application, postoperative nausea and vomiting data, and any developing complications were noted.

RESULTS: Hundred and two patients (51 patients in each group) were evaluated. We found no statistically significant differences in age, gender or comorbidities ($p>0.05$). Postoperative resting and dynamic visual analog scale scores did not differ statistically ($p>0.05$). When the presence of nausea and vomiting, complication rates, the duration of the block application and postoperative first analgesic requirements were compared, we found no significant difference between the groups ($p>0.05$ for each). The satisfaction score was found to be significantly higher in group 1 ($p=0.011$).

CONCLUSION: We determined that ultrasound guided TPVB and ESPB were not superior to each other in terms of postoperative analgesic potency in LC. However, ESPB is a newer block, simpler to administer and not inferior in analgesic efficacy compared to TPVB.

Keywords: Erector spinae plane block, laparoscopic cholecystectomy, postoperative analgesia, regional anesthesia, thoracic paravertebral block, visual analog scale

INTRODUCTION

The gold standard for cholecystectomy is laparoscopic cholecystectomy (LC), which is a frequently preferred surgical procedure because of its lower postoperative pain, lower hospital costs, and lower long-term morbidity.[1] The PROSPECT (*procedure specific postoperative pain management*) protocol recommends multimodal analgesia after LC, as in many surgeries.[2] The main goals in the treatment of pain after surgery include eliminating or reducing the discomfort and facilitating the healing process, avoiding the adverse effects of treatment.[3]

Due to the unfavorable effects of opioid analgesics on managing postoperative pain, various regional anesthesia procedures have recently gained popularity. Sellheim first described one of them, the

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thoracic paravertebral block (TPVB), in 1905. Kappis later modified it with a method closer to the one used today and this is now used for postoperative pain management after thoracic and abdominal surgeries. Erector spinae plane block (ESPB), is a new technique created for acute and persistent thoracic pain and it was defined by Forero et al.[4] in 2016. It is another regional anesthesia technique utilized in thoracic and abdominal procedures as an alternative to TPVB for postoperative analgesia.[5,6] In current publications, both block types are applied for analgesia after thoracic, abdominal, and spinal surgeries individually.

To date, there had not been a study which contrasted these two kinds of blocks in LC, as far as we were aware. We aimed to compare the effectiveness of TPVB and ESPB achieved with ultrasonography in elective LC cases on postoperative analgesia.

MATERIALS AND METHODS

This prospective, double-blinded, randomized, clinical trial was performed in Afyonkarahisar Health Sciences University Hospital Anesthesiology and Reanimation Clinic and a general surgery clinic after approval of the Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (approval number: 2021/3, date: 11.09.2020). All procedures carried out in this research involving human subjects were in accordance with the 2013 Helsinki Declaration and its later amendments or comparable ethical standards, as well as the ethical requirements of the institutional and/or national research committee.

The patients who were designated to take part in this study were included after a routine preoperative anesthetic evaluation. This study comprised patients who were scheduled for elective LC between March, 2021 and July, 2021 and had an American Society of Anesthesiologists (ASA) score of 1-2, had no mental defect, and were between the ages of 18 and 70 years. This study excluded individuals who were under or over the study's inclusion age, had ASA scores of 3 to 4, had a local or systemic infection, an arrhythmia, cardiac, hepatic, or renal failure, or a history of allergies to local anesthetics or any analgesic drugs. Informed consent was obtained from all participants. The VAS was explained to all patients who would take part in this study.

It was decided enumerate the patients according to their registration order. The site (www.randomizer.org) randomly divided the patient sequence numbers into two groups. Patients with TPVB were allocated to group 1, and patients with ESPB were allocated to group 2. We designated a research coordinator to distribute and preserve the randomization results.

The practitioner shared the order of patient enrollment with the coordinator, and the coordinator specified which block would be performed according to the randomization list. We performed unilaterally the blocks with the guidance of ultrasound (US), (Usmart®-3200T Nexgen, Terason). The participants were blinded to the allocation. The anesthetists who applied general anesthesia and followed up after the surgery and the surgeon had no information about which block was applied.

In the nerve block practice room, routine anesthetic monitoring was carried out, and a 0.9% saline infusion was started after establishing peripheral venous access. Following the detection of the processus spinosum in the cervical region after the most conspicuous C-7, we marked caudally one by one under US guidance. The patients were in a seated position with their heads angled slightly forward. The injection location was designated as being 2.5-3 cm to the right side lateral of the Th-8 spinous process and the relevant area was cleansed. 2 mL of 2% lidocaine was injected into the subcutaneous tissue at the location of the needle insertion.

The paravertebral area, subsequent transverse processes, pleura, and superior costotransverse ligament were all identified after the linear US probe was placed on the specified area for paravertebral block administration in the longitudinal plane. The superior costotransverse ligament was passed using the in-plane approach, which involved directing an 80 mm 22-gauge peripheral block needle (Stimuplex®, B Braun, Melsungen, Germany) into the thoracic paravertebral region. 3 mL of 0.9% saline was first administered in order to confirm the needle placement when it was determined that there was no vascular interference with aspiration. TPVB was provided by injecting 20 mL of 0.25% bupivacaine (Buvasin, Vem İlaç, İstanbul, Türkiye).

In group 2, with the in-plane technique, the block needle was directed, and we inserted the needle tip between the spinal transverse process and the anterior fascia of the erector spina muscle group. As soon as it was determined that there had been no vascular intervention, 3 mL of 0.9% saline was injected. After simultaneous monitoring of the hydro-dissection and distribution was also established, 20 mL of 0.25% bupivacaine was then injected to achieve ESPB.

The period between the block needle's insertion into the skin and its removal is referred to as the duration of block application. Complications defined as hypotension, bradycardia, vascular puncture, pneumothorax, paresthesia, total spinal block and local anesthetic toxicity were recorded if they occurred.

Twenty minutes after the block application, the sensory block was evaluated on the midclavicular line. Ice packs were used to test for cold sensations. If there was a sensory loss in the upper and lower two dermatomes at the Th-8 level, the block was deemed effective, and the patient was taken to the operating room.

General anesthesia induction was applied to all patients with 2 µg/kg fentanyl, 2-3 mg/kg propofol, and 0.6 mg/kg rocuronium bromide. We performed intubation with an appropriate size endotracheal tube 3 minutes after we administered the muscle relaxant. For the maintenance of anesthesia, 50% O_2 + 50% air and 6% desflurane (Suprane®, Baxter, USA) were used.

400 mg ibuprofen (Dorifen, Vem İlaç, İstanbul, Türkiye) i.v. was administered to all patients for postoperative analgesia approximately 10 minutes before the end of the operation. To prevent postoperative nausea and vomiting, 10 mg metoclopramide (Nastifran®, Menta Pharma, İstanbul, Türkiye) IV was administered to all patients. At the end of the surgery, the effect of the muscle relaxant was antagonized by using 2 mg/kg Sugammadex (Bridion®, Sanofi, Tekirdağ, Türkiye) after the removal of the inhaler agent and the patient was extubated, and then taken to the postoperative recovery room. Arrival time in the recovery room was accepted as the zero hour. An observer carried out the first VAS assessment there.

Afterward, the patients were followed up in the general surgery clinic. VAS scores up to the postoperative 24th-hour, 24-hour patient satisfaction and the presence of nausea or vomiting were analyzed and recorded. The time of the first analgesic requirement in the first 24 hours after

surgery was recorded. We performed postoperative pain assessment by the observer using the VAS. Patient satisfaction with analgesic therapy was recorded by a five-point Likert scale at the postoperative 24th hour with values between 1 (terrible) and 5 (very good).

When resting or dynamic VAS was greater than 4 in the postoperative follow-up, the patients received additional analgesic therapy. Pain severity categorized as 0-4 bearable pain; 5-6 mild pain; 7-8, moderate pain; 9-10 severe pain. According to the postoperative pain step treatment protocol, respectively, we used paracetamol for mild pain, tramadol for moderate pain, and meperidine for severe pain. If resting or dynamic VAS is still greater than 4 one hour after the analgesic application in the protocol, we switch to a higher-level analgesic.

Gender, age, height, weight, body mass index (BMI), ASA risk scores, and the operation times of the patients were recorded. Postoperative interventions were performed by a researcher who did not know to which study groups the patients belonged, and the data were recorded.

Statistical Analysis

Using the Kolmogorov-Smirnov test, Histogram, Skewness and Kurtosis coefficients, we investigated the normality assumptions of continuous variables. For continuous data, mean and standard deviation (mean ± standard deviation), and median (minimum-maximum) values are provided; for categorical variables, frequency (n) and percentage (%) values are provided. The connections between the categorical variables were examined using Pearson's chi-square (2) and Fisher's exact analysis, and the non-normally distributed continuous variables were compared with the two-level variables using the Mann-Whitney U test. All analyses were performed using the IBM SPSS.23 program, and the level of significance was agreed to be $p<0.05$.

The G*Power 3.1 (Faul, Erdfelder, Lang, and Buchner, 2007) application was used to calculate the necessary sample size prior to the data collection phase. The sample size was 51 for each group, for a total of 102, where the effect size was 0.5, the alpha level was 0.05, and the power was 80%.

RESULTS

Figure 1 shows the CONSORT diagram of enrollment for this study. Data from 102 patients, 61 (59.9%) women, and 41 (40.1%) men, were used in the final analysis. There were no statistically significant differences in the age, gender, weight, length, BMI, ASA scores, or comorbidity of the patients (Table 1).

The zero, 2nd, 4th, 8th, 12th, and 24th hour resting VAS scores did not differ

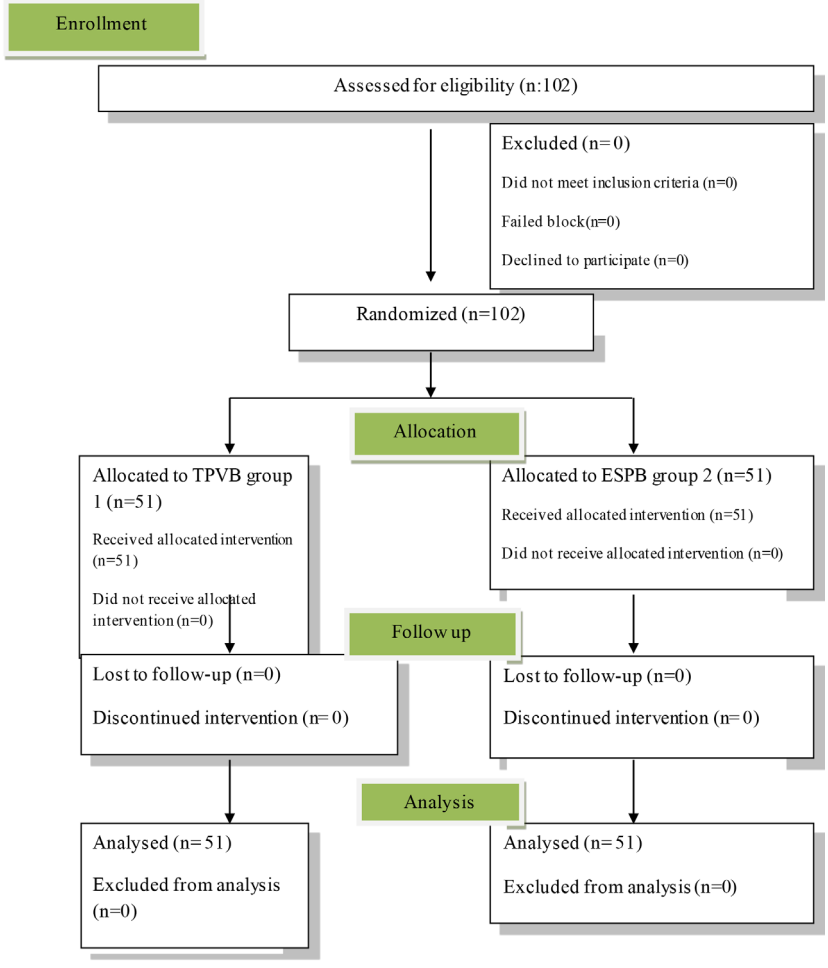

Figure 1. CONSORT flow chart describing participant progression through the study.

ESPB: Erector spinae plane block, TPVB: Thoracic paravertebral block.

statistically (p=0.131, 0.980, 0.888, 0.360, 0.217 and 0.301, respectively), and the dynamic VAS scores did not differ either (p=0.237, 0.750, 0.835, 0.479 0.422 and 0.489, respectively). Figure 2, 3 show mean resting and dynamic VAS scores according to block types.

The mean duration of block applications was 8.20±6.15 minutes in group 1, and 6.08±3.47 minutes in group 2 (p=0.156). The first analgesic requirement occurred at 3.57±5.46 hours postoperatively in group 1, while this value was 4.18±5.47 in group 2 (p=0.338).

There were no differences between the study groups regarding operation time (p=0.353), first mobilization time (p=0.054), or length of hospital stay (p=0.749). We found postoperative analgesia satisfaction scores to be considerably higher in group 1 (p<0.05) (Table 2).

In total, additional analgesic was given to 22 patients in group 1, and 28 patients in group 2. None of the patients needed a second dose of analgesic medication in either group. In group 1, paracetamol was administered to 14 (27.5%) patients for mild pain, and tramadol was administered to 8 (15.7%) patients for moderate pain. Since severe pain did not develop in group 1, meperidine was not administered. In addition, the number of patients who did not need analgesic treatment was 29 (56.9%) in group 1. In group 2, paracetamol was administered to 12 (23.5%) patients, tramadol was administered to 13 (25.5%) patients, and meperidine was administered to 3 (5.9%) patients. In group 2, 23 (45.1%) patients did not need analgesics (Table 3).

The number of patients with hypotension, bradycardia or both were equal in both groups. Shoulder pain was seen in 2 patients in group 1 postoperatively, while it was seen in 1 patient in group 2 (p=0.986). Nausea and vomiting occurred within the first 14 hours postoperatively. When the presence of nausea and vomiting and the time of nausea and vomiting were compared, we found no significant differences between the groups. Serious complications, such as local anesthetic toxicity, pneumothorax, and total spinal block were not experienced in either block type (Table 3).

Table 1. Sociodemographic and medical characteristics of the patients according to block types

	Group 1 (n=51)	Group 2 (n=51)	p
Gender (M/F)	24/27	17/34	0.161
Age	49.47±14.55	50.41±14.39	0.733
Weight (kg)	78.68±15.37	81.82±14.60	0.293
Length (cm)	166.82±9.68	165.07±8.19	0.328
BMI (kg/cm^2)	28.24±4.79	30.14±5.62	0.690
ASA score (1/2)	14/37	11/40	0.490
Comorbidity			0.249
None	15 (29.4)	11 (21.6)	
HT	6 (11.8)	8 (15.7)	
Asthma	1 (2.0)	3 (5.9)	
Anemia	2 (3.9)	0 (0.0)	
DM	1 (2.0)	5 (9.8)	
CAD	5 (9.8)	2 (3.9)	
Obesity	5 (9.8)	7 (13.7)	
HT + DM	5 (9.8)	4 (7.8)	
Other	11 (21.5)	11 (21.5)	

Values are expressed as frequency or mean ± standard deviation. M: Male, F: Female, BMI: Body mass index, ASA: American Society of Anesthesiologist class, HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, chi-square test was used.

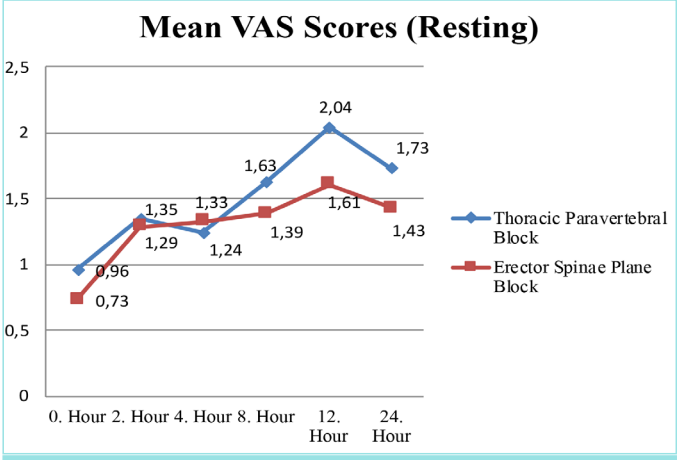

Figure 2. Mean resting VAS scores according to block types.
VAS: Visual analog scale.

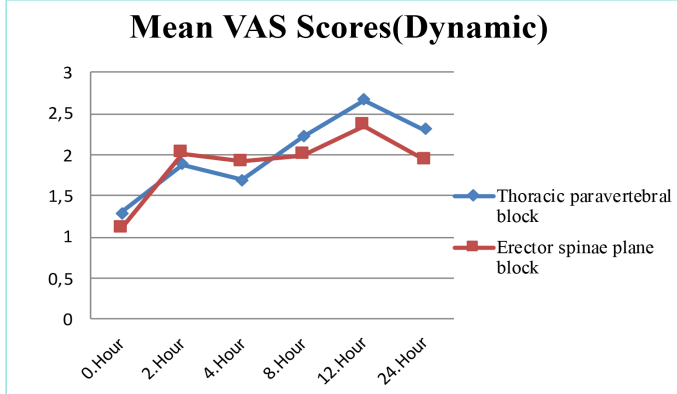

Figure 3. Mean dynamic VAS scores according to block types.
VAS; Visual Analog Scale.

Table 2. Comparison of medical characteristics of patients according to block types

	Group 1 Mean ± SD	Group 2 Mean ± SD	p
Duration of block application (minute)	8.20±6.15	6.08±3.47	0.156
Time of first analgesic requirement (hour)	3.57±5.46	4.18±5.47	0.338
Operation time (minute)	82.22±24.28	87.14±26.44	0.353
First mobilization time (hour)	7.24±1.80	6.56±1.29	0.054
Length of stay in hospital (day)	29.49±4.30	29.57±4.97	0.749
Patient satisfaction	**4.49±0.86**	**4.14±0.85**	**0.011**

Values are expressed as mean ± standard deviation. Mann-Whitney U test was used. SD: Standard deviation.

Table 3. Some medical characteristics of patients after block application according to block types

	Group 1	Group 2	Total	p
	n (%)	n (%)	n (%)	
Type of complication*				0.986
None	43 (84.3)	44 (86.3)	87 (85.3)	
Bradycardia	3 (5.9)	3 (5.9)	6 (5.9)	
Hypotension	1 (2.0)	1 (2.0)	2 (2.0)	
Bradycardia + hypotension	2 (3.9)	2 (3.9)	4 (3.9)	
Shoulder pain	2 (3.9)	1 (2.0)	3 (2.9)	
Performed analgesic drug*				0.102
None	29 (56.9)	23 (45.1)	52 (51.0)	
Paracetamol	14 (27.5)	12 (23.5)	26 (25.5)	
Tramadol	8 (15.7)	13 (25.5)	21 (20.6)	
Meperidine	0 (0.0)	3 (5.9)	3 (2.9)	
Presence of nausea*				0.603
Absence	41 (80.4)	43 (84.3)	84 (82.4)	
Presence	10 (19.6)	8 (15.7)	18 (17.6)	
Time of nausea*				0.378
1st hour	2 (20.0)	0 (0.0)	2 (11.1)	
2nd hour	3 (30.0)	1 (12.5)	4 (22.2)	
4th hour	3 (30.0)	3 (37.5)	6 (33.3)	
6th hour	0 (0.0)	1 (12.5)	1 (5.6)	
8th hour	1 (10.0)	2 (25.0)	3 (16.7)	
14th hour	1 (10.0)	1 (12.5)	2 (11.1)	
Presence of vomiting†				0.715
Absence	46 (90.2)	48 (94.1)	94 (92.2)	
Presence	5 (9.8)	3 (5.9)	8 (7.8)	
Time of vomiting*				0.407
2nd hour	2 (40.0)	1 (33.3)	3 (37.5)	
4th hour	1 (20.0)	1 (33.3)	2 (25.0)	
6th hour	1 (20.0)	0 (0.0)	1 (12.5)	
8th hour	1 (20.0)	0 (0.0)	1 (12.5)	
14th hour	0 (0.0)	1 (33.3)	1 (12.5)	

Values are expressed as frequency or percentage. *Pearson's chi-square test was used. †Fisher's exact test was used.

DISCUSSION

In this randomized clinical trial, the postoperative analgesic efficacy of US-guided TPVB and ESPB in LC was compared, and we showed both to have similar efficacy. There were no significant differences between the postoperative zero, 2nd, 4th, 8th, 12th, and 24th-hour resting and dynamic VAS scores. We found no significant differences in terms of comparisons of analgesic consumptions, the duration of block application, or postoperative nausea and vomiting.

There are many studies comparing these two block types in different operations, such as breast surgery and video-assisted thoracoscopic surgery (VATS). Although there are studies investigating the postoperative analgesic effects of these blocks separately in LC cases, we could not find any study comparing them.

It has been proven that the effects of both blocks on perioperative and postoperative analgesic efficiency, VAS scores, and additional analgesic requirements are significantly superior to control groups.[7,8] However, it has been reported that there is no statistically significant difference between the two blocks.[9,10] In another study comparing these two blocks in VATS, the authors reported that patients who underwent TPVB at the 1st, 2nd, and 24th hours postoperatively had lower resting pain scores, and dynamic pain scores were similar in both block groups.[11] In our study, there were no significant differences in terms of analgesic requirements or VAS scores. Although not statistically significant, the mean VAS scores increased up to the 12th hour postoperatively in both types of block.

In the study of El Ghamry and Amer[12] in which they compared both blocks in modified radical mastectomy operations, the superiority of the blocks over each other could not be shown. They concluded both blocks reduced intra-operative and postoperative opioid consumption.[12] No significant difference was found in another study between the blocks in modified radical mastectomies comparing the first analgesic requirement, the total dose of rescue analgesia, and pain scores.[13]

A published meta-analysis suggested that the type of operation may play a role when comparing the analgesic efficacy of these blocks. According to the results of that study, it was emphasized that TPVB was good in thoracic surgeries, while the analgesic efficacies of these two blocks were found to be similar in breast surgeries.[14]

It was reported that postoperative pain scores with TPVB applied at Th-6 and Th-7 levels in LC were significantly lower in a TPVB group compared to a control group, and TPVB also reduced postoperative tramadol consumption.[15,16] Li et al.[17] showed that in LC, TPVB application provided better peri-operative analgesia and prolonged block time in patient groups who underwent TPVB with the addition of an adjuvant.

In the study by Tulgar et al.[18], in which they examined the postoperative analgesic effects of ESPB in LC, they concluded that the postoperative first 3 hours of pain scores were lower in the block group than in the control group. Tramadol requirement in the first 12 hours postoperatively was found to be lower in the block group.[18] In our study, postoperative analgesic requirements were similar in both block groups.

Since a TPVB is more invasive, the duration of block administration has been found to be significantly longer in many studies.[8,14] Although it was not statistically significant in our study, the mean duration of block application was longer in the TPVB group.

In a case report published by Beyaz et al.[19], TPVB was performed on two patients who underwent cholecystectomy, and complications such as bradycardia and hypotension developed. In our study, we observed very few cases with hypotension and bradycardia.

Study Limitations

The fact that so few patients were enrolled was the primary drawback of the current study. In order to verify these findings, a larger sample is needed. In addition, if we had used a patient-controlled analgesia device, we could have produced more objective results.

CONCLUSION

Postoperative pain management is essential for a swift recovery from surgery, a brief hospital stay, and a quick return to regular activities. In

our research, we found that the postoperative analgesic effectiveness of ESPB and US-guided TPVB were comparable in LC. We believe that because of its analgesic quality and simplicity of administration, ESPB is a practical alternative to TPVB for postoperative pain control.

MAIN POINTS

- Laparoscopic cholecystectomy, which is frequently carried out today, requires postoperative analgesia.
- Nowadays, regional anesthesia methods are more and more common.
- Since ESPB carries a lower anatomical risk than TPVB, it is a better choice when compared with TPVB. In our study, no significant block-related side effects were observed.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (approval number: 2021/3, date: 11.09.2020).

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: B.A.B., R.S., M.A., E.D.B., Concept: B.A.B., R.S., M.A., E.D.B., Design: B.A.B., R.S., M.A., E.D.B., Data Collection and/or Processing: B.A.B., M.A., Analysis and/or Interpretation: B.A.B., R.S., E.D.B., Literature Search: B.A.B., R.S., Writing: B.A.B., R.S., M.A., E.D.B.

DISCLOSURES

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RESEARCH ARTICLE

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Revitalizing Sexual Function in Heart Failure patients: The Impact of Sodium-Glucose Co-Transporter 2 Inhibitors on Erectile Dysfunction

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Abstract

BACKGROUND/AIMS: The prognosis of heart failure (HF) is closely related to the structural integrity of the endothelium. Endothelial dysfunction is observed as a characteristic feature of HF and it plays an important role in the development of erectile dysfunction (ED) in patients with HF. Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have been shown to increase microvascular endothelial cell function through their pleiotropic effects. Therefore, we aimed to investigate the effects of SGLT-2i treatment on ED in patients with HF.

MATERIALS AND METHODS: Forty sexually active HF patients with reduced left ventricular ejection fraction [(LVEF) <40%] and ED were enrolled in this study. In all patients, their functional status was assessed according to the New York Heart Association functional classification, and erectile function was assessed by the Sexual Health Inventory for Men (SHIM) questionnaire at baseline and after three months of SGLT-2i treatment.

RESULTS: SGLT-2i treatment resulted in a significant improvement in the SHIM scores (12.7±5.6 vs. 15.4±5.5, p<0.001). Predictors of improved SHIM scores with SGLT-2i were assessed using multivariable regression. Age (p=0.002), baseline SHIM scores (p=0.042), and lower extremity peripheral vascular disease (p=0.002) were identified as negative predictors of improvements in SHIM scores, while changes in brain natriuretic peptide levels (p=0.035) emerged as a significant predictor of improvement in SHIM scores.

CONCLUSION: This cross-sectional study suggests that treatment by SGLT-2i could potentially provide advantages to patients with HF who also experience ED, enhancing their functional status.

Keywords: Heart failure, SGLT-2 inhibitors, SHIM score, sexual function, endothelial dysfunction

INTRODUCTION

Heart failure (HF) is a health concern which has a considerable impact on the adult population in developed nations, affecting around 1-2% of individuals.[1,2] The strong connection between endothelial dysfunction and shear stress significantly impacts the etiology of HF. Shear stress is frequently responsible for inducing the release of endothelial nitric oxide (NO). The reduction in shear stress which occurs in HF causes a concomitant reduction in endothelium-derived NO release, leading to an elevation in the oxidative stress.[3] Studies have shown that elevated levels of oxidative stress contribute to a reduction of NO bioavailability, impairing endothelial function.[4,5] This impairment may lead to decreased endothelium-dependent vasorelaxation[6,7] in penile endothelial cells, leading to erectile dysfunction (ED). Indeed, the incidence of ED may be as high as 84% in men with chronic compensated HF, the New York Heart Association (NYHA) class 1-3.[8]

Studies have shown that treatment with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) reduces the likelihood of combined cardiovascular

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and all-cause mortality, first hospitalization, and hospitalization length in HF patients.[9,10] The physiological effects of SGLT-2i are thought to be mediated through antioxidant, anti-inflammatory, and anti-fibrotic pathways.[9,11,12] They also affect microvascular endothelial cell activity by increasing NO levels and endothelial bioavailability, thus improving endothelial dysfunction.[13] Although the positive effects of SGLT-2i on endothelial dysfunction have been established, their potential impact on ED in humans is currently unknown.

In line with all this evidence, this study evaluated the potential effects of SGLT-2i treatment on ED in patients diagnosed with HF with reduced ejection fraction (HFrEF).

MATERIALS AND METHODS

Study Population

The study was designed by the principles of the Declaration of Helsinki and the principles of Good Clinical Practice and did not violate the ethical rules of research involving human subjects. All participants provided their informed consent to participate in the study. Approval for the study was obtained from the Bioethics Committee of Karabük University (approval number: 2023/1258, date: 25.01.2023).

The present study was designed as a cross-sectional study. The study group consisted of HFrEF patients who continued to have symptoms despite receiving optimal medical therapy according to the 2021 European Society of Cardiology Guidelines for diagnosing and treating HF[9] and who were subsequently prescribed SGLT-2i as an adjunctive therapy. A total of fifty sexually active HF patients aged 30 to 70 years with reduced left ventricular ejection fraction [(LVEF) <40%] were recruited between January, 2021 and November, 2022 in the outpatient cardiology clinic of the faculty of medicine. Exclusion criteria included requiring positive inotropic medication, being admitted with acute decompensation, NYHA class 4, changes in their HF treatment during the study, having an end-stage renal disease requiring hemodialysis or peritoneal dialysis, malignancy, having undergone medical or surgical ED treatment, or having ED due to urogenital causes. Five patients did not complete the follow-up Sexual Health Inventory for Men (SHIM) questionnaire and withdrew from this study. Additionally, three patients were excluded due to hospitalization for acute HF, and two patients were excluded due to changes in their dosages of other HF treatments without modifications in medication. Therefore, the statistical analysis was performed with the remaining forty patients (Figure 1).

The demographic profiles of all of the patients, along with their medical history, NYHA functional class, comorbidities, and medication details, were meticulously documented. The patients were defined as being hypertensive if their blood pressure was >140/90 mmHg on two measurements or if they were receiving antihypertensive medications. The diagnosis of diabetes mellitus (DM) was determined based on a fasting blood glucose level equal to or higher than 126 mg/dL or the use of antidiabetic medications. Lower extremity peripheral vascular disease (PVD) was defined by symptoms such as leg pain, cramping, or weakness, accompanied by identifying stenosis or occlusion of 50% or more in the main arteries of the lower extremities using imaging modalities.

All patients underwent blood analysis and echocardiographic evaluation, under resting conditions at baseline. Circulating brain natriuretic peptide (BNP) levels were analyzed by an immunoassay technique (Elecsys®, Roche Diagnostics) in venous blood samples obtained from the antecubital vein using an ethylenediaminetetraacetic acid test tube.

Echocardiographic Evaluation

Baseline and three-month follow-up transthoracic echocardiography were performed on all patients using the Vivid 7, 2.5 MHz probe, and the results were interpreted by two independent cardiologists according to the guidelines of the American Society of Echocardiography[14]. In the patients, LVEF was evaluated using the modified Simpson technique on apical four-chamber imaging.

Assessment of Erectile Dysfunction

All patients provided written and verbal consent to complete the SHIM questionnaire.[15] Erectile function was assessed using the SHIM questionnaire at the beginning of this study. After an initial assessment, a follow-up evaluation was conducted three months after SGLT-2i treatment. This follow-up assessment included re-administering the SHIM questionnaire and evaluating the patient's clinical status, LVEF, NYHA functional classes, and current BNP levels. This timeframe was chosen based on previous reports suggesting that it takes 12-16 weeks for the effects of SGLT-2i to become noticeable.[16,17]

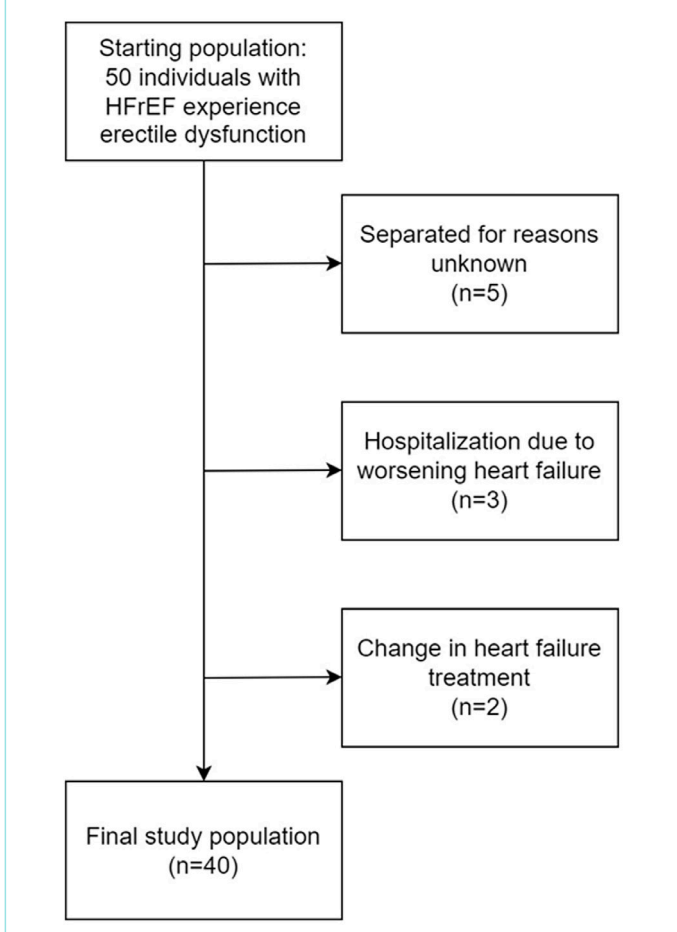

Figure 1. Study flowchart. The diagram describes the protocol used for the enrollment of patients with HFrEF in the present study.

HFrEF: Heart failure with reduced ejection fraction.

The SHIM questionnaire is a widely used scale for assessing ED in men. The total score of the questionnaire ranges from 1 to 25, with higher scores indicating better erectile function. Accordingly, the SHIM score is divided into five categories: severe ED (1-7), moderate ED (8-11), mild-moderate ED (12-16), mild ED (17-21), and non-ED (22-25).[15]

Statistical Analysis

All data were analyzed using the statistical package SPSS version 26.0 (SPSS Inc., Chicago, IL). Data visualizations were performed with the R version 4.0.2 (packages: tidyverse, ggsankey). The normality of the distributions of the parameters was assessed by the Kolmogorov-Smirnov test. Quantitative variables with a normal distribution are given as the mean ± standard deviation and those with non-normal distribution are given as median (minimum-maximum); categorical variables are given as number and percentage values. In order to compare repeated measurements, the statistical analysis utilized Student's t-test for paired samples. In cases where the data did not meet the assumptions of normality, Wilcoxon's test was employed as a non-parametric alternative. McNemar's chi-square test was used to compare the SHIM classes and NYHA functional classes before and after SGLT-2i treatment. Correlations were assessed using the Spearman's rank correlation coefficient. In order to evaluate the potential influence of confounding factors, a multivariable stepwise regression analysis was performed. A p-value <0.05 was considered statistically significant.

Sample Sizing

This study included 40 patients comparing their SHIM scores before and after SGLT-2i treatment. The statistical power of this study was determined using the G*Power program, which provided a power value of 0.56. Based on a prior study on changes in SHIM score,[18] an expected change of at least 5% over time, an 80% power, and an α level of 0.05, groups of at least eight subjects were required for the analysis.

RESULTS

The demographic and laboratory characteristics of the study population are presented in Table 1, with a mean age of 57.9±9.9 years and a mean duration of SGLT-2i treatment of 100±8 days. The majority of the patients (92.5%) received beta-blockers, while 33 patients (82.5%) were taking a mineralocorticoid receptor antagonist. All patients were treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or angiotensin-neprilysin inhibitors.

After a three-month follow-up, patients receiving SGLT-2i demonstrated a significant improvement in SHIM scores compared to their baseline values (15.4±5.5 vs. 12.7±5.6, p<0.001). However, no significant changes were observed in the transitions between ED groups (p>0.05) (Figure 2), and likewise, although there was a minimal increase in LVEF, it was not statistically significant (31.0±7.8% vs. 32.5±7.5%, p=0.068).

The findings regarding the effect of SGLT-2i on SHIM score, BNP, and NYHA functional classes before treatment are presented in Table 2. In order to investigate the potential age-related variability regarding the impact of SGLT-2i on ED, the patients were divided into two groups according to their age: under 50 years (n=10) and over 50 years (n=30).[19] Although the baseline SHIM scores were lower in the older group, both age groups showed a significant increase in SHIM scores after treatment with SGLT-2i (<50 years group: 16.5±3.8 vs. 19.2±3.5, p=0.010; ≥50 years group: 11.7±5.7 vs. 14.5±5.5, p<0.001).

Table 1. Demographic and laboratory characteristics of the patients (n=40)

Variables	n (%)	Mean ± SD
Age (year)		
BMI (kg/cm^2)		
SGLT-2 inhibitor duration (day)		
Left ventricular ejection fraction (%)		
Ischemic CMP, n (%)	27 (67.5)	
Hypertension, n (%)	23 (57.5)	
Diabetes mellitus, n (%)	20 (50.0)	
Lower extremity PVD, n (%)	6 (15.0)	
Hyperlipidemia, n (%)	31 (77.5)	
COPD, n (%)	11 (27.5)	
Atrial fibrillation, n (%)	17 (42.5)	
ICD, n (%)	17 (42.5)	
Smoking, n (%)	8 (20.0)	
Urea, (mg/dL)		43.2±11.4
Creatinine (mg/dL)		1.1±0.2
eGFR (mL/min/1.73 m^2)		71±19.8
Sodium (mEq/L)		139±2.7
Potassium (mEq/L)		4.4±0.5
Medications		
Antiplatelet, n (%)	21 (52.5)	
Anticoagulant, n (%)	17 (42.5)	
ACE inhibitor, n (%)	25 (62.5)	
ARB, n (%)	10 (25.0)	
ARNI, n (%)	5 (12.5)	
Beta blocker, n (%)	37 (92.5)	
CCB, n (%)	6 (15.0)	
MRA, n (%)	33 (82.5)	
Furosemide, n (%)	35 (87.5)	
Thiazide, n (%)	16 (40.0)	
Statin, n (%)	17 (42.5)	
Digoxin, n (%)	7 (17.5)	

SD: Standard deviation, BMI: Body mass index, SGLT-2i: Sodium-glucose co-transporter-2 inhibitors, CMP: Cardiomyopathy, PVD: Peripheral vascular disease, COPD: Chronic obstructive pulmonary disease, ICD: Implantable cardioverter defibrillator, eGFR: Estimated glomerular filtration rate, ACE: Angiotensin-converting enzyme, ARB: Angiotensin-2 receptor blockers, ARNI: Angiotensin receptor blocker-neprilysin inhibitor complex, CCB: Calcium channel blockers, MRA: Mineralocorticoid receptor antagonists.

The study patients were divided into two subgroups based on their diabetes status and smoking history,[20,21] as these factors have been associated with endothelial dysfunction and, consequently, ED. After treatment with SGLT-2i, both the diabetic (p<0.001) and the non-diabetic (p<0.001) patients showed a significant improvement in their SHIM scores. Although the smokers had lower baseline SHIM scores, they demonstrated a similar improvement in their SHIM scores as the non-smokers following the administration of SGLT-2i [10.5 (4-17) vs. 13 (7-22), p=0.010; 11.5 (4-22) vs. 16 (6-24), p<0.001, respectively].

Treatment with SGLT-2i was also associated with statistically significant reductions in BNP levels [483 pg/mL (98-2122) vs. 264 pg/mL (48-1297), p<0.001], as well as significant changes in the distribution of NYHA

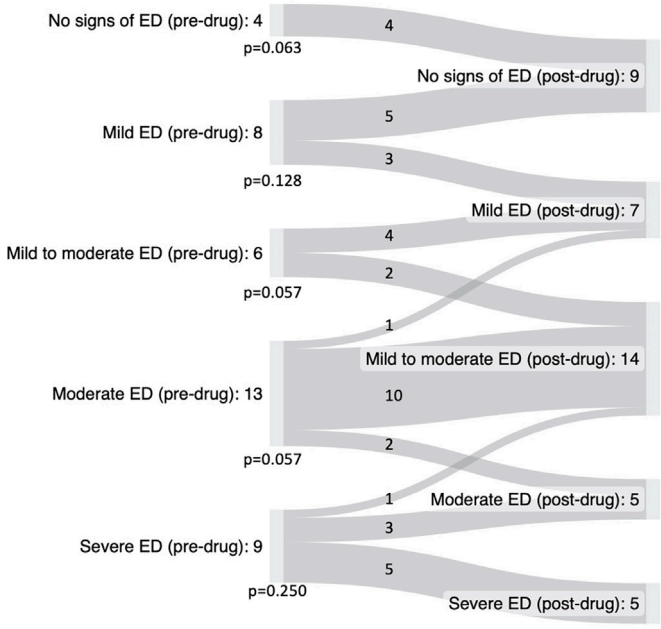

Figure 2. The transition of patients between ED groups after SGLT-2i treatment.

ED: Erectile dysfunction, SGLT-2i: Sodium-glucose co-transporter 2 inhibitor.

Table 2. Comparing pre- and post-treatment values of SHIM scores, BNP, and NYHA functional classes with the use of SGLT-2i

	Pre-SGLT-2i value	Post-SGLT-2i value	p
SHIM score	12.7±5.6	15.4±5.5	<0.001
50< years old (n=10)	16.5±3.8	19.2±3.5	0.010
≥50 years old (n=30)	11.7±5.7	14.5±5.5	<0.001
Non-smoker (n=32)	11.5 (4-22)	16 (6-24)	<0.001
Smoker (n=8)	10.5 (4-17)	13 (7-22)	0.010
DM (-) (n=20)	13.2±5.5	16.0±4.9	<0.001
DM (+) (n=20)	12.2±5.9	14.9±6.1	<0.001
Absence of lower extremity PVD (n=34)	13.4±5.6	16.3±5.3	<0.001
Presence of lower extremity PVD (n=6)	8.8±3.9	10.5±4.2	0.036
SHIM classification*			
Non-ED group, n (%)	4 (10.0)	9 (22.5)	0.006
Group with ED, n (%)	36 (90.0)	31 (77.5)	<0.001
Left ventricular ejection fraction (%)	31.0±7.8	32.5±7.5	0.068
BNP (pg/mL)	483 (98-2122)	264 (48-1297)	<0.001
NYHA class*			
NYHA 1, n (%)	-	21 (52.5)	-
NYHA 2, n (%)	30 (75.0)	18 (45)	0.043
NYHA 3, n (%)	10 (25.0)	1 (2.5)	0.004

*McNemar chi-square test was used. SHIM: Sexual Health Inventory for Men, BNP: Brain natriuretic peptide, NYHA: New York Heart Association, SGLT-2i: Sodium-glucose co-transporter 2 inhibitor, DM: Diabetes mellitus, PVD: Peripheral vascular disease, ED: Erectile dysfunction.

classes 2 (p=0.043) and 3 (p=0.004). Before SGLT-2i treatment, 75.0% of the patients were in NYHA class 2, and 25.0% were in NYHA class 3. After treatment with SGLT-2i, only 2.5% of the patients remained in NYHA class 3, whereas 45% were in NYHA class 2, and 52.5% were in NYHA class 1.

A multivariable stepwise regression analysis was conducted in order to identify predictors of improved SHIM scores in response to SGLT-2i treatment. The analysis considered several factors, including age, baseline SHIM scores, baseline LVEF, baseline BNP, lower extremity PVD, changes in BNP, diabetic status, and smoking status. Age (p=0.002), baseline SHIM scores (p=0.042), and lower extremity PVD (p=0.002) were identified as negative predictors of improvements in SHIM scores. In contrast, changes in BNP (p=0.035) emerged as a significant predictor of improvements in SHIM scores (Table 3).

DISCUSSION

Our study was the first to show that SGLT-2i treatment improves sexual function in patients with HFrEF. In addition, SHIM scores also indicated that SGLT-2i treatment decreased the number of patients diagnosed with ED.

Endothelial dysfunction plays an important role in the pathophysiology of ED and some cardiovascular diseases.[22,23] The imbalance between vasoconstriction and vasodilation caused by endothelial dysfunction leads to excessive systemic vasoconstriction and decreased peripheral tissue perfusion in HF patient.[24,25] Indeed, most HF patients may suffer from ED,[8,26] and in our study, 90% of HF patients were diagnosed with EDs of various severities.

Impaired NO production is one of the mechanisms underlying endothelial dysfunction. Increased vascular oxidative stress or reduced shear stress in HF leads to decreased vascular NO release and bioavailability.[26] NO has been reported to be the major neurotransmitter of non-adrenergic non-cholinergic neurons innervating the corpus cavernosum or erectile tissue in rabbits[27] and humans[28] and to play a significant role in the relaxation of the corpus cavernosum. Thus, improving the NO pathway will contribute to the treatment of ED.[29]

The physiological effects of SGLT-2i are thought to be mediated by antioxidant, anti-inflammatory, and anti-fibrotic pathways.[9,11,12] It has been reported that mitochondrial reactive oxygen species (ROS) production and cytoplasmic ROS accumulation decreased in empagliflozin-treated cardiac microvascular endothelial cells, increasing endothelial NO bioavailability.[30] Three months of SGLT-2i treatment was associated with increased levels of brachial artery flow-mediated dilatation in 22 patients with chronic HF and type 2 DM suggesting that the NO pathway is positively affected.[17] Indeed, in a rat model of type 2 DM, empagliflozin significantly improved erectile

Table 3. Predictors of improved SHIM scores with SGLT-2i treatment via multivariable stepwise regression analysis

	β	Std. Err	p
Age	-0.245	0.103	0.002
Baseline SHIM score	-0.078	0.037	0.042
Lower extremiy PVD	-1.685	0.496	0.002
Change in BNP levels	0.002	0.001	0.035

SHIM: Sexual Health Inventory for Men, SGLT-2i: Sodium-glucose co-transporter 2 inhibitor, β: Beta, PVD: Peripheral vascular disease, BNP: Brain natriuretic peptide.

responses, as evidenced by increased intracavernous pressure and mean arterial pressure, along with enhanced nitrergic relaxations of cavernosal strips.[31] Our finding that three months of SGLT-2i treatment led to a significant increase in SHIM scores in HFrEF patients may indicate improved endothelial function.

Sexual activity is known to be closely related to aerobic capacity and endurance. Jaarsma et al.[32] reported that the decline in exercise capacity due to chronic HF is associated with the level of sexual function. The same study also showed a weak but significant correlation between the NYHA functional class and sexual performance.[32] In our study, three months of SGLT-2i treatment significantly improved the NYHA functional class. Although the exercise tolerance of the patients was not assessed, it is possible that improvements in the NYHA class also positively affected the changes in the SHIM scores.

ED is known to be associated with age and many comorbidities, including DM, hypertension, and PVD.[33-36] Although they benefited from SGLT-2i treatment, regression analysis shows that age and lower extremity PVD attenuated improvements in SHIM scores. In addition, considering that hypertensive patients were 57.5% and diabetic patients were 50% in our patient group, the improvements in the SHIM scores observed in this study following SGLT2i treatment is significant and could be valuable.

Brain natriuretic peptide, a marker used in diagnosing and following various cardiovascular diseases, is known to be elevated in HF.[37,38] In our study, 92.5% of patients were receiving beta-blockers, while all patients were treated with ACE inhibitors, angiotensin receptor blockers, or angiotensin-neprilysin inhibitors. Although beta-blockers have been shown to decrease[39] and ACE inhibitors to increase BNP levels,[40] our results showed that three months of SGLT-2i treatment led to a significant decrease in serum BNP levels in the HFrEF patients.

Study Limitations

While our study provides valuable insights into the potential benefits of SGLT-2i towards improving sexual function in male patients with HF, the strict exclusion criteria applied to better understand the effects of these inhibitors on ED resulted in a small sample size which may limit the statistical power and generalizability of this study. Another limitation is that we did not have evaluations conducted by a urology specialist to assess erectile function before and after SGLT-2i treatment. Additionally, the evaluation of erectile function before and after SGLT-2i treatment using imaging methods such as penile Doppler ultrasonography could have provided more comprehensive insights into the impact of these inhibitors on erectile function. Moreover, our study was conducted at a single center, which may limit the generalizability of its findings.

CONCLUSION

Our study suggests that treatment by SGLT-2i improves the SHIM scores in patients with HFrEF.

MAIN POINTS

- The prognosis of heart failure is strongly associated with the integrity of the endothelium.
- Endothelial dysfunction is a prominent characteristic in heart failure patients and plays a significant role in the development of erectile dysfunction in these individuals.
- Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have the potential to improve microvascular endothelial cell function due to their multifaceted effects.
- This study aims to investigate the impact of SGLT-2i treatment on erectile dysfunction in patients with heart failure.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Karabük University (approval number: 2023/1258, date: 25.01.2023).

Informed Consent: All participants provided their informed consent to participate in the study.

Authorship Contributions

Surgical and Medical Practices: İ.E., Y.A., Concept: İ.E., Y.A., Design: İ.E., Y.A., Data Collection and/or Processing: İ.E., Analysis and/or Interpretation: İ.E., Literature Search: İ.E., Y.A., Writing: İ.E., Y.A.

DISCLOSURES

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

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RESEARCH ARTICLE

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A Cross-Sectional Study of Hypertension Prevalence, Awareness, Treatment, Ratios under Control and Related Factors in Turkish Cypriot Individuals Living in North Cyprus

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Abstract

BACKGROUND/AIMS: With an incidence of more than one billion worldwide, hypertension (HT) is a major cause of premature death. The aim of this study was to evaluate the prevalence, awareness, treatment, and ratios under control of HT and its associated factors among individuals living in North Cyprus.

MATERIALS AND METHODS: Blood pressure, height, and weight measurements were taken when a doctor visited individuals' homes in this cross-sectional study. The socio-demographic characteristics of the individuals, as well as their dietary patterns, daily salt, alcohol and smoking consumption frequencies, whether they had been diagnosed with HT before, and whether they regularly used antihypertensive drugs were investigated in this research.

RESULTS: The prevalence of HT was 34.5%. The prevalence among males (n=200) was 44.4% and the prevalence among females (n=203) was 24.6%. 71.3% of the hypertensive patients were aware and 28.7% of them were unaware of their disease status. 27.3% of the hypertensive patients' blood pressure was under control, and 66.9% of the hypertensive patients were using antihypertensive drugs. 84.8% of the hypertensive patients had a body mass index considered as being overweight or obese. It was determined that 64.7% of the hypertensive patients were fed animal-based foods and 93% of the hypertensive patients whose blood pressure was not under control consumed salt in amounts greater than 6 g/day.

CONCLUSION: It was determined that approximately one-third of adults had HT, approximately one-fourth of HT patients were unaware that they had HT, and only one-fourth of HT patients had their blood pressure under control.

Keywords: Hypertension, prevalence, North Cyprus, body mass index, salt consumption

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INTRODUCTION

The prevalence of uncontrolled hypertension (HT) is a major risk factor for cardiovascular disease and stroke.[1] It is projected that the cardiovascular mortality rate associated with HT will be 23 million by 2030. The fact that individuals are not aware of the existence of their HT or do not receive treatment paves the way for the emergence of preventable or fatal diseases.[2] Therefore, with an early diagnoses of HT, regulating systolic blood pressure (SBP) below 140 mmHg and diastolic blood pressure (DBP) below 90 mmHg and making the necessary life changes are important in terms of preventing cardiovascular complications and deaths.[3] There are differences between countries in study reports on the ratios of awareness, diagnosis, prevalence, treatment, and control of HT. According to the literature, the prevalence of HT is 22.6% in Canada, 29% in the USA, 30% in England, 30.7% in India, and 39.6% in Greece.[4-7]

In parallel with the increase in average life expectancy, the incidence of chronic diseases is increasing, and so the concept of "quality of life" comes to the fore. In addition to the anxiety caused by the thought of living with a lifelong disease, an individual with a chronic disease also experiences physical, psychological, social, and economic problems.[8] Due to all of these changes, the quality of life of this individual and their family are negatively affected. In the control of HT-related diseases, drug use and lifestyle change positively affect the course of the disease.[9] With a consumption of more than 6 grams per day on average, salt is one of the main factors which increases BP. Other factors which increase BP include alcohol and cigarette consumption. A healthy lifestyle for HT patients can be defined as having an ideal body weight, leading an active lifestyle, eating a diet low in salt and saturated fat, and not drinking excessively.[7]

The aim of the study was to evaluate the prevalence, awareness, treatment, and control ratios of HT and its associated factors for the first time among individuals living in North Cyprus.

MATERIALS AND METHODS

Individuals and Study Design

This cross-sectional study was conducted between April and August, 2022 with physicians visiting the individuals' homes. This study was approved by the Ethics Committee of Cyprus Science University (approval number: 2022/12.001, date: 07.12.2022). The individuals who participated in our study are those who are Turkish Cypriots living in North Cyprus and over 18 years of age. 210,121 citizens live in 6 towns and 187 villages. Individuals were randomly selected from 6 towns (n=258) and 16 villages (n=145), taking into account the towns' populations. Those individuals who voluntarily agreed to participate in this study were informed about its purpose and method by the physician, and oral and written consents were obtained from these individuals.

The questionnaire consisted of two parts, the first part consisted of 2 questions (age and gender) about the socio-demographic characteristics of the individuals, and the second part consisted of 6 questions about the patients' attitudes and behaviors regarding HT. In the second part of the questionnaire, in which health behaviors were questioned, the individuals' nutrition model, daily salt consumption amounts, smoking and alcohol consumption frequency, and whether they had ever been diagnosed as HT patients by a doctor before were investigated. Finally, those individuals who had been previously reported to have HT by their doctor were questioned as to whether they regularly used antihypertensive drugs. The amount of salt consumed daily was determined by using the food consumption frequency questionnaire by looking at the amount and frequency of consumption of foods containing salt. The consumption of foods rich in salt such as bread, olives, cheese, halloumi, pickles, ready-to-eat foods, and dried nuts were investigated.

Anthropometric Measurements

The height of the individuals was measured with a meter placed horizontally on the wall, in the barefoot position, with the heels together and perpendicular to the body in the line of sight of the head. The weight of the individuals without shoes while wearing light clothes was measured using a sensitive weighing scale. The height and weight values of the individuals were measured by the researchers and their body mass index [BMI (kg/m^2)] was calculated from the determined values.

BP Measurement

The individual's BP was measured in a sitting position using a conventional or electronic sphygmomanometer with the arm and heart on a table at the same level. The BP values of the individuals were recorded as the average value which was obtained by using two different BP devices with classical cuffs (Erka Perfect 201 001 02 Aneroid) and electronic (Omron M7 HEM-7361T-EBK). A 5-minute rest period was given between the two BP measurements which were taken by the same person. The initial hearing of Korotkoff sounds were recorded as SBP and their disappearance as DBP. BP measurements of individuals with high BP were measured again after 5-10 min. The blood pressures of the 6 individuals who had high blood pressure were within normal values in the measurements made 5-10 minutes later so the blood pressures of these individuals were accepted as normal. Individuals who expressed nervousness during their BP measurement were excluded from this study.

Definitions

Individuals were diagnosed according to criteria from the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of Hypertension (JNC-7).[10] HT was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg.[11]

Based on the guidelines of the Turkish Society of Endocrinology and Metabolism, BMI (kg/m^2) was evaluated as underweight <18.5 kg/m^2, normal=18.5-24.99 kg/m^2, overweight=25.0-29.99 kg/m^2 and obese ≥30.0 kg/m^2.[12]

Statistical Analysis

The processing and evaluation of the data were carried out with the help of a computer using IBM SPSS (version 22.0). For descriptive analyses, data were expressed as frequencies and percentages. Pearson's chi-square (χ^2) test was used to find the relationship between categorical variables and the t-test was used to compare continuous variables. BMI was further divided into quartiles and the means of BP indexes (SBP and DBP) were compared by ANOVA. Pearson's correlation was used to find the relationship between BP (SBP and DBP) and BMI. A p-value <0.05 was considered statistically significant.

RESULTS

Of the 403 individuals in this study, 203 (50.4%) were female, 200 (49.6%) were male, and the gender ratio (male:female) was 1:1.02. The individuals' mean age was 48.3±16.7 years, the males' mean age was 48.7±17.0, and the females' mean age was 47.8±16.5. 37.5% (n=151) of the individuals were in the age range of 18-39, 35.7% (n=144) were in the age range of 40-59, and 26.8% (n=108) were in the age range of 60 years or over. 61.1% (n=246) of the individuals had a BMI considered as being overweight or obese. This ratio was 78.5% (n=157) for males and 43.9% (n=89) for females. 53.6% (n=216) of individuals were smokers and 30.3% (n=122) had never smoked. It was determined that smoking was more common in females than in males (p<0.001). The ratio of smokers for males was 38% (n=76) and 69% (n=140) for females. 30.5% (n=123) had never used alcohol before and 19.1% (n=77) consumed alcohol at least two times per week. When the frequency of alcohol consumption was evaluated by gender, it was found that males consumed alcohol more often than females (p<0.001). The ratio of those who drank alcohol at least 2 days a week in males was 30.5% (n=61) and 7.9% (n=16) in females. When the dietary models of the individuals were questioned, it was determined that 59.6% (n=240) of them consumed animal-based foods. The males were found to consume more animal-based foods than the females (p<0.001). This ratio was 75% (n=150) in males and 44.3% (n=90) in females. The salt daily consumption of 89.3% (n=360) of the individuals was more than 6 grams. This ratio was found to be 88.5% (n=177) for the males and 90.1% (n=183) for the females (Table 1).

The prevalence of HT was 44.4% (n=89) for the males (n=200) and 24.6% (n=50) for the females (n=203) (Table 2). It was found that the prevalence of HT among those aged 18-39 (n=151) was 6.6% (n=10), among those aged 40-59 (n=144), it was 37.5% (n=54), and for those aged 60 or over (n=108), it was 69.4% (n=75) (Table 2). 71.3% (n=99) of hypertensive patients (n=139) were aware, and 28.7% (n=40) were unaware that they had HT, and only 27.3% (n=38) of HT patients had their BP under control. It was determined that 66.9% (n=93) of the HT patients (n=139) used antihypertensive drugs on a regular basis, while 33.1% (n=46) did not use any antihypertensive drugs at all (Table 3).

The individuals' mean SBP measurements were found to be 125.3±19.1. Average SBP was found to be significantly higher in males (129.7±18.2) than in females (120.9±19.1) (p<0.05). It was determined that the mean DBP value of the individuals was 78.7±10.3. DBP averages for males (81.5±10.4) were found to be significantly higher than those for females (75.9±9.3) (p<0.05) (Table 4).

SBP levels were found to rise with age in females and to decrease in males at 70-79, and 80 and over after reaching a peak in the age range of 60-69 years. Males were found to have significantly higher SBP levels than females in the 18-29, 30-39, 40-49, 50-59, and 60-69 age groups (p<0.05 in all groups, Table 4, Figure 1). Males (81.5±10.4) were found to have a significantly higher DBP than females (75.9±9.3) (p<0.05). When DBP levels were compared between gender and age groups, it was found that females had significantly lower BP levels than males in the 18-29, 30-39, 40-49, 50-59, and 60-69 age groups (p<0.05 in all groups, Table 4, Figure 1). The scatter plot showing the relationship between age and SBP and DBP is shown in Figure 2a, b. A significant correlation

Table 1. Distribution of health-related characteristics of individuals according to gender

Characteristics	Male, (n=200)		Female, (n=203)		Total, (n=403)		p
	n	%	n	%	n	%	
Smoking frequency							
Non-smoker	76	38.0	46	22.7	122	30.3	**<0.001**[1*]
Smoker	76	38.0	140	69.0	216	53.6	
Ex-smoker	48	24.0	17	8.4	65	16.1	
Alcohol consumption							
Every day	17	8.5	0	0.0	17	4.3	**<0.001**[1*]
At least two days/week	44	22.0	16	7.9	60	14.9	
Occasionally	99	49.5	104	51.2	203	50.4	
Never	40	20.0	83	40.9	123	30.5	
Salt consumption (g/day)							
6≤	177	88.5	183	90.1	360	89.3	0.354[2]
6>	23	11.5	20	9.9	43	10.7	
Diet models							
Plant-based foods	50	25.0	113	55.7	163	40.4	**<0.001**[2*]
Animal-based foods	150	75.0	90	44.3	240	59.6	
BMI classification (kg/m²)							
18.5>	0	0.0	10	4.9	10	2.5	**<0.001**[1*]
18.5-24.99	43	21.5	104	51.2	147	36.5	
25.0-29.99	111	55.5	57	28.1	168	41.7	
30.0≤	46	23.0	32	15.8	78	19.4	

[1]Pearson's chi-square test (χ^2), [2]Fisher's exact test; *p<0.05. BMI: Body mass index.

was found between SBP (r=0.430, p<0.05) and DBP (r=0.164, p<0.05) with age.

When the relationship between BMI and SBP or DBP was evaluated, it was found that the SBP and DBP of underweight [(109.0±16.9) and (70.3±7.7), respectively] and normal weight [(115.9±14.1) and (74.2±7.8), respectively] individuals were lower than those of overweight [(130.1±17.7) and (81.0±9.5), respectively] and obese individuals [(134.7±21.8) and (83.5±12.2), respectively] (p<0.05 in all groups). The scatter plot showing the relationship between BMI and SBP or DBP is given in Figure 2c, d. A significant correlation was found between SBP (r=0.384, p<0.05) and DBP (r=0.377, p<0.05) with BMI.

DISCUSSION

The prevalence of HT in Greece was 39.6%, it was 35.1% in Pakistan, 31.2% in Türkiye and 30% in England.[13-16] When these ratios were examined, the prevalence of HT was determined to be 34.5% according to our results and this was found to be compatible with the findings of previous studies. When the prevalence of HT was evaluated by gender, different results were reported in the literature. Some study results showed that the prevalence of HT was higher in males, and some study results showed that it was higher in females, while other studies showed that the prevalence was equal in both sexes. In one study in Canada, the prevalence of HT among females was 24.3% and among males, it was 21.7%.[17] In another study conducted in Türkiye, the prevalences of HT in females and males were 36% and 30%, respectively.[18] In a study in Greece, the prevalence of HT in females was 36.5% and in males, it was 42.7%.[16] In another study conducted in Nigeria, unlike other research results, it was determined that the prevalence of HT was equal in both genders.[19] In our study, the prevalence was seen to be 44.5% among males and 24.6% among females. It was determined that the majority of HT patients were males and the prevalence was 1.8 times higher in males than in females. The different prevalences for HT among these reports may be due to parameters such as age groups, BMI, and the lifestyles (daily salt consumption, alcohol and cigarette consumption) of the individuals included in these studies.

Table 2. Prevalence of hypertension by gender and age groups

		Prevalence of hypertension
		n (%)
Gender	Male	89 (44.4)
	Female	50 (24.6)
	Total	139 (34.5)
Age groups	18-39 age	10 (6.6)
	40-59 age	54 (37.5)
	60≤ age	75 (69.4)
	Total	139 (34.5)

Table 3. Awareness, drug use, and blood pressure control ratios of hypertensive individuals

Parameters (n=139)		n	%
Awareness	Aware	99	71.3
	Unaware	40	28.7
Antihypertensive drug use	Yes	93	66.9
	No	46	33.1
BP under control	Yes	38	27.3
	No	101	72.7

BP: Blood pressure.

The ratio of those who were aware of their disease was 45% in China,[20] 51.4% in India,[5] 54.7% in Türkiye,[8] 65% in England, 81% in the USA, 83% in Canada[4] and 71.3% in the current study. The ratio of patients receiving medical treatment was 36.2% in China,[20] 47.4% in Türkiye,[8] 51% in England, 74% in the USA, 80% in Canada[4] and 66.9% in our study. The ratios of HT patients who reached the target BP were given as 66% in Canada, 53% in the USA,[4] 11.1% in China,[20] 28.7% in Türkiye,[8] 27% in England[4] and 27.3% in our study - with our result being compatible with the results of the studies conducted in Türkiye and England. One of the most important factors in the low ratio of HT control is the low percentage of awareness of HT. Approximately one-third of HT patients were unaware of their status and did not use any antihypertensive medicine. In addition, there was a lack of adequate antihypertensive treatment.

Age is an important risk factor for HT as its prevalence correlates with increasing age. According to the United States Centers for Disease Control (CDC), the prevalence of HT differs for males and females across all age groups and ethnicities.[21] A significant ratio (45-50%) of hypertensive patients in Türkiye are in the middle age group.[15] According to the results of a study on chronic diseases and their risk factors conducted in Türkiye, it was reported that one out of every three people between the ages of 45-54 had HT.[4] Consistent with previous study reports, our results showed that the prevalence of HT increased with age. In our study, when the prevalence of HT was evaluated according to age groups, almost one out of every three people (37.5%) in the 40-59 age group had HT. In another study conducted upon individuals over the age of 65 in Türkiye, the prevalence of HT was reported to be 67% in males and 82% in females.[20] In our study which was conducted in North Cyprus, similar to the ratios in Türkiye, the prevalence of HT was determined to be 69.4% over 60 years age.

While the unchangeable risk factors for HT include the presence of diabetes and kidney disease, advanced age, and a family history of HT, excessive salt consumption, alcohol consumption, tobacco use, insufficient physical activity and unbalanced/inadequate eating habits are among the risk factors which can be changed.[1] One of the other factors associated with HT evaluated within the scope of this study was

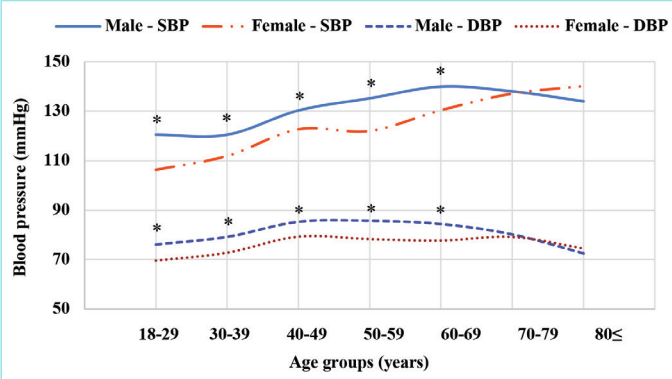

Figure 1. Distribution of mean values SBP and DBP measures according to gender and age groups.

Independent samples t-test; *p<0.05; SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Table 4. Mean values of SBP and DBP measures according to age groups and gender

Variables	Age groups (years)	Male, (n=200) $\bar{X} \pm SD$ (min.-max.)	Female, (n=203) $\bar{X} \pm SD$ (min.-max.)	Total, (n=403) $\bar{X} \pm SD$ (min.-max.)	p
SBP	18-29	120.5±12.0 (100.0-147.0)	106.3±9.5 (90.0-128.0)	113.8±12.9 (90.0-147.0)	**<0.001**[1*]
	30-39	120.5±12.8 (100.0-160.0)	111.9±15.1 (90.0-170.0)	115.94±14.7 (90.0-170.0)	**0.003**[1*]
	40-49	130.3±16.4 (105.0-160.0)	122.7±15.8 (90.0-160.0)	126.0±16.4 (90.0-160.0)	**0.034**[1*]
	50-59	135.2±19.5 (100.0-180.0)	122.0±18.9 (100.0-170.0)	130.1±20.2 (100.0-180.0)	**0.013**[1*]
	60-69	139.9±18.3 (110.0-180.0)	130.4±13.9 (100.0-160.0)	135.2±16.8 (100.0-180.0)	**0.035**[1*]
	70-79	138.0±21.4 (110.0-180.0)	137.1±24.6 (110.0-220.0)	137.5±22.8 (110.0-220.0)	0.912
	80≤	134.0±21.8 (105.0-180.0)	140.1±25.1 (110.0-190.0)	136.8±22.9 (105.0-190.0)	0.578
DBP	18-29	76.1±7.2 (55.0-85.0)	69.6±6.8 (60.0-80.0)	73.0±7.7 (55.0-85.0)	**0.002**[1*]
	30-39	79.2±7.3 (70.0-100.0)	72.8±8.1 (60.0-95.0)	75.8±8.4 (60.0-100.0)	**<0.001**[1*]
	40-49	85.3±9.5 (60.0-110.0)	79.3±8.0 (60.0-100.0)	81.9±9.1 (60.0-110.0)	**0.003**[1*]
	50-59	85.7±12.3 (60.0-120.0)	78.3±9.6 (60.0-100.0)	82.8±11.8 (60.0-120.0)	**0.018**[1*]
	60-69	84.4±11.8 (60.0-110.0)	77.7±4.8 (60.0-80.0)	81.1±9.6 (60.0-110.0)	**0.009**[1*]
	70-79	80.2±8.6 (65.0-100.0)	79.2±16.3 (60.0-140.0)	79.7±13.0 (60.0-140.0)	0.833
	80≤	72.5±11.8 (60.0-100.0)	74.5±6.7 (60.0-80.0)	73.4±9.5 (60.0-100.0)	0.578

[1]Independent samples t-test, *p<0.05. SD: Standard deviation, min.: Minimum, max.: Maximum, SBP: Systolic blood pressure, DPB: Diastolic blood pressure.

BMI. BMI was found to be higher in HT individuals and there was a linear relationship between HT and BMI.[18] The fact that obesity is a mechanism responsible for HT brings with it the recommendation to reduce the body weight of hypertensive individuals.[22] In our study, a higher ratio of BMI and a higher prevalence of HT were detected in males than in females. CDC data from 2015 to 2018 indicate that there are gender and age-related differences in obesity ratios.[23] The strong correlation between HT and obesity, and the fact that males have a higher BMI than females may be among the factors explaining the higher prevalence of HT in males in comparison to females in our study results.[24]

Since smoking and alcohol consumption also increase BP, they are among the main risk factors for HT.[25-28] In our study, the presence of HT was found to be lower in non-smokers and individuals who had quit smoking when compared to current smokers. Our study results were consistent with the results of other studies in the literature. In the current study, the ratio of hypertensive patients whose BP was not under control and consumed salt over 6 g/daily was 93%.

Since salt consumption is known to be one of the main factors increasing BP, salt restriction, which is recommended in the guidelines as one of the non-pharmacological treatments of HT, is reported to have a BP lowering effect in both normotensive and hypertensive patients. Salt restriction also increases the efficiency of antihypertensive drugs.[29,30] The daily consumption amount is suggested as being less than 6 grams. However, as in many countries, the amount of salt consumed in our country is almost more than twice this rate. The main reason why salt consumption is so high is the high salt content of processed and packaged food products, rather than the salt used on the table.[27,28] In our study, although the dietary models were not fully examined, the dietary models of the individuals were evaluated on the basis of plant and animal food. The foods consumed in the traditional Cypriot diet contain high levels of salt (halloumi, olives, cheese, tsamarella, pickles, kebabs) and/or sugar. They consume these salty foods at breakfast, lunch and dinner. In the traditional diet of Cyprus, people consume grilled meat, pickled meat such as tsamarella (salted goat meat without bones), pickled celery, watermelon and walnut pastes, halloumi and crushed olives.

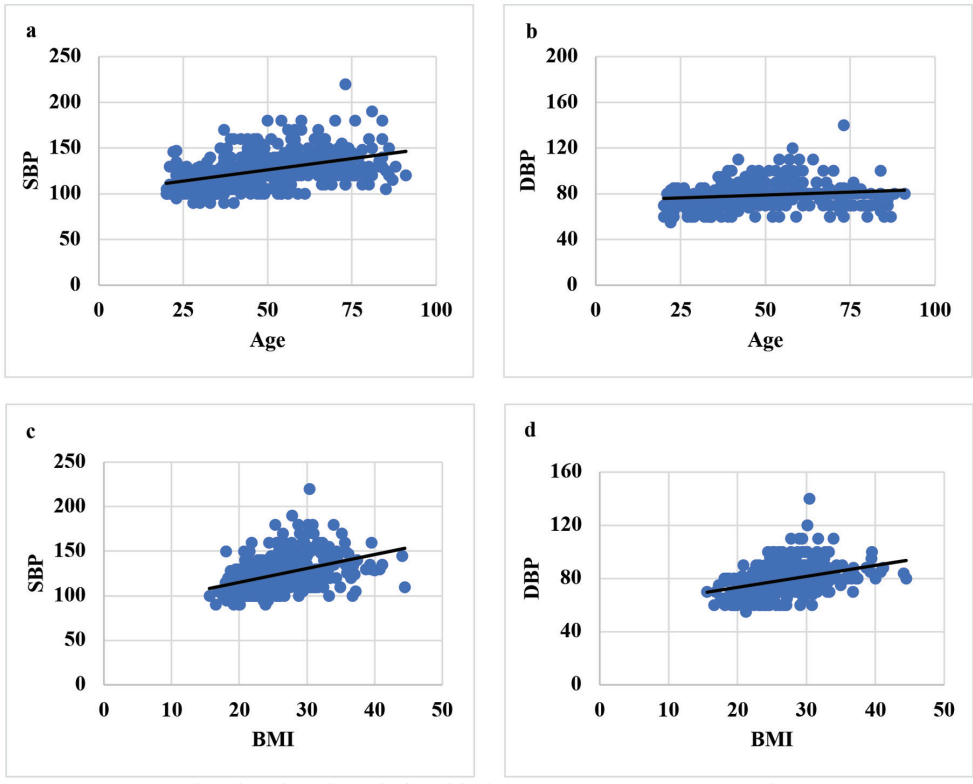

Figure 2. Scatterplot showing the relationship between age, BMI, SBP and DBP measurements of the individuals.

[a]: (r=0.430, p=0.000[1*]), [b]: (r=0.164, p=0.001[1*]), [c]: (r=0.384, p=0.000[1*]), [d]: (r=0.377, p=0.000[1*]), [1]Pearson's correlation test; [*]p<0.05; BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Since HT is a life-threatening disease, it is very important to decrease the prevalence of HT. Approximately one-fourth of hypertensive patients are unaware that they have HT and three-fourths of hypertensive patients' BP is not under control. It has been determined that 84.8% of hypertensive individuals are overweight or obese, and 93% whose BP is not under control consume more than 6 grams of salt per day.

Study Limitations

There were some limitations in our study. First, the number of individuals included in this study was limited, the other limitation was that the evaluation of daily salt consumption was carried out without measuring 24-hour urinary sodium excretion leading to an approximation of the consumption as being above or below 6 grams.

CONCLUSION

HT awareness is low in our country, which is similar to the rest of the world. In order to reduce the prevalence of HT, being overweight/obese should be avoided and daily salt consumption should be reduced. HT awareness should be increased for BP control in patients with HT, and lifestyle changes should be implemented effectively in addition to the use of antihypertensive drugs.

MAIN POINTS

- Hypertension awareness is low all over the world and also in North Cyprus.
- The prevalence of hypertension was 34.5% in Turkish Cypriot individuals living in North Cyprus.
- The daily salt consumption of 89.3% of the individuals was more than 6 grams.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Cyprus Science University (approval number: 2022/12.001, date: 07.12.2022).

Informed Consent: It was obtained.

Authorship Contributions

Surgical and Medical Practices: E.B., Concept: E.B., H.K.S., A.A., Design: E.B., Data Collection and/or Processing: E.B., Analysis and/or Interpretation: G.Ö., Literature Search: E.B., G.Ö., A.A., Writing: E.B., G.Ö., H.K.S., A.A.

DISCLOSURES

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

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RESEARCH ARTICLE

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Effect of Thiocolchicoside on Midline Closure in Early Chicken Embryos

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Abstract

BACKGROUND/AIMS: Thiocolchicoside (TCC) is a semi-synthetic derivative of colchicine analog, a muscle relaxant with analgesic and anti-inflammatory activity. Studies have shown that colchicine inhibits microtubule polymerization and stops mitotic activity, and that TCC is a competitive antagonist of g-aminobutyric acid A and glycine receptors. It is known that the use of TCC during pregnancy may have teratogenic effects. We aimed to examine the effects of drugs with TCC as their active ingredient, which are frequently used in clinical practice, on the development of chicken embryos and midline closure.

MATERIALS AND METHODS: A total of 80 eggs were incubated in an incubator for 24 hours. At the 24th hour of incubation, the eggs were divided into 4 groups. Increasing doses of TCC (8 mcg, 16 mcg, 32 mcg) in 0.1 cc solutions were applied to these groups and half of the control group was administered physiological saline, corresponding to the air sac. All eggs were then closed with sterile tapes and replaced in the incubator. On the 10th day of incubation, the eggs were hatched and the embryos were evaluated morphologically and histopathologically.

RESULTS: TCC caused a high rate of early embryo death (EED) in all groups in which it was applied. Although midline closure defects were detected in some of the developing embryos, it was not statistically significant.

CONCLUSION: EED and midline closure defects were observed in some developing embryos in the TCC applied groups. It will be possible to understand the mechanism of embryonic damage, to reveal teratogenic effects and to minimize the formation of congenital defects with more comprehensive studies.

Keywords: Thiocolchicoside, neural tube defect, chicken embryo

INTRODUCTION

Neural tube defects (NTDs) are severe birth defects of the central nervous system caused by a failure of the morphogenetic process of neural tube closure during embryogenesis.[1] NTDs are malformations caused by abnormal neural tube closure at between 3 and 4 weeks of gestation,[2] with a global incidence of 1.8 per 1,000 live births and 3 per 1,000 live births in Türkiye. Spina bifida and anencephaly, the two most common types of NTDs, affect approximately 300,000 newborns worldwide annually.[3]

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Although NTDs can be found in all geographies areas, they are a major public health problem which is especially common in low-income countries and they cause psychological, economic, and sociological problems. Although the causal mechanism is not fully understood, genetic, nutritional, and environmental factors or a combination of these factors play a definite role in the development of NTDs.[4]

Most NTD cases have a genetic etiological component and involve the interaction of several environmental risk factors. Although more than 200 NTD-causing gene expressions have been identified in various studies, the folate-dependent enzymes methylenetetrahydrofolate reductase (MTHFR), MTHFR C677T, and two polymorphisms of MTHFR A1298C are among the best known risk factors. For this reason, 400 mg of folic acid supplementation has been recommended before pregnancy as a prophylaxis.[5-8]

This anomaly has been the subject of extensive research because there are preventable conditions which can cause NTDs. Even though natal/prenatal diagnosis and treatment methods have improved, being aware of the etiological factors which may cause NTDs and keeping them under control is still the unchanged fundamental approach.[9,10]

Thiocolchicoside (TCC) is a semi-synthetic derivative of colchicine, a natural anti-inflammatory glycoside obtained from the seeds of the flower of *Superba gloriosa*.[11] TCC has a selective and strong affinity for g-aminobutyric acid A (GABA-A) receptors and it acts on muscle contractures by activating GABA inhibitory pathways, thus acting as a potent muscle relaxant. GABA is the main inhibitory neurotransmitter in the human cortex. GABAergic neurons are involved in the effective mechanisms of myorelaxants, anxiolytics, sedatives, and anesthetics. GABA can also modulate heart rate and blood pressure[12] and it has an affinity for inhibitory glycine receptors (i.e., it has glycomimetic and GABA mimetic activities). Glycine is an inhibitory neurotransmitter and functions as an allosteric regulator of N-methyl-D-aspartate receptors.[13]

Studies have shown that TCC is a competitive antagonist of GABA-A and glycine receptors.[12] A maximum daily dose of 8 mg is recommended when given intramuscularly. The use of TCC in pregnancy may have teratogenic effects.[14-16]

The aim of the present study was to investigate the effects of TCC, a commonly used muscle relaxant in clinical practice, on the development of chicken embryos and midline closure.

MATERIALS AND METHODS

This study was carried out in the Animal Laboratory of Kahramanmaraş Sütçü İmam University, Ziraat Faculty of Medicine, Department of Animal Husbandry. Ethical approval was obtained from Kahramanmaraş Sütçü İmam University, Ziraat Faculty of Medicine (approval number: 2022/03, date: 27.05.2022). Patient approval was not obtained as it was performed on animals. All protocols were in accordance with the National Laboratory Animals Care Guidelines.

Pathogen-free, fertile, day zero white broiler eggs were obtained from the CIVKUR facility in Adıyaman. A total of 80 eggs were weighed (mean weight 65±5 gr) and incubated for 24 hours at 37.8±0.2 ºC and 50-75% humidity in an incubator with automatic rotation every 2 hours.

The air sac injection technique was chosen because of the low infection risk, homogeneous distribution of the injected agent, and minimal mechanical damage which may occur in the embryo due to an increase in intra-ovarian pressure compared to other methods.[17] Since there is literature evidence that other techniques themselves may cause NTD, it was decided to conduct this study using the air sac injection technique.[18]

At the 24th hour of incubation, all eggs were sterilized with alcohol, and 0.5 mm windows were opened onto the air sacs. The eggs were divided into four basic groups (n=20 per group). TCC was dissolved in saline under sterile conditions, and 0.1 cc stock solutions were prepared at predetermined concentrations. This 0.1 cc solution was injected into the eggs using an insulin injector.

Group 1a: (Sham group). The eggs were punctured and closed without injection (n=10). This group was set up to examine the possible effects of changing the pressure inside the egg by piercing the shell.

Group 1b: (Solvent) The eggs were injected with 0.1 cc of saline (n=10). This group was set up to study the possible side effects of the solvent and any volume-occupying substance injected into the egg.

Group 2: 8 mg/day/individual (embryo dose ≥8 micrograms/0.1 cc) (n=20).

Group 3: 16 mg/day/individual (embryo dose ≥16 micrograms/0.1 cc) (n=20).

Group 4: 32 mg/day/individual (embryo dose ≥32 micrograms/0.1 cc) (n=20).

After the punctures were sealed with sterile tape, the eggs were transferred to an incubator (Cimuka, Ankara, Türkiye) with 180° automatic rotation. Temperature and humidity were checked twice a day. The eggs were opened on day 10 of the incubation period to evaluate embryological development.

Macroscopic Examination

Embryo development was evaluated macroscopically. Non-fertilized embryos were separated and excluded from this study. Head circumference, head-tail length, and embryo weight were measured in those embryos with adequate development. Light microscopy was used to classify the embryos based on whether the neural tube was closed or open along the craniospinal axis. The measurement values obtained were analyzed statistically.

Histopathological Examination

For histopathological examination of the embryos, four 2-3 mm-thick transverse sections, one from the cranial and three from the spinal regions, were taken from each embryo using a microtome knife. The samples were fixed in 10% buffered formalin for 48 hours and dried. The samples were cleaned in xylene and embedded in paraffin. These tissue sections were stained with hematoxylin-eosin stain for morphological examination. All sections were evaluated by a pathologist under a light microscope (Olympus BX51, Tokyo, Japan) at 20X and 40X magnification based on the Hamburger-Hamilton Chicken Embryo Classification System.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 21.0 of the statistical package program. The crosstabs chi-square test was used to evaluate whether there was

a statistically significant difference between the groups in terms of fertilization, [early embryo death (EED)], and NTD parameters. A p-value <0.189 was considered statistically significant. In addition, the Kruskall-Wallis test was used to compare head circumference, head-tail length, and weight parameters between the groups.

RESULTS

In group 1 (control group), 17 embryos had closed neural tubes (85%), 2 had no development (EED) (10%), and 1 had a significant developmental delay (5%). NTD was not observed in any of the embryos in this group. The embryo with a developmental delay could not be sectioned. In group 2, after the administration of 8 micrograms/0.1 cc of TCC injection, 8 embryos had closed neural tubes (40%), 10 had no development (EED) (50%), 1 had a significant developmental delay (5%), and 2 had open neural tubes (10%). The embryos with developmental delays were also sectioned and examined (Table 1).

In group 3, after the administration of 16 microgram/0.1 cc of TCC injection, 5 embryos had closed neural tubes (25%), 14 had no development (EED) (70%), and 1 had an open neural tube (5%). In group 4, after the administration of 32 micrograms/0.1 cc of TCC injection, 5 embryos had closed neural tubes (25%), 14 had no development (EED) (70%), and 1 had an open neural tube (5%) (Table 1).

Viability was 90% in the control group, and statistical analysis showed no significant difference in the experimental groups injected with TCC in terms of fertilization (p>0.001) (Table 2).

Furthermore, no significant difference was found between the experimental groups in terms of NTD (p>0.001) (Table 3). The developing embryos were quantitatively measured and evaluated using the Kruskall-Wallis test (Table 4). There were no significant differences between the control group and the TCC-treated groups in terms of weight and head circumference, but the head-tail length was significantly longer in the TCC-treated groups than in the control group.

Table 1. Results of the experimental groups injected with varying thiocolchicoside doses

Embryo observation	8 mcg	16 mcg	32 mcg	Control
No development (early embryo death)	10	14	14	2
Developmental delay	1	0	0	1
Neural tube open	2	1	1	0
Neural tube closed	8	5	5	17

Table 2. Statistical analysis of the groups in terms of fertilization (p=0.189)

	Value	df	Asymp. sig. (p-value) <0.189 was considered statistically significant. sig. (two-sided)
Pearson's chi-square likelihood	3.604[a]	3	0.308
Ratio	4.769	3	0.189
Linear-by-linear association	0.142	1	0.706
(n) of valid cases	80		

[a]Chi-square tests, Asymp.: Asymptotic, sig.: Significance.

DISCUSSION

TCC, alone or in combination with other substances, is a commonly used agent in orthopedics, physical therapy, rheumatology, and neurosurgery outpatient clinics due to its beneficial muscle relaxant activity. Based on this information and previous studies, our research hypothesis was that TCC, a colchicine derivative commonly used in clinical practice, causes developmental delays and NTDs in embryos.

Since the chemical structure of TCC is similar to that of colchicine, it is expected to have a similar side effect profile.[14] Colchicine functions primarily by inhibiting microtubules (MT) polymerization. MT polymerization affects many cellular processes, including shape maintenance, signaling, division, migration, and cellular transport. MTs are structures involved in cell shaping, the transportation of intracellular substances, the release of cytokines and chemokines, cell migration, the regulation of ion channel activity, and cell division. Colchicine stops mitosis in metaphase by inhibiting MTs and it has a limiting effect on mitochondrial activity.[18-20]

In 2013, the European Medical Association (EMA) mandated that the use of TCC-containing medicines by mouth or injection should be restricted across the European Union. These medicines are now only recommended as an adjunctive treatment for painful muscle contractures caused by spinal conditions in adults and adolescents aged 16 years and older. The EMA also stated that the dose of TCC administered orally or intramuscularly should be limited. This is based on experimental evidence showing that TCC has a tendency to damage dividing cells, resulting in aneuploidy (an abnormal number or arrangement of chromosomes).[21]

Fernandez et al.[22] tested three different colchicine doses ($5x10^{-5}$ M, $5x10^{-6}$ M, and $5x10^{-7}$ M) with two experimental treatments (*in ovo* and *in vitro*) and concluded that *in vitro* colchicine treatment was always effective in depolymerizing the MTs of neuroepithelial cells.

O'Shea conducted a study with mouse embryos in 1982 and reported that colchicine inhibited the assembly and elongation of MTs, therefore, neural folds could not form.[23] This effect supports the idea that impaired

Table 3. Statistical analysis of the groups in terms of neural tube defects (p=0.174)

	Value	df	Asymp. sig. (two-sided)
Pearson's chi-square likelihood ratio	0.510[a]	3	319
Linear-by-linear association	0.972	3	174
(n) of valid cases	0.892 39	1	169

[a]Chi-square tests, Asymp.: Asymptotic, sig.: Significance.

Table 4. Statistical comparison of weight, head circumference, and head-tail length between groups (p<0.0125)

	Weight	Head-tail length	Head circumference
Chi-square	1.253	12.617	1.696
df	3	3	3
Asymp. sig. (p-value) <0.189 was considered statistically significant. sig.	0.740	0.006	0.638

Asymp.: Asymptotic, sig.: Significance.

MT function may also cause NTDs, which is consistent with the findings of our study.

It has been demonstrated that MTs undergo major changes in organization and stability during neurulation and are essential for the timely completion of neural convergence by promoting cell elongation and polarity.[24]

MTs align along the apical-basal axis of the mammalian neuroepithelium early in neural tube closure. They functionally participate in interkinetic nuclear migration, which indirectly affects cell shape. MTs are pioneers in defining the neural rod midline prior to cavitation, both by localizing apical proteins to the tissue midline and directing cell division through a symmetric MT apparatus which helps to further define the medial localization of apical polarity.[25]

In a study conducted by Briner[26] on pregnant rats in 2001, it was reported that the GABA antagonist bicuculline may cause NTDs by causing enlargement in the vertebral arch. In the present study, the fact that TCC had an effect by binding to GABA receptors supports our hypothesis.

Lee et al.[27] injected varying doses of caffeine into early chicken embryos and found that increased doses caused NTDs. The authors reported that this effect was caused by a decrease in the number and contractility of actin microfilaments.[27]

Considering that TCC also has anti-inflammatory activity, an increase in the incidence of NTDs was observed in experimental studies and case studies previously conducted with non-steroidal anti-inflammatory drugs.[28-31]

According to the severity of possible teratogenic effects, drugs are categorized by the Food and Drug Administration into five categories: A, B, C, D, and X.[32] The pregnancy category of TCC is X, and its use is contraindicated in women with the potential to become pregnant. For drugs in this category, studies on experimental animals and pregnant women have shown that the drug is harmful to the fetus. The benefits of using these drugs are insignificant compared to the harm they may cause to the fetus. Pregnant women and women with the potential to become pregnant should not use drugs in category X under any circumstances.[32]

Various agents causing NTDs have been previously investigated by different methods. However, this is the first study conducted with chicken embryos to investigate the effects of TCC, a muscle relaxant and painkiller which we frequently use in our daily lives, on neural tube development.

The absence of embryonic development observed at high rates with increasing doses of TCC injection (70% in group 2, 50% in group 3, and 50% in group 4) suggests that TCC causes infertility because it stops mitotic activity in the early embryonic stage, causes genetic anomalies, or affects MT functions and causes cytoskeleton damage.

Therefore, TCC should be used with extreme caution during the fertile period, awareness should be raised in the community, and infertile individuals should be questioned about TCC use. Health services should be organized to prevent NTDs, and all necessary training should be provided to health personnel.[33]

Study Limitations

The results obtained from animal studies do not fully reflect the conditions in humans, and the teratogenic mechanism of TCC has not been elucidated to date. Therefore, more studies are needed to demonstrate the teratogenic effects of TCC on embryonic development and to minimize its congenital defects.

CONCLUSION

In the present study, NTD was not observed in group 1, whereas two embryos in group 2, one in group 3, and one in group 4 showed NTD in histopathological examinations. Although there was no statistically significant difference in the incidence of NTDs between the groups, among the few embryos which were able to develop, 20% in group 2, 16% in group 3, and 16% in group 4 had NTDs. Considering these high rates, we believe that the statistical analysis of our study, which examined the effects of TCC on midline closure in chicken embryos for the first time in the literature, may reveal a significant difference in terms of NTD incidence if conducted with a larger number of chicken embryos.

MAIN POINTS

- Neural tube defects (NTDs) are severe birth defects of the central nervous system caused by a failure of the morphogenetic process of neural tube closure during embryogenesis. Although NTDs can be found in all geographic areas, they are a major public health problem which is especially common in low-income countries and they cause psychological, economic, and sociological problems.
- Thiocolchicoside (TCC), alone or in combination with other substances, is a commonly used agent in orthopedics, physical therapy, rheumatology, and neurosurgery outpatient clinics due to its beneficial muscle relaxant activity.
- Our study, which examined the effects of TCC on midline closure in chicken embryos for the first time in the literature, may reveal a significant difference in terms of NTD incidence if conducted with a larger number of chicken embryos.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from Kahramanmaraş Sütçü İmam University, Ziraat Faculty of Medicine Animal Experiments Local Ethics Committee (approval number: 2022/03, date: 27.05.2022).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Authorship Contributions

Surgical and Medical Practices: R.E., E.C.K., Concept: R.E., E.C.K., K.D.S., Z.Y., Design: R.E., K.D.S., Data Collection and/or Processing: R.E., E.C.K., Z.K.A., İ.E.S., Z.Y., Analysis and/or Interpretation: R.E., E.C.K., Z.K.A., Literature Search: R.E., E.C.K., H.T., Writing: R.E., H.T.

DISCLOSURES

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

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RESEARCH ARTICLE

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Piperacillin/Tazobactam Resistance in Clinical Isolates of *Pseudomonas* and *Klebsiella* Species at a University Hospital in North Cyprus: A Retrospective Study

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Abstract

BACKGROUND/AIMS: Antibiotic resistance has become a significant problem for healthcare systems, with the *Pseudomonas aeruginosa* and *Klebsiella* species being of particular concern due to their high resistance rates. These resistant strains are making healthcare-associated infections increasingly difficult to treat, leading to a pressing public health crisis. This retrospective study aimed to evaluate the incidence of piperacillin/tazobactam (PTZ) resistance in clinical isolates of the *Pseudomonas* and *Klebsiella* species.

MATERIALS AND METHODS: Patient demographics and antimicrobial susceptibility outcomes were examined from the medical records at a university hospital in North Cyprus, between January, 2016 and March, 2022 in order to determine the extent of resistance to PTZ in these strains. A total of 812 *Pseudomonas* and 865 *Klebsiella* isolates from various hospital departments were assessed for PTZ resistance using the Vitek 2-Compact System (BioMérieux) and SPSS.

RESULTS: According to our findings, the resistance rates for PTZ were 22.9% and 26.6% for the *Pseudomonas* and *Klebsiella* species, respectively. Interestingly, the demographic distributions of resistance rates displayed a difference between genders and age groups. The elderly group had the highest resistance rates. Female patients exhibited lower resistance rates than male patients. In terms of hospital departments, the intensive care unit had the highest resistance rates (37.3% and 42.6% for *Pseudomonas* and *Klebsiella* isolates, respectively), followed by cardiology (27.9% and 33.3%) and chest disease and allergy (27.6% and 30.8%).

CONCLUSION: Given the high rates of PTZ resistance observed in this study, it is imperative to manage PTZ with caution and implement comprehensive infection prevention and control measures in healthcare facilities in order to address this public health concern.

Keywords: Piperacillin/tazobactam, resistance, *Pseudomonas*, *Klebsiella*, North Cyprus

INTRODUCTION

The escalation of antimicrobial resistance poses a significant threat to humanity. Multidrug-resistant bacteria which cause diseases have emerged and spread globally, creating a challenge for public health.[1] Misuse and overuse of antimicrobial agents have increased bacterial resistance to the available drugs, rendering antimicrobial treatments less effective.[2,3] *Enterobacteriaceae* are considered the most significant bacteria which result in diseases in humans. Among them, *Escherichia coli* is the species with the highest clinical relevance, while *Pseudomonas aeruginosa* (*P. aeruginosa*) is accountable for the highest rate of failure in antibacterial therapy.[4,5]

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The *P. aeruginosa* and *Klebsiella* species cause nosocomial infections such as urinary tract infections, surgical site infections, pneumonia, and bloodstream infections. Unfortunately, these bacteria are becoming increasingly resistant to various antibiotics, including piperacillin/tazobactam (PTZ).[6,7] PTZ is commonly used to cover Gram-negative bacteria empirically and remains active against a significant proportion of Extended Spectrum Beta Lactam-Gram-negative resistant strains.[8] Researchers have also reported PTZ resistance,[9,10] but few studies have evaluated PTZ in a clinical setting regarding the isolates of the *Pseudomonas* and *Klebsiella* species. Long-term antibiotic use, infection management practices, underlying health status, patient age, and local transmission are the risk factors which make bacterial pathogens susceptible to PTZ resistance.[11-14] This retrospective study aimed to evaluate PTZ resistance rates in *Pseudomonas* and *Klebsiella* isolates to provide surveillance data for the rational use of this antibiotic and effective infection control measures in a secondary care hospital in Nicosia, Turkish Republic of North Cyprus.

MATERIALS AND METHODS

Sample Collection

This study was conducted at a university hospital, located in North Cyprus. Diverse clinical samples, including abscess/wound material, aspirate fluid, blood, bronchial lavage, catheter tip, cerebrospinal fluid, pleural fluid, semen, sputum, urethral discharge, urine, and vaginal discharge, were collected from patients in various hospital departments. All reports of *Pseudomonas* pathogens from January 2016 to March 2023, and *Klebsiella* pathogens from January 2017 to March 2023 were included in this study. The specific inclusion/exclusion criteria applied were as follows: *Pseudomonas* isolates between January 1, 2016, and March 30, 2022, and all *Klebsiella* isolates from January 1, 2017, to March 30, 2022. All *Pseudomonas* and *Klebsiella* isolates from the same patient isolated in different years were included. Repeated tests of patients documenting the same species of *Pseudomonas* or *Klebsiella* isolates in the same month were excluded unless it was a different species of *Pseudomonas* or *Klebsiella*. The bacterial species were identified, and their resistance to PTZ was evaluated using the automated VITEK 2 system (BioMérieux). The results were interpreted using the Clinical and Laboratory Standards Institute guidelines for determining PZT resistance. The MIC breakpoint for PZT susceptibility/resistance was ≤4 µg/mL. The Near East University Scientific Research Ethics Committee approval was obtained for this study (approval number: NEU/2023/115-1742, date: 21.06.2023). However, informed consent was not required because this was a retrospective research study. The data used for analysis were taken from pre-existing sources and de-identified to ensure participant anonymity.

Statistical Analysis

We carried out separate assessments for children (0-17 years old), adults (18-64 years old), and older individuals (≥65 years old). Qualitative data values are represented using frequency and percentages. In order to investigate the relationship between two or more demographic variables in the population, we utilized the chi-square test. The level of significance was set at a 95% confidence interval (CI) with a p-value of 0.05. The main findings of our research are presented in tables, and all statistical analyses were performed using IBM SPSS version 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 812 *Pseudomonas* and 865 *Klebsiella* isolates were retrospectively reviewed and screened for PTZ resistance. These isolates were collected from various units of the university hospital between January 1, 2016 and March 31, 2022. The demographics of the study population are given in Table 1 while Table 2 summarizes the demographic representation of the patient's population from whom PTZ-resistant *Pseudomonas* or *Klebsiella* species were isolated. For *Pseudomonas* isolates, females accounted for 46.7% (n=379) of the study population, while males accounted for 53.3% (n=433). The age groups for *Pseudomonas* isolates included 370 adults (37.8%), 401 elderly (49.4%), and 104 children (12.8%). Similarly, for *Klebsiella* isolates, females accounted for 56.1% (n=485) of the study population, while males accounted for 43.9% (n=380). The *Klebsiella* isolate age groups consisted of 292 adults (33.8%), 439 elderly (50.8%), and 134 children (15.5%). For simplification and statistical analysis, the ages of the patients were divided into three groups: pediatrics (0-17 years), adults (18-64 years), and the elderly (65 years or older). The age of patients from whom clinical samples were obtained ranged in age from 0 to 96 years. Table 3 displays the susceptibility rates of *Pseudomonas* and *Klebsiella* isolates to PTZ. The overall resistance rates among *Pseudomonas* isolates, including *P. aeruginosa, Pseudomonas luteola, Pseudomonas putida,* and *Pseudomonas fluorescens*, was 22.9% (n=186). Notably, *P. aeruginosa*

Table 1. Demographics of the patient's population

Characteristic	*Pseudomonas* isolates, n (%)	*Klebsiella* isolates, n (%)
Gender		
Female	379 (46.7)	485 (56.1)
Male	433 (53.3)	380 (43.9)
Total	812 (100)	865 (100)
Age group		
Adult[a]	307 (37.8)	292 (33.8)
Elderly[b]	401 (49.4)	439 (50.8)
Pediatric[c]	104 (12.8)	134 (15.5)
Total	812 (100)	865 (100)

[a]Represents patients within the age range of 18-64 years, [b]Represents patients within the age range of 65 years and above, [c]Represents patients within the age range of 0-17 years and above.

Table 2. Demographic representation of the patient's population from whom PTZ-resistant *Pseudomonas* and *Klebsiella* species were isolated

Characteristics	*Pseudomonas* isolates, n (%)		*Klebsiella* isolates, n (%)	
Gender	**Resistant**	**Sensitive**	**Resistant**	**Sensitive**
Female	60 (15.8)	319 (84.2)	127 (26.2)	358 (73.8)
Male	126 (29.1)	307 (70.9)	103 (27.1)	277 (72.9)
Total	186 (22.9)	626 (77.1)	230 (26.6)	635 (73.4)
Age group				
Adult[a]	70 (22.8)	237 (77.2)	70 (24.0)	222 (76.0)
Elderly[b]	96 (23.9)	305 (76.1)	140 (31.9)	299 (68.1)
Pediatric[c]	20 (19.2)	84 (80.8)	20 (14.9)	114 (85.1)
Total	186 (22.9)	626 (77.1)	230 (26.6)	635 (73.4)

[a]Represents patients within the age range of 18-64 years, [b]Represents patients within the age range of 65 years and above, [c]Represents patients within the age range of 0-17 years and above.

exhibited the highest resistance rate of 22.9% (n=181), surpassing the other *Pseudomonas* species. Among the other species, resistance was observed in *Pseudomonas fluorescens* (n=1), *Pseudomonas luteola* (n=2), and *Pseudomonas putida* (n=2). Conversely, *Pseudomonas stutzeri, Pseudomonas mendocina,* and *Pseudomonas pseudoalcaligenes* did not demonstrate any resistance. Subsequently, the susceptibility rates of individual *Pseudomonas* species were determined, with *P. aeruginosa* having the highest susceptibility rate of 77.1% (n=609/790). The rest had the following susceptibilities: *Pseudomonas fluorescens* (n=2), *Pseudomonas luteola* (n=2), *Pseudomonas putida* (n=9), *Pseudomonas stutzeri* (n=2), *Pseudomonas mendocina* (n=1), and *Pseudomonas pseudoalcaligenes* (n=1).

In contrast to *Klebsiella pneumoniae (K. pneumoniae)*, which exhibited the highest resistance rate of 26.9% (n=217), *Klebsiella oxytoca* and *Klebsiella ozaenae* displayed lower resistance profiles, with 21.2% (n=11) and (n=2), respectively. PTZ susceptibility mirrored these resistance trends, with 73.1% (n=591) of *K. pneumoniae* isolates, 78.8% (n=41) of *Klebsiella oxytoca* isolates, and all *Klebsiella ozaenae* (n=2) and *Klebsiella rhinoscleromatis* isolates (n=1) demonstrating susceptibility to the antibiotic.

Table 3. Percentage susceptibility of *Pseudomonas* and *Klebsiella* isolates to piperacillin/tazobactam

Isolate	**Resistant, n (%)**	**Sensitive, n (%)**
Pseudomonas aeruginosa	181 (22.9)	609 (77.1)
Pseudomonas fluorescens	1	2
Pseudomonas luteola	2	2
Pseudomonas mendocina	0	1
Pseudomonas pseudoalcaligenes	0	1
Pseudomonas putida	2	9
Pseudomonas stutzeri	0	2
Total	186 (22.9)	626 (77.1)
***Klebsiella* species**		
Isolate	**Resistant, n (%)**	**Sensitive, n (%)**
Klebsiella oxytoca	11 (21.2)	41 (78.8)
Klebsiella ozaenae	2	2
Klebsiella pneumoniae	217 (26.9)	591 (73.1)
Klebsiella rhinoscleromatis	0	1
Total	230 (26.6)	635 (73.4)

Table 3 summarizes the demographic data of the patients from whom resistant *Pseudomonas* and *Klebsiella* species were isolated. The resistance rate was 15.8% among females and 29.6% among males. PTZ sensitivity was observed in 84.2% of the female population, compared to 70.9% of the male population. Furthermore, PTZ-resistant *Pseudomonas* isolates were identified in 22.8% of adults, 23.9% of the elderly, and 19.2% of children. Similarly, PTZ-susceptible *Pseudomonas* isolates were distributed across the age groups in the following proportions: 77.2% for adults, 76.1% for the elderly, and 80.8% for children.

Similarly, the resistance rate for *Klebsiella* isolates was 26.2% among females and 27.1% among males. PTZ susceptibility was found in 73.8% of female isolates and 72.9% of male isolates. Furthermore, PTZ-resistant *Klebsiella* were identified in 24.0% of adults, 31.9% of the elderly, and 14.9% of children. Correspondingly, PTZ-susceptible *Klebsiella* isolates were distributed across the age groups in the following proportions: 76.0% for adults, 68.1% for the elderly, and 85.1% for children.

Table 4 summarizes the results of the chi-square tests conducted to assess the associations between PTZ resistance and gender and age groups in *Pseudomonas* and *Klebsiella* isolates. In *Pseudomonas* isolates, a significant association between PTZ resistance and gender was observed ($p<0.001$), while no such association was evident in *Klebsiella* isolates ($p=0.761$). Conversely, our study identified a significant association between PTZ resistance and age for *Klebsiella* isolates ($p<0.001$), but no association was found in *Pseudomonas* isolates ($p=0.585$).

Table 5 presents the percentage distribution of PTZ resistance among *Pseudomonas* isolates collected from January 1, 2016, to March 30, 2022, and *Klebsiella* isolates collected from January 1, 2017, to March 30, 2022. Among *Pseudomonas* isolates, the highest resistance rate occurred in 2021, with 46 isolates (28.4%), followed by 2017 (29 isolates, 19.2%), 2020 (23 isolates, 19.7%), 2019 (19 isolates, 19.8%), 2016 (13 isolates, 14.8%), and 2022 (10 isolates, 27.8%). Similarly, for *Klebsiella* isolates, the peak resistance rate was observed in 2021, involving 73 isolates (36.3%), followed by 2020 (46 isolates, 27.2%), 2019 (33 isolates, 21.3%), 2017 (31 isolates, 21.2%), and 2022 (22 isolates, 39.3%).

The analysis of PTZ resistance in different sample types revealed that for *Pseudomonas* species, aspiration fluid had the highest value of 48.4% (n=75), followed by urine, sputum, abscess/wound, catheter tip, and blood with values of 11.4% (n=35), 23.9% (n=34), 16.7% (n=20), 27.8% (n=10), and 17.8% (n=8), respectively. In contrast, *Klebsiella* bacteria

Table 4. The result of the chi-square test conducted to determine the association between PTZ resistance and gender and age groups in both *Pseudomonas* and *Klebsiella* isolates

Characteristics	***Pseudomonas* isolates, n (%)**					***Klebsiella* isolates, n (%)**				
Gender	**Resistant, n (%)**	**Sensitive, n (%)**	**X^2**	**p**	**df**	**Resistant, n (%)**	**Sensitive, n (%)**	**X^2**	**p**	**df**
Female	60 (15.8)	319 (84.2)	20,147	<0.001	1	127 (26.2)	358 (73.8)	0.092	0.761	1
Male	126 (29.1)	307 (70.9)				103 (27.1)	277 (72.9)			
Total	186 (22.9)	626 (77.1)				230 (26.6)	635 (73.4)			
Age group										
Adult[a]	70 (22.8)	237 (77.2)	1.040	0.585	2	70 (24.0)	222 (76.0)	16,685	<0.001	2
Elderly[b]	96 (23.9)	305 (76.1)				140 (31.9)	299 (68.1)			
Pediatric[c]	20 (19.2)	84 (80.8)				20 (14.9)	114 (85.1)			
Total	186 (22.9)	626 (77.1)				230 (26.6)	635 (73.4)			

[a]Represents patients within the age range of 18-64 years, [b]Represents patients within the age range of 65 years and above, [c]Represents patients within the age range of 0-17 years and above.

Table 5. Percentage distribution of PTZ susceptibility within the years 2016 to 2022 in *Pseudomonas* and *Klebsiella* isolates

Year	*Pseudomonas* species		*Klebsiella* species	
	Resistant, n (%)	Sensitive, n (%)	Resistant, n (%)	Sensitive, n (%)
2016	13 (14.8)	75 (85.2)	**	**
2017	29 (19.2)	122 (80.8)	31 (21.2)	115 (78.8)
2018	46 (28.4)	116 (71.6)	25 (18.1)	113 (81.9)
2019	19 (19.8)	77 (80.2)	33 (21.3)	122 (78.7)
2020	23 (19.7)	94 (80.3)	46 (27.2)	123 (72.8)
2021	46 (28.4)	116 (71.6)	73 (36.3)	128 (63.7)
2022	10 (27.8)	26 (72.2)	22 (39.3)	34 (60.7)
Total	186 (22.9)	626 (77.1)	230 (22.6)	635 (73.4)

**Data for *Klebsiella* isolates began in the year 2017 to March 2022.

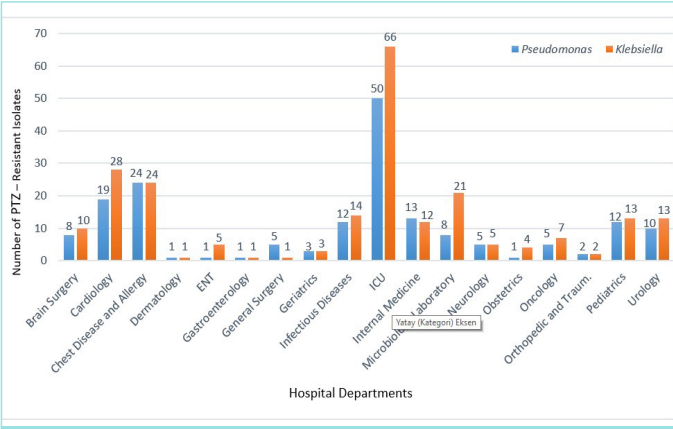

Figure 1. The distribution of resistant *Pseudomonas* and *Klebsiella* isolates according to the different hospital departments from which they were isolated.

PTZ: Piperacillin/tazobactam, ENT: Ear, nose, and throat surgery, ICU: Intensive care unit.

showed the highest resistance rates in urine (19.4%, n=96), followed by aspirate fluid, sputum, blood, and abscess/wound with resistance rates of (39.3%, n=44), (36.1%, n=41), (35.6%, n=21), and (27.1%, n=13), respectively.

Figure 1 shows the distribution of resistant *Pseudomonas* and *Klebsiella* isolates according to the different hospital departments from which they were isolated. A comprehensive examination of PTZ resistance across various hospital wards revealed that the intensive care unit (ICU) exhibited the highest resistance rates for both *Pseudomonas* and *Klebsiella* isolates. Specifically, the resistance rates for *Pseudomonas* species were distributed as follows: ICU (50 isolates, 37.3%), chest disease and allergies (n=24, 27.6%), cardiology (n=19, 23.3%), internal medicine (n=13, 23.6%), infectious diseases (n=12, 28.6%), pediatric health (n=12, 16.9%), brain surgery (n=10, 20%), urology (n=10, 18.2%), microbiology laboratory (n=8, 14.5%), general surgery (n=5), neurology (n=5), oncology (n=5, 18.5%), ear, nose, and throat surgery (ENT) (n=1), geriatrics (n=3), dermatology (n=1), and gastroenterology (n=1), respectively.

The resistance patterns of PTZ in *Klebsiella* isolates mirrored those observed in *Pseudomonas* isolates, with the ICU displaying the highest resistance rate (66 isolates, 42.6%) among the hospital departments. Following closely were cardiology (28 isolates, 33.3%), chest diseases and allergies (24 isolates, 30.8%), microbiology laboratory (21 isolates, 38.9%), infectious diseases (13 isolates, 30.2%), internal medicine (12 isolates, 18.2%), urology (13 isolates, 17.8%), pediatric health (9 isolates, 7.8%), brain surgery (8 isolates, 25%), and oncology (7 isolates, 20%). The resistance rates for the other departments were as follows: dermatology (1 isolate), ENT (5 isolates), neurology (4 isolates), obstetrics (4 isolates), geriatrics (3 isolates), pediatric surgery (3 isolates), orthopedics and traumatology (2 isolates), gastroenterology (1 isolate), general surgery (1 isolate), hematology (1 isolate), nephrology (1 isolate), and plastic surgery (1 isolate).

DISCUSSION

Assessing the incidence and antibacterial susceptibility patterns of bacterial isolates is necessary in order to determine the optimal empirical treatment for infections caused by nosocomial pathogens.[15,16] Likewise, analyzing patient data epidemiologically can help manage patients appropriately in healthcare facilities. This study aimed to determine the resistance of *Pseudomonas* and *Klebsiella* isolates to the antibiotic PTZ. This study found that the resistance rates for PTZ were 22.9% for the *Pseudomonas* and 26.6% for the *Klebsiella* species, which were significantly different from the report of the National Healthcare Safety Network.[6,14] This increase in resistance rates may be attributed to Harris et al.'s[17], identification of PTZ as a risk factor for resistance in *P. aeruginosa*, as well as Oliver et al.'s[18] observation that antibiotic use frequently leads to resistance against the antibiotic.

PTZ resistance in *P. aeruginosa* has emerged as a concerning public health issue, with *P. aeruginosa* isolates exhibiting the highest resistance rate (22.9%) among the *Pseudomonas* species. The other *Pseudomonas* species, including *Pseudomonas stutzeri, Pseudomonas mendocina,* and *Pseudomonas pseudoalcaligenes*, displayed minimal resistance, with no resistance observed for the latter two species. *Pseudomonas luteola, Pseudomonas mendocina, Pseudomonas pseudoalcaligenes,* and *Pseudomonas stutzeri* had the lowest PTZ sensitivity rates, while *P. aeruginosa* had the highest sensitivity rate (77.1%). *K. pneumoniae* isolates showed a similar pattern of resistance, with the highest resistance rate (26.9%) observed for *K. pneumoniae*, followed by *Klebsiella oxytoca* (21.2%). The least resistance was observed in *Klebsiella ozaenae* (n=2). *Klebsiella rhinoscleromatis* was completely sensitive to PTZ, and the remaining *Klebsiella* species exhibited moderate sensitivity, with *K. pneumoniae* demonstrating the highest sensitivity (68.3%).

In our investigation, a noteworthy pattern emerged in the demographic distribution of PTZ resistance among *Pseudomonas* and *Klebsiella* isolates, revealing intriguing differences between the male and female gender groups. Our study revealed a consistent pattern of higher PTZ resistance in males compared to females, with an overall resistance rate of 22.9% for *Pseudomonas* and 26.6% for *Klebsiella*. The male gender exhibited resistance rates of 29.1% for *Pseudomonas* and 27.1% for *Klebsiella*, while the female gender had resistance rates of 15.8% for *Pseudomonas* and 26.2% for *Klebsiella*. The association between gender and PTZ resistance was statistically significant for *Pseudomonas* species at a 95% CI ($p<0.001$), but not for *Klebsiella* species ($p=0.761$). This study's findings concerning gender disparity to antibiotic resistance differ from those reported by Lee et al.[19], which observed higher susceptibility rates of Gram-negative bacteria to cefotaxime and cefoxitin in females (85%) compared to males (below 75%). This contrast underscores the complexity of antibiotic resistance patterns and prompts consideration of factors contributing to gender-specific variations, including differences in bacterial species or study populations. Additionally, our results align with the report by Ruiz-Garbajosa and Cantón[20] which investigated PTZ resistance rates in *P. aeruginosa* across EU hospitals (36.1%), Spanish hospitals (29.7%), and U.S. hospitals (27.1%). This broader comparison situates our findings within a global context, emphasizing the importance of understanding regional and international trends in antibiotic resistance. The underlying reasons for these gender-based differences in PTZ resistance are still unclear, and further investigation is needed to explore potential factors such as hormonal influences, genetic predispositions, or healthcare-seeking behaviors. The high rates of PTZ resistance in both males and females highlight the need to investigate the mechanisms driving these disparities. The higher resistance rates in males may be presumed to be related to their occupation, antibiotic use, and higher risk factors for resistance. The factors which make the female gender more susceptible to antimicrobial resistance could include employment types, excessive domestic care work, and limited access to healthcare.[21]

Furthermore, the elderly age group exhibited the highest rates of PTZ resistance, reaching 23.9% and 31.9% for *P. aeruginosa* and *Klebsiella* species, respectively. This finding underscores the need for further investigation to identify the factors contributing to the elevated resistance levels among the elderly population, which could potentially be linked to decreased immunity, prolonged antibiotic use, or increased exposure to environmental pathogens. The adult age group exhibited resistance rates of 22.8% and 24% for *Pseudomonas* and *Klebsiella* species, respectively, while the pediatric age group demonstrated the lowest resistance rates at 12.2% and 14.9% for *Pseudomonas* and *Klebsiella* species, respectively. The association between age groups and PTZ resistance was statistically significant for *Klebsiella* species at a 95% CI ($p<0.001$), but not for *Pseudomonas* species ($p=0.585$). These findings suggest that the factors influencing PTZ resistance differ between *Pseudomonas* and *Klebsiella* species, with gender playing a role in *Pseudomonas* isolates and age playing a role in *Klebsiella* isolates.

A comprehensive analysis of PTZ resistance patterns across various hospital wards revealed a consistent trend of higher resistance rates in ICUs compared to other departments. For both *Pseudomonas* and *Klebsiella* isolates, the ICU exhibited the highest resistance rates, with 50 (37.3%) and 66 (42.6%) isolates exhibiting resistance, respectively. This finding is consistent with previous studies which have linked ICU environments with increased antibiotic resistance due to the prolonged use of antibiotics in critically ill patients.[22,23]

The high incidence of PTZ resistance in both *Pseudomonas* and *Klebsiella* strains in the ICU may be attributed to several factors, including a vulnerability of the critically ill patient population, a high use of invasive procedures, and the ICU serving as a focal point for infections, as well as various factors which promote the rapid transmission of multidrug-resistant pathogens in the ICU, such as new mutations, the selection of resistant strains, and inadequate infection surveillance and treatment.[24] The high resistance rates observed in ICUs underscore the need for stringent antibiotic stewardship programs in these settings. A targeted antibiotic use and the timely discontinuation of unnecessary antibiotics can help to curb the spread of resistant bacteria and protect vulnerable patients from healthcare-associated infections.

In Table 5, the resistance rates of *Pseudomonas* and *Klebsiella* species exhibited notable variations over the period 2016-2022. For *Pseudomonas* species, the resistance rate demonstrated a fluctuating trend, rising from 14.8% in 2016 to 28.4% in 2018, dipping in 2019, and subsequently oscillating between 19.7% and 28.4% in the subsequent years. A slight increase to 27.8% was observed in 2022. The overall resistance rate for *Pseudomonas* species across the study period was 22.9%.

In contrast, the resistance rates for *Klebsiella* species followed a distinct pattern. The resistance rate increased from 2017 to 2018, reaching 27.2%. A notable surge to 36.3% occurred in 2021, followed by a decline to 31.9% in 2022. The overall resistance rate for *Klebsiella* species across the study period was 22.6%. A comparison of the resistance rates of *Pseudomonas* and *Klebsiella* species shows that they exhibited a relative similarity over the years, with some fluctuations in specific years. Generally, both species displayed an upward trend in resistance rates, with *Klebsiella* species presenting a slightly higher overall rate of 26.6% compared to *Pseudomonas* species at 22.9%.

These findings underscore the dynamic and multifaceted nature of the antibiotic resistance patterns for *Pseudomonas* and *Klebsiella* species over the study period. The observed fluctuations may be influenced by various factors, such as changes in antibiotic prescribing practices, patient demographics, or the emergence of resistant strains. Further investigation into the underlying causes of these trends could contribute to a deeper understanding of antibiotic resistance dynamics in this healthcare facility.

The findings of this study are consistent with those of De et al.[25], who observed that susceptibility patterns in regional hospitals reflect their antibiotic policies. These results suggest that the use of PTZ to manage infections caused by *Pseudomonas* and *Klebsiella* strains at this tertiary healthcare facility could potentially have contributed to the high rates of PTZ resistance reported in this study.

Study Limitations

Since this was a single-center retrospective study, it is difficult to extrapolate the results to other healthcare facilities. The study's findings may not be generalizable across hospitals due to variations in patient population characteristics, antimicrobial usage, and regional patterns of resistance. For its data, this study used retrospective information from medical records. Limitations in terms of data accuracy, completeness, and potential bias may exist, as with any retrospective study. Moreover,

this study examined PTZ resistance in *Klebsiella* and *Pseudomonas* species. The use of alternative antibiotics or the existence of additional resistance mechanisms were not examined in this study as additional causes of antibiotic resistance. As a result, it is possible that the findings did not fully explain the patterns of overall antibiotic resistance present in these bacterial strains.

CONCLUSION

This study investigated the frequency of PTZ resistance among clinical isolates of *Pseudomonas* and *Klebsiella* species. The results showed that approximately 23% of *Pseudomonas* strains and 27% of *Klebsiella* strains were resistant to PTZ. Socio-demographic analysis revealed that both the male and female gender groups exhibited PTZ resistance in both species, with higher resistance rates observed in males for both *Pseudomonas* and *Klebsiella* isolates. Resistance rates were also evaluated by age groups, with the elderly age group showing the highest resistance rates in both species, followed by adults and then pediatric patients.

Patients in the ICU, chest disease, and cardiology departments had the highest rates of PTZ resistance in *Pseudomonas* species, while patients in the ICU, cardiology, chest disease and allergy, and microbiology laboratory departments had the highest rates in *Klebsiella* isolates. These findings revealed a high rate of PTZ resistance in *Pseudomonas* and *Klebsiella* bacteria in this institution, which necessitates careful antimicrobial use and periodic antibacterial sensitivity evaluations in the ICUs. Addressing this issue is crucial in order to reduce the development and transmission of antimicrobial-resistant diseases.

MAIN POINTS

- This retrospective study aimed to evaluate piperacillin/tazobactam (PTZ) resistance rates in *Pseudomonas* and *Klebsiella* isolates in North Cyprus.
- This study found that the overall resistance rates for PTZ were 22.9% for the *Pseudomonas* and 26.6% for *Klebsiella* species, significantly higher than the rates reported by the National Healthcare Safety Network.
- In both *Pseudomonas* and *Klebsiella* isolates, the intensive care unit exhibited the highest resistance rates, with 50 (37.3%) and 66 (42.6%) of isolates showing resistance, respectively.
- The resistance rates for both the *Pseudomonas* and *Klebsiella* species displayed notable fluctuations over the period 2016 to 2022.

ETHICS

Ethics Committee Approval: The Near East University Scientific Research Ethics Committee approval was obtained for this study (approval number: NEU/2023/115-1742, date: 21.06.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: C.E.N., G.E.D., N.Ç., Design: C.E.N., Data Collection and/or Processing: C.E.N., N.Ç.; Analysis and/or Interpretation: C.E.N., G.E.D., Literature Search: C.E.N., Writing: C.E.N., G.E.D.

DISCLOSURES

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

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ORIGINAL ARTICLE

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Behaviors of Transition to Complementary Feeding Scale: A Scale Development Study

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Abstract

BACKGROUND/AIMS: The aim of this methodological-descriptive study was to assess the validity and reliability of the "Behaviors of Transition to Complementary Feeding Scale (BTCF-S)."

MATERIALS AND METHODS: This study was designed as methodological-descriptive one. The sample of this study consisted of 370 mothers with 6-24-month-old babies. The data were obtained using the Parent's Information Form and BTCF-S.

RESULTS: The Cronbach's alpha values for this scale and its five subscales were 0.95, 0.95, 0.83, 0.85, 0.75 and 0.85, respectively. Item-total correlations for this scale varied between 0.30 and 0.83 ($p<0.001$). The Indices of Model Fit used in this study were as follows: the root mean square error of approximation: 0.073, the goodness-of-fit-index: 0.91 and the comparative fit index: 0.90. In the construct validity testing, the Kaiser-Meyer-Olkin value was 0.93 and Bartlett's sphericity test was 6,923.86 ($p<0.001$). The results of the factor analysis indicated a scale with 28 items, and five factors, where $R^2=64.56\%$. The total Cronbach's alpha value for this scale is 0.95.

CONCLUSION: According to our results, it was shown that this scale is a valid and reliable instrument which can be used to detect the behaviors of transition to complementary feeding among 6-24-month-old babies of Turkish mothers. The BTCF-S is a convenient tool for professionals in managing and preventing behavioral problems in the transition to complementary feeding.

Keywords: Behavior, complementary feeding, infant nutrition, reliability, validity

INTRODUCTION

Acquiring habits of healthy nutrition is important at all times of life and starts when a baby is still in the womb. This is even more important in the first two years of life, when growth and development occur at an extremely rapid pace.[1-4] Nutrition in the first 6 months of life fundamentally consists of breast milk. Babies of ages 6-24 months go through a transition into being fed complementary foods in addition to breast milk. The transition to complementary foods is a significant step in the life of a baby and a time in which the infant first becomes acquainted with different types of foods.[5-8] The psychosocial problems which are experienced at this junction have an impact on the growth and wellbeing of the child in their later years. It is for this reason that the feeding behaviors in the transition to complementary feeding gain importance.[1,9,10]

Eating behaviors start to develop in the first years of life. Nutrition is one of the basic needs which must be met in infants and children. Nutrition plays a fundamental role in ensuring healthy growth and development.[1-3] This process is affected by various factors. Behaviors

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related to the transition to complementary feeding constitute one such factor. Problems which may arise in this transition may continue throughout an individual's lifetime. The transition to complementary feeding can affect a child's eating behavior and health. Studies have indicated that a rational plan of nutrition in the infant's transition to complementary food can lower the risk of obesity, iron deficiency and anemia and prevent negative effects such as eating disorders.[2,10] Researchers have also shown that positive eating behaviors acquired in the process of the transition to complementary foods can facilitate self-feeding at an early stage and achieve a faster transition to eating foods consumed by the rest of the family.[2,10-13]

It is because of this that correctly identifying the problems related to a baby's transition to complementary feeding is important.[5,10-13] The use of effective tools which can correctly and efficiently measure transition behaviors in the shift to complementary feeding can be particularly helpful. Silverman et al.[14] developed the *Infant and Child Feeding Questionnaire* in order to identify feeding problems in children up to the age of four. The *Child Eating Behavior Questionnaire* scale, which is used to measure eating behaviors, is a scale developed for children. However, this scale is not suitable for younger age groups.[15] This scale investigates the nutritional issues encountered in children between the ages 2-9 years. Another measure which is used is the *Child Feeding Questionnaire*, which assesses the eating status of preschool children. Mallan et al.[16] *Baby Eating Behavior Questionnaire* evaluates the feeding behavior of infants. The Turkish literature includes various descriptive and prevalence studies related to a baby's transition to complementary feeding.[3,6,13] However, no instrument was found in the literature which measures the eating behaviors and transition behaviors in a baby's shift to complementary feeding.

The aim of this study was to develop a culture-specific measuring tool to be used in assessing transition behaviors in the shift to complementary feeding in 6-24-month-old babies, and to test the instrument's validity and reliability.

MATERIALS AND METHODS

Design

This study was carried out in order to assess the validity and reliability of the "Behaviors of Transition to Complementary Feeding Scale (BTCF-S)" in Türkiye. This research was methodologically designed and was a cross-sectional and descriptive study.

Participants

In this study, the population consisted of 440 people. From this population, 370 parents were selected for the sample from the volunteers who wanted to participate in this research. Considering the voluntary basis in selecting the sample from this universe, the study sample consisted of 370 individuals. In scale development, ten times as many individuals as the number of individuals to be determined in sample selection should be included in the research. Therefore, this principle was considered in the study's sample selection (n=420).[17-19]

Ethical Considerations

Ethical approval was obtained from Zonguldak Bülent Ecevit University Clinical Research Ethics Committee (approval number: 2019-173-16/10, date: 18.12.2019).

For the conduct of this study, institutional permissions and written consent were obtained from the participants via a voluntary consent form. In addition, the researchers were informed about the research and all personal information was kept confidential.

Data Collection Tools

Parent's Information Form

This form was developed by the researchers. The form includes demographic information from the participants. The form also includes data on the breastfeeding status of the babies.

BTCF-S

This scale was developed in order to evaluate behaviors in the transition to complementary feeding in babies between the ages of 6-24 months. To create the item pool of the scale, face-to-face interviews were held with a group which was similar to the study sample. Mothers with previous experience with complementary feeding were asked in the interviews to write down their experiences with the transition to complementary food. Twenty mothers participated in these discussions, which resulted in the creation of an item pool of common responses. In addition, a conceptual search was made of the relevant literature. Ultimately, a pool of items of the scale was created in line with the literature and with what was learned in the interviews with the mothers. After these interviews with the mothers, a pool of 48 items was created. This form was presented to 12 experts in draft form for content validity. The scale had five subscales pertaining to the reasons for the development of various behaviors of transition to complementary feeding: "*positive behaviors during feeding*", "*willingness to feed*", "*negative behaviors during feeding*", "*unwillingness to feed*", and "*rejection of feeding*". The answers to the scale items were prepared as a five-point Likert scale. Accordingly, the answers are scored from one to five which correspond with never and always. Some of the items, namely items 2, 5, 9, 10, 11, 12, 13, 18, 19, 20, 21, 22, 23, 24, 25, and 26 are scored in reverse. Scores from this scale range from a minimum of 28 points to a maximum of 140 points. The higher the score, the more there is a display of behaviors indicating a transition to complementary feeding.

Statistical Analysis

SPSS version 25 and AMOS 25 package program were used to analyze the statistical data. In factor analysis, first EFA and then CFA were performed. The internal consistency of the scale was evaluated with Cronbach's alpha and the maximum likelihood method. The intra-class correlation coefficient (ICC) was used for test-retest analysis. The relationships between the item-total and item-subscale correlations were examined with Pearson's correlation analysis.

RESULTS

Demographic Variables

Participants in this study were at least 21 and at most 45 years old. When their average age was examined, it was found to be 31.42±4.50 years. 55.4% of the mothers were university graduates and 31.6% were housewives. 52.7% of the mothers had one child, and 37% had two children. It was found that the income of 34.6% of the mothers was equal to their expenditure.

Validity

Content validity was used to obtain expert opinions. A draft scale prepared by the researcher and consultant was submitted for the opinion and evaluation of experts in the field. The expert group of 12 people consisted of faculty members in the field of pediatric nursing, pediatric nurses, and mothers. As a result of the suggestions made in the evaluation of the experts, the scale items were rearranged by the researchers. As a result of the review, 48 items in the draft scale were preserved. The scale draft was resent to the experts. The experts evaluated each item in terms of appropriateness and understandability, scored each statement between 1-4 points, and were asked to write their opinions and suggestions regarding each item.

The content validity index (CVI) was used to evaluate the expert opinions. According to this method, at least five and at most 40 expert opinions are needed to assess each item in the scale. In considering the views of a total of 12 experts, the content validity rate of each item was calculated. The item content validity index (I-CVI) and the scale's content validity index (S-CVI) were calculated. The experts found I-CVI to be between 0.91-0.98 for each item, and S-CVI was 0.96 for the scale.[20-23]

In the EFA, the KMO coefficient was found to be 0.934 and Barlett's sphericity test result was found to be χ^2=6,923.861, p<0.001. The eigenvalues of the five factors were found to be less than one. The variances were 19.6%, 12.8%, 12.1%, 10.1% and 9.9% for the five subscales designated as factors 1, 2, 3, 4 and 5, respectively. The total explained variance was 64.56%. The factor loadings were between 0.52-0.79 for factor 1; they were between 0.57-0.76 for factor 2, between 0.50-0.72 for factor 3, between 0.47-0.73 for factor 4 and between 0.71-0.85 for factor 5 (Table 1).

In the CFA, factor loadings were between 0.61-0.92 for Factor 1, they were between 0.56-0.85 for factor 2, between 0.57-0.86 for factor 3, between 0.46-0.75 for factor 4 and between 0.68-0.88 for factor 5. In scale evaluation, fit indices need to be maintained. In this scale, the indexes were GFI: 0.91, normed fit index: 0.95, non-normed fit index: 0.93, CFI: 0.90, incremental fit index: 0.90, χ^2/df: 2.90, p<0.001 and root mean square error of approximation (RMSEA): 0.073, respectively. The lowest correlation coefficient of the sub-dimensions of this scale was 0.50 and it varied between 0.50-0.81 for all factors (Figure 1).

Table 1. Factor loadings, eigenvalues and explained variance (%) for the five extracted factors after varimax rotation (n=370)

Sub-scales	Items	Factor loads	Eigen-value	Explained variance
F1	I.15. My baby looks happy when feeding/eating.	0.789	5,495	19,626
	I.12. My baby feeds/eats with an appetite.	0.772		
	I.14. My baby likes mealtimes.	0.765		
	I.4. My baby enjoys eating.	0.733		
	I.3. My baby has fun feeding/eating.	0.731		
	I.38. My baby enjoys his/her food.	0.701		
	I.20. My baby is unwilling to feed/eat.	0.638		
	I.40. My baby is calm between feedings/meals.	0.520		
F2	I.21. My baby is eager to feed him/herself.	0.757	3,586	12,808
	I.22. My baby wants to taste everything that is put before him/her.	0.744		
	I.24. My baby picks up the food placed before him/her and puts it into his/her mouth.	0.719		
	I.1. My baby enjoys feeding him/herself.	0.643		
	I.25. My baby likes tasting new foods.	0.566		
F3	I.19. My baby cries at feeding/mealtimes.	0.718	3,387	12,096
	I.16. My baby is restless when feeding/eating.	0.682		
	I.2. My baby cries when feeding/eating.	0.676		
	I.17. My baby gets angry when feeding/eating.	0.597		
	I.11. My baby needs music/cartoons/videos/games when feeding/eating.	0.573		
	I.29. My baby backs away when food is put before him/her.	0.497		
F4	I.18. My baby hurls or throws food on the floor at mealtimes.	0.729	2,823	10,082
	I.32. My baby spits out his/her food.	0.660		
	I.33. My baby kicks, scratches or displays other aggressive behavior during feeding/mealtimes.	0.572		
	I.30. My baby plays with his/her food when it is put in front of him/her.	0.566		
	I.28. My baby shuts his/her mouth at feeding/mealtimes.	0.482		
	I.27. My baby keeps his/her food in his/her mouth for a long time.	0.465		
F5	I.34. My baby rejects any new food put before him/her.	0.854	2,786	9,950
	I.35. My baby does not like to eat food that smells different or is of a different consistency.	0.811		
	I.26. My baby rejects new food.	0.707		
Total				**64,562**

F: Factor, I: item.

Reliability

Content and construct validity methods, which are frequently used methods, were used for the reliability analysis. The CVI cut-off point for content validity was set at 0.78 (Polit and Beck[21]). Since the CVI value of six of the items in the scale were lower than the cut-off point, they were removed from the scale and test-retest analyses were performed on the 42-item form. In the factor analysis of the 42-item scale, 14 items with factor loadings below 40% were removed from the scale and a 28-item research form was obtained.

Since the scale items were planned as sub-dimensional, the varimax rotation method was used in the EFA analysis. It was concluded that the factor loadings of the five factors obtained in the EFA analysis were in the range of 0.40-0.84. The varimax rotation method is another method used in the analysis of sub-dimensional scales.[24,25] While the loadings of each factor varied between 0.40 and 0.84, the Cronbach's alpha coefficient was between 0.75 and 0.95. The Cronbach's alpha coefficient of this scale was 0.95.

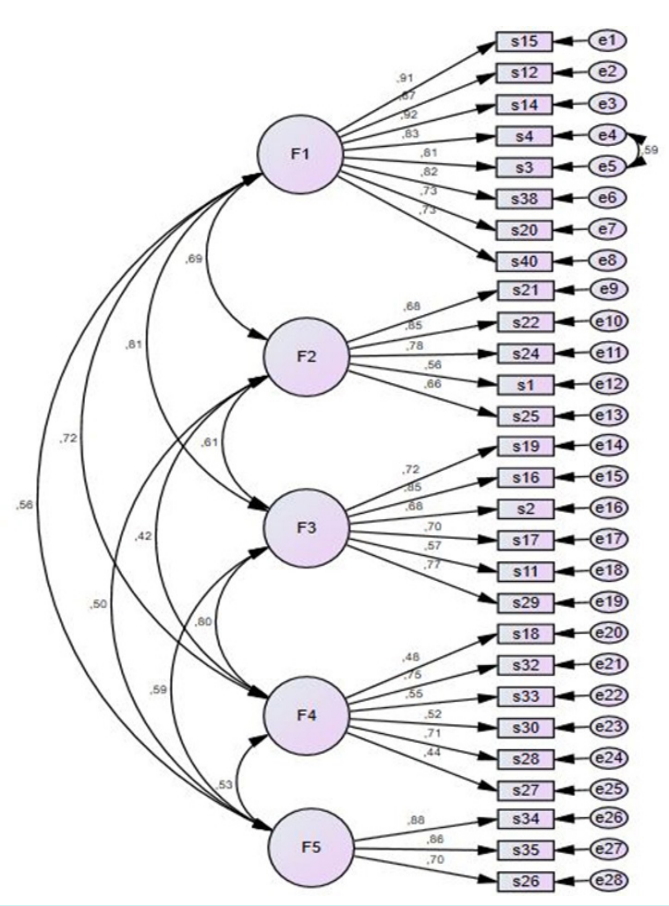

Figure 1. Confirmatory factor analysis of BTCF-S.

Model fit indices. GFI: 0.91, NFI: 0.95, NNFI: 0.93, CFI: 0.90, IFI: 0.90, χ^2/df: 2.90, p<0.001, RMSEA: 0.073.

BTCF-S: Behaviors of Transition to Complementary Feeding Scale, GFI: Goodness-of-fit index, NFI: Normed fit index, NNFI: Non-normed fit index, CFI: Comparative fit index, IFI: Incremental fit index; χ^2/df: Chi-square/degrees of freedom, RMSEA: Root mean square error of approximation.

DISCUSSION

Validity

For a scale to measure concrete and abstract concepts together, it must have validity and reliability.[21] In order to talk about the concept of validity in a scale, the scale items must accurately measure the concept being measured. For an instrument to be valid, it means that it is appropriate to the concept and measures that subject without error, that is, it measures what it is intended to measure.[24,25] Content, scope and structure validity are used in the validity analysis in order to ensure that the concept being measured is a real measurement.[9,24-26] In this study, content and construct validity were explored. Criterion validity was not used since there was no appropriate scale which could be applied to the sample group.

CVI was used to evaluate the inter-interpreter agreement. High CVI values indicate high inter-interpreter agreement. In this study, I-CVI and S-CVI values were greater than 0.78, and there was high agreement among the commentators. There are five sub-dimensions with eigenvalues greater than one. These dimensions explain 64.5% of the total variance and are quite high. When the literature was examined, it was seen that the acceptable limit for variance is 40.0-60.0%. The explained variance value of this study was above the acceptable limit.[17,23,27] According to these findings, the factor structure of this scale was evaluated as being quite strong.

In order for a scale to have a strong factor structure, the factor loadings of the scale items must be 0.40 or above. In this study, item loadings in each subscale were 0.40 or above. These loadings revealed that this scale had a strong factor structure.

According to the CFA analysis of this scale, there was no factor loading below 0.30 in all of the sub-dimensions. In the analysis, it was seen that there was no problem in the fit indices and the RMSEA value was below 0.080. According to the results of factor loadings and goodness of fit indices, the relationship between subscales was found to be strong and significant (Figure 1). The literature reveals that, in invalidity analysis, fit index values should be 0.90 or above and the RMSA value should be lower than 0.08.[18,28] The results of these studies show that the results obtained from our scale were compatible with the literature. The results obtained from our study revealed that the model indices were good and they explained all factors for this scale and all its sub-dimensions. These results showed that the factor analysis of this scale was appropriate and that this scale can be used with its sub-dimensions. The results obtained from explanatory and confirmatory factor analysis revealed the construct validity of this scale.

Reliability

It is seen that the acceptable alpha value for a measurement tool to be reliable is between 0.60 and 0.80.[17,27] The lowest value obtained from this study was 0.75, and the alpha coefficients in this scale and its sub-dimensions ranged between 0.75 and 0.95. The total scale alpha coefficient was 0.95, which is quite high. Thus, these results pointed to a reliable scale.

Another method which is recommended for reliability analysis is the test-retest method. The ICC test is frequently used in test-retest analysis. This test reveals the ICC.[24,29] A review of the literature indicated that an ICC of >0.74 is assessed as excellent.[9,24,29] In this scale, the ICC analysis showed ICC values of 0.92 for subscale F1, 0.896 for subscale F2, 0.842

for subscale F3, 0.809 for subscale F4 and 0.861 for subscale F5; the ICC value for the total scale was 0.938. All of the values were found to be higher than 0.78, indicating that this scale and its subscales had high reliability.

Both the item-total and item-subscale correlation coefficients in this study were higher than 0.30. According to the item analysis, it was seen that the correlation values of the item total scores of the scale and the scale sub-dimensions were not below 0.30 and were between 0.30-0.83. These results show that this scale and its sub-dimensions showed sufficient and acceptable correlation in item analysis.[19,29] It was seen that this scale adequately measured the concept it aimed to measure and the reliability of the item total scores was high ($p<0.001$).

The responses of the individuals were therefore deemed reliable, and the items clearly and sufficiently explained the desired topic.

Study Limitations

During the conduct of this study, due to the COVID-19 pandemic, there were issues in reaching some parents. This situation emerged as a limitation of this research.

CONCLUSION

This scale, which was developed to investigate the transition behaviors of babies aged 6-24 months to complementary feeding, is a valid and reliable measurement tool for babies and children in this age range. By using this scale, problems relating to the transition to complementary feeding can be investigated and solutions can be sought for these problems. Thanks to BTCF-S, experimental studies can be carried out and babies and parents can be strengthened. This scale can explore the issues which can arise in infants' feeding behaviors in the transition to complementary feeding and may help professionals set up parental education programs regarding feeding behaviors.

MAIN POINTS

- When the literature was examined, there was no scale which measured the transition to complementary feeding behaviors in 6-24 months babies.
- The scale developed is a valid and reliable instrument which can be employed in identifying the behaviors of 6-24-month babies in the transition to complementary feeding.
- This scale can explore problems which can arise in infants' feeding behaviors in the transition to complementary feeding.
- When parental evaluation is required, this scale allows parents to recognize the feeding behaviors of their baby.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from Zonguldak Bülent Ecevit University Clinical Research Ethics Committee (approval number: 2019-173-16/10, date: 18.12.2019).

Informed Consent: It was obtained.

Authorship Contributions

Surgical and Medical Practices: N.A., M.K., P.M.T., Concept: N.A., M.K., Design: N.A., M.K., P.M.T., Data Collection and/or Processing: N.A., P.M.T., Analysis and/or Interpretation: N.A., M.K., Literature Search: N.A., Writing: N.A., M.K., P.M.T.

DISCLOSURES

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

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RESEARCH ARTICLE

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Prevalence of Malnutrition in Hospitalized Children

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Abstract

BACKGROUND/AIMS: To identify the prevalence of malnutrition among hospitalized children on admission to hospital and discharge from hospital, to supply a classification of those patients with malnutrition, and to observe their changes in nutritional conditions during their hospital stay.

MATERIALS AND METHODS: This study comprised 400 children hospitalized in the pediatrics department of our tertiary hospital between August, 2014 and May, 2015, ranging in age from one month to eighteen years. Those patients in the emergency clinic, the pediatric intensive care, those with a birth weight under 2,500 g, premature patients and foreign patients were excluded from this study. At the time of hospitalization, measurements of bodyweight, height, mid-upper arm circumference (MUAC), triceps and subscapular skinfold thickness (SST); and at the time of discharge, measurements of the bodyweight were taken. In addition, the patients' age, sex, diagnosis, and length of hospital stay were recorded.

RESULTS: The mean age of the 400 patients was 59.2±61.9 months (median age: 32 months), and 57.8% of the patients were male. According to the Gomez classification, malnutrition was identified in 37.6% of the patients. According to the Waterlow classification, malnutrition was found in 30.8% of the patients at the time of admission and 31.5% at the time of discharge. The mild malnutrition rate decreased from 21% to 20.5%, the moderate malnutrition rate increased from 5.8% to 7.2%, and the severe malnutrition rate decreased from 4% to 3.8% at discharge. Of those patients who did not have acute malnutrition at the time of hospitalization, 4.7% had developed malnutrition by discharge. According to analysis of the MUAC, triceps skinfold thickness (TST), and SST, the patients' respective malnutrition rates were 45%, 16.4%, and 16.8%. According to the MUAC values, 12% of the malnourished patients did not meet the criteria for malnutrition using the Waterlow classification. According to the TST data, 25% of the malnourished patients did not meet the criteria for the Waterlow classification of malnutrition. According to the SST values, 29% of the patients with malnutrition did not have malnutrition according to the Waterlow classification.

CONCLUSION: Children in hospitals still have high rates of malnutrition; thus, it is important to check each patient's nutritional condition at the time of admission, periodically throughout hospitalization with detailed analyses, and to begin effective treatment as soon as possible.

Keywords: Child, hospitalization, malnutrition

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INTRODUCTION

In underdeveloped and developed countries, malnutrition is a serious public health issue which primarily affects children under the age of five.[1] 5.0 million children under the age of five died in 2020, with malnutrition accounting for almost 45% of those deaths, according to a World Health Organization (WHO) report released in January, 2022.[2]

It was stated in the UNICEF 2014 report that Türkiye has a stunted child rate of 12%, a wasted child rate of 1%, and 2% of children under the age of 5 are underweight.[3] According to the 2018 data of the Population and Health Survey of Türkiye, 6% of children under the age of 5 in Türkiye are stunted, 2% are underweight and 2% are wasted.[4]

According to reports, the prevalence of malnutrition among hospitalized children varies between 19% and 80% depending on the country's degree of development.[5-10] Recognition of malnutrition and regulation of its treatment at the time of hospitalization are important in terms of lowering morbidity and mortality.[5-11]

Malnutrition in children is not formally defined in any one way. The most frequently applied anthropometric classifications over time have been those developed by Gomez et al.[12], Waterlow and the WHO.[13-14] Gomez's approach of relating weight to age and Waterlow's way of relating weight to height and height to age are the two methods for assessing nutritional status which are most well-known. The WHO standards are still in use today. These standards establish the comparison of anthropometric measures with the reference standard using scales, the most popular of which are based on percentiles and standard deviations (SD) (or z-score: the number of SDs by which the collected data deviates from its reference median).[15] Despite the fact that standard percentile curves for countries have long been used to interpret these parameters, SDS or z-values have been utilized recently since they are a better measure of how much they depart from typical children in the community.[15] However, since it takes time to measure the subjects' weights and heights and assess their z-scores or SDS values, it does not appear viable to apply this method in every instance. For years, skinfold thickness and mid-upper arm circumference (MUAC) have been used to screen for childhood malnutrition and assess compliance with nutrition programs. Caliper measurements of skinfold thickness and MUAC are useful in making rapid nutritional assessments in individuals who cannot be weighed.[16]

The current study assessed the nutritional conditions of hospitalized children and investigated the impacts of hospitalization on their nutritional conditions over time.

MATERIALS AND METHODS

This study comprised 400 children hospitalized in our tertiary hospital's pediatrics department between August 15th, 2014, and May 15th, 2015, ranging in age from 1 month to 18 years. Those patients hospitalized in the emergency department, the pediatric intensive care unit, or the neonatal intensive care unit were not included in this study. The study excluded those individuals who had a birth weight of less than 2,500 g, those who had a history of premature delivery, were foreign nationals, or those who stayed in the hospital for less than 24 hours.

The age, sex, and diagnosis of the patients were recorded. During the first 48 hours after hospitalization, measurements of body weight, height, MUAC, triceps skinfold thickness (TST), and subscapular skinfold thickness (SST), as well as body weight and height in the final 24 hours before discharge were taken. The same medical professional took these measurements using the exact same tools. The weight measurements of those patients with diarrhea or dehydration were evaluated after hydration. Children under two years old were weighed undressed using a 20 kg capacity, 5 g sensitive digital baby scale (Weewell, China), and the body weights of those children aged over two years were measured using a 100 g sensitive adult weighing scale (Uwe-PM 150, England). Children under 2 years old had their heights measured on a flat surface while lying back with their heads fixed and their feet together using a 1 m length measure sensitive to 0.1 cm, and children older than 2 years old had their heights measured in the standing position using a tape measure fixed to the wall with a 0.1 cm sensitivity.

The left elbow joint was slightly bent from the center of the olecranon notch to the acromion notch as the MUAC was measured with an inelastic band at a 1 mm grade. TST was determined using a Holtain Skinfold Caliper (Holtain Ltd., Crymch, UK) at the intersection of the acromion and olecranon notches with an accuracy of 0.2 mm. SST was determined using a Holtain Skinfold Caliper (Holtain Ltd., Crymch, UK) with the arm hanging down, just below the scapula and parallel to the edge of the bone, holding the graspable skin fold diagonal to the body with 0.2 mm accuracy.

Gomez classification, Waterlow classification, and the WHO 2006 classification were utilized so as to identify malnutrition. The patients were evaluated for acute and chronic malnutrition according to the Waterlow classification using height for age and weight for height measurements and acute malnutrition was divided into three classes, *mild*, *moderate*, or *severe*. For all patients, the length of stay was determined by including the day of hospitalization and leaving out the day of discharge. In addition to these, z-scores of body weight, height, middle arm circumference, TST, and SST values were calculated.

The indicators recommended by the WHO to determine the nutritional conditions of children aged under 5 years are height-for-age z-score, weight-for-height z-score, and weight-for-age z-score.[17]

The Centers for Disease Control and Prevention 2000 guidelines were used to compute the triceps and SST z-scores in patients older than 1.5 years.[18]

Children under the age of five had their MUAC measured. Severe malnutrition was defined as 11.5 cm or less and moderate malnutrition as between 11.5 and 12.5 cm.[19]

Statistical Analysis

For data analysis, the SPSS 15.0 for Windows application was utilized. For categorical variables, descriptive statistics are presented as numbers and percentages, and for numerical variables, as mean, SD, minimum and maximum. Using chi-square analysis, the percentage of categorical variables was compared between the groups. When the conditions were not met, the Monte Carlo Simulation was used. The Mann-Whitney U test and the Kruskal-Wallis test were utilized to compare two independent groups because the numerical variables were not regularly distributed. Values of $p<0.05$ were used as the analytical alpha level of significance.

The present study was approved by the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 511, date: 26.05.2015).

The parents of the children who participated in this study provided written informed permission.

RESULTS

Of the 400 patients, 169 (42.3%) were girls and 231 (57.8%) were boys. Their mean age was 59.2±61.9 months. According to anthropometric measurements made at hospitalization, their bodyweight z-score was between -9 and 10.8 with a mean z-score of -0.39, and their height z-score was between -76 and 29.2 with a mean z-score of -0.39.

Hundred and fifty patients (37.6%) were found to be malnourished at the time of hospitalization when the patients were examined using the Gomez classification. Of all of the patients, 94 (23.5%) were mildly malnourished, 43 (10.8%) were moderately malnourished, and 13 (3.3%) were severely malnourished. The 10-18-year-old age category had the highest malnutrition rate (50%) when assessed by age categories. Gomez's classification found that the 10-18-year-old age category had the highest prevalence of moderate and severe malnutrition ($p<0.05$).

The Waterlow classification determined that 123 patients (30.8%) were malnourished when they were admitted. Of all the patients, 84 were mildly malnourished, 23 were moderately malnourished, and 16 were severely malnourished. Acute malnutrition was detected in 80 (20%) patients, acute malnutrition in 43 (10.8%) patients with a chronic background, and chronic malnutrition in 87 (21.8%) patients. The age groups with the highest malnutrition at admission were 6-10 years (34%) and 10-18 years (37.2%) (Table 1).

For patients under the age of five years, the WHO growth norms were used to produce z-scores (weight for age, height for age, and weight for height). Thirty-two patients (12.7%) were underweight, and 20 patients (8%) were severely underweight, as determined by the WHO's z-score criteria. Twenty-eight (11.1% of the patients) were categorized as wasted and 37 (14.7%) as stunted using the WHO's z-score criteria (Table 2).

When the patients' levels of chronic malnutrition were assessed at the time of hospitalization, mild malnutrition was found in 98 patients (24.5%), moderate in 16 (4%), and severe in 16 (4%). In the 0-2-year age category, the prevalence of chronic malnutrition was highest (39.3%; $p=0.421$) (Table 3).

According to the Waterlow classification, 126 (31.5%) of the patients were malnourished at their time of discharge. Of all the patients, 82 were mildly malnourished, 29 moderately malnourished, and 15 severely malnourished. Acute malnutrition was found in 79 (19.8%) patients, acute malnutrition on a chronic basis in 47 (11.8%), and chronic malnutrition in 82 (20.5%). The age range of 10 to 18 years (41%) had the highest level of malnutrition at the time of discharge (Table 4).

The length of hospital stay in all patients ranged from 1 to 141 days, with a mean hospital stay of 8.3±10.5 days. When evaluated according to the Gomez classification system, the duration of hospitalization was 6.35±4.98 days in those patients without malnutrition, 9.44±16.47 days in those with mild malnutrition, and 10.85±12.00 days in patients with moderate malnutrition. It was 15.80±15.45 days in patients with severe malnutrition. There was a statistically significant relationship between the degree of malnutrition and the length of hospital stay. Patients with

Table 1. Frequency of acute malnutrition detected during hospitalization and its distribution by age groups

Age (years) (n)	Severe, n (%)	Moderate, n (%)	Mild, n (%)	Total, n (%)
0-2 (n=191)	8 (4.2)	9 (4.7)	34 (17.8)	51 (26.7)
2-6 (n=78)	1 (1.3)	6 (7.7)	18 (23.1)	25 (32.1)
6-10 (n=53)	3 (5.7)	2 (3.8)	13 (24.5)	18 (34)
10-18 (n=78)	4 (5.1)	6 (7.7)	19 (24.4)	29 (37.2)
Total (n=400)	16 (4.0)	23 (5.8)	84 (21)	123 (30.8)

Table 2. Distribution of malnutrition according to the WHO standard definitions of underweight, wasted, and stunted for children by age

	Weight-for-age z-score			Height-for-age z-score			Weight-for-height z-score		
	<-2 and ≥-3, n (%)	<-3, n (%)	Total, n (%)	<-2 and ≥-3, n (%)	<-3	Total, n (%)	<-2 and ≥-3, n (%)	<-3, n (%)	Total, n (%)
0-2 years (n=191)	5 (2.6)	15 (7.8)	20 (10.4)	15 (7.8)	16 (8.4)	31 (16.2)	8 (4.2)	10 (5.2)	18 (9.4)
2-5 years (n=60)	7 (11.7)	5 (8.3)	12 (20)	3 (5)	3 (5)	6 (10)	6 (10)	4 (6.6)	10 (16.6)
(n=251)	12 (4.7)	20 (8)	32 (12.7)	18 (7.1)	19 (7.6)	37 (14.7)	14 (5.55)	14 (5.55)	28 (11.1)

WHO: World Health Organization.

Table 3. Frequency of chronic malnutrition detected during hospitalization and its distribution by age groups

Age (years) (n)	Severe, n (%)	Moderate, n (%)	Mild, n (%)	Total, n (%)
0-2 (n=191)	8 (4.2)	9 (4.7)	58 (30.4)	75 (39.3)
2-6 (n=78)	2 (2.6)	2 (2.6)	17 (21.8)	21 (27)
6-10 (n=53)	1 (1.9)	1 (1.9)	8 (15.1)	10 (18.9)
10-18 (n=78)	5 (6.4)	4 (5.1)	15 (19.2)	24 (30.7)
Total (n=400)	16 (4.0)	16 (4)	98 (24.5)	130 (32.5)

severe malnutrition had the longest lengths of hospital stay (p<0.05) (Table 5).

When the length of hospital stay was analyzed according to the Waterlow classification, it was 7.28±6.37 days in those patients without malnutrition and 9.49±16.98 days in those with chronic malnutrition and 11.44±12.98 days in patients with chronically acute malnutrition. When compared according to this classification, hospital stay was longer in those patients with acute malnutrition in a chronic background, but this difference was not statistically significant (p>0.05) (Table 5).

The mean MUAC was 16.20±4.38 cm in all patients. The mean MUAC was 5.66±2.28 cm (median: 5 cm) in those patients with malnutrition and 5.70±2.93 cm (median: 5 cm) in those without malnutrition (p=0.342). According to the MUAC values, 23% of the malnourished patients did not meet the criteria for malnutrition according to the Gomez classification, and 12% did not meet the malnutrition criteria using the Waterlow classification (Table 5).

The mean TST was 8.14±3.97 mm in all patients, 15.87±3.50 mm (median: 5 mm) in those patients with malnutrition, and 16.46±4.94 mm (median: 5 mm) in those without malnutrition (p=0.827) (Table 6). According to the TST data, 20% of the malnourished patients did not meet the criteria for the Gomez classification of malnutrition and 25% did not meet the criteria for the Waterlow classification of malnutrition.

The mean SST was 5.68±2.67 mm in all patients, 8.08±3.11 mm (median: 8 mm) in those patients with malnutrition, and 8.18±4.52 mm (median: 7 mm) in those without malnutrition (p=0.072) (Table 6). According to the SST data, 24% of the patients with malnutrition did not have malnutrition according to the Gomez classification, and 29% did not have malnutrition according to the Waterlow classification.

Table 4. Frequency of acute malnutrition detected at discharge from the hospital and its distribution by age groups

Age (year) (n)	Severe, n (%)	Moderate, n (%)	Mild, n (%)	Total, n (%)
0-2 (n=191)	7 (3.6)	8 (4.1)	34 (17.8)	49 (25.5)
2-6 (n=78)	2 (2.5)	9 (11.5)	19 (24)	30 (38)
6-10 (n=53)	2 (3.7)	3 (5.5)	10 (19)	15 (28.2)
10-18 (n=78)	4 (5)	9 (12)	19 (24)	32 (41)
Total (n=400)	15 (3.8)	29 (7.2)	82 (20.5)	126 (31.5)

Table 5. Length of hospital stay by the severity of malnutrition

	Length of hospital stay (days)		
Gomez	**Mean ± SD**	**Min.-max.**	**p**
Normal	6.35±4.98	1-41	0.012
Mild	9.44±16.47	1-141	
Moderate	10.85±12.00	1-63	
Severe	15.80±15.45	2-51	
	Length of hospital stay (days)		
Waterlow	**Mean ± SD**	**Min.-max.**	**p**
Normal	7.28±6.37	1-41	0.241
Acute	7.54±6.81	1-36	
Chronic	9.49±16.98	1-141	
Chronic-acute	11.44±12.98	1-63	

SD: Standard deviation, Min.: Minimum, max.: Maximum.

Table 6. Malnutrition frequency according to mid-upper arm circumference, triceps, and subscapular skinfold thickness data

	Triceps skinfold thickness				Subscapular skinfold thickness			
	Moderate malnutrition		Severe malnutrition		Moderate malnutrition		Severe malnutrition	
	n	%	n	%	n	%	n	%
1.5-2 years (n=34)	7	20.59	4	11.76	8	23.53	3	8.82
2-6 years (n=78)	7	9.21	6	7.89	13	16.88	1	1.30
6-10 years (n=53)	7	13.21	1	1.89	5	9.43	0	0.00
10-18 years (n=78)	4	5.13	4	5.13	1	1.28	10	12.82
	Mid-upper arm circumference				Mid-upper arm circumference			
	Severe malnutrition				Moderate malnutrition			
	n		%		n		%	
0-2 years (n=191)	56		29.47		47		24.74	
2-5 years (n=60)	5		8.20		5		8.20	

DISCUSSION

Despite the development of new methods for the evaluation of nutrition and treatment methods in the last 30 years, malnutrition has remained an important health problem. Malnutrition which already exists in a child when hospitalized can get worse by not monitoring their nutritional status.[7,8,20] The purpose of the current study was to evaluate the situation at our hospital in order to draw attention to this crucial issue.

In our study, according to the Waterlow classification, the acute malnutrition rate at the time of hospitalization was 30.8%, with 20% acute malnutrition, 10.8% acute on chronic malnutrition, and 21.8% chronic malnutrition.

The rates for the same patient groups at discharge were 19.8% for acute malnutrition, 11.8% for acute on chronic malnutrition, and 20.5% for chronic malnutrition. The malnutrition rate for these patients at the time of discharge was 31.5%.

In comparison to demographic surveys carried out with children in our nation, the prevalence of malnutrition was higher in our study.[3,4] This was owing to the fact that the majority of the patients in our study were young children from low-income, crowded homes who were admitted to hospitals due to chronic illnesses or infectious disorders which served as a precursor to the development of malnutrition. Given that the study's host hospital was a tertiary care facility, it was only normal for the nutritional status of the patient profile to suffer as a result of the admission of patients who were generally more severe and complex.

In research carried out in developed countries, the frequency of malnutrition was 13.3% in Canada, 19% in the Netherlands, and 5-27% in Australia.[5,6,9] In studies conducted in countries with low socioeconomic status, the frequency of hospital malnutrition was 39% in Thailand, and 35.2% in Brazil, which are higher than out rates.[7,10]

In the studies on malnutrition in hospitals conducted in our country, Genel et al.[21] found the acute malnutrition rate to be 21.3%, the chronic malnutrition rate to be 24.2%, and the acute on chronic malnutrition rate to be 11.9%. In 511 pediatric patients between the ages of 1 month and 18 years, according to the Waterlow classification, Kapçı et al.[11] found that 23.9% had acute malnutrition, 21.5% had chronic malnutrition, and 7.3% had acute on chronic malnutrition. Güleç et al.[22] found that the acute malnutrition rate was 20.4%, the chronic malnutrition rate was 19.2%, and the acute on chronic malnutrition rate was 7.7% in children aged 1-36 months in our hospital in 2011. With similar results to the literature, we can conclude that malnutrition has not been adequately detected and it is still not sufficiently prevented. According to Topal and Tolunay[23], the rate of acute malnutrition was 35.3%, chronic malnutrition was 14.6%, and acute malnutrition combined with chronic malnutrition was 9.8%. In a multicenter study conducted in 2015 in 37 hospitals, including our hospital, in 26 cities where children from 1 month to 18 years participated, the acute malnutrition rate was found to be 11.2% and the chronic malnutrition rate was found to be 16.6%.[24]

The cause for these disparate outcomes might be attributed to the various patient profiles which hospitals accept for admission, variations in the study methodology, and socioeconomic disparities among countries and regions.

In accordance with the Gomez classification system, severe malnutrition was found in 3.3% of the patients in our study, moderate malnutrition was found in 10.8%, and mild malnutrition was found in 25.3% of the patients. In research conducted in Adana by Topal and Tolunay[23], the prevalence of severe malnutrition was 5.4%, moderate malnutrition was 11.2%, and mild malnutrition was 20.2%. As according to Güleç et al.[22] examination of 260 patients in İstanbul using the Gomez classification, the prevalence of mild malnutrition were 32%, moderate malnutrition was 9.2%, and severe malnutrition was 6.1%. Our rates of severe and mild malnutrition were lower than those found in other studies.

According to previous studies, one key risk factor for malnutrition is an underlying chronic condition. According to Beşer et al.[24], underlying disease incidence was 47.5%. Another study conducted in Thailand[7] discovered that 64% of people had an underlying chronic illness. Fifty-three (43%) out of 123 patients in our study who had acute malnutrition at hospitalization and 34 (39%) out of 87 patients who had chronic malnutrition had an underlying chronic illness. Our findings also indicate that a major risk factor for malnutrition is an underlying chronic illness.

Mild malnutrition developed in 6.1% and moderate malnutrition in 0.7% of the patients who were admitted to the hospital without malnutrition. Moderate malnutrition developed in 5.9% of patients with mild malnutrition and severe malnutrition developed in 8.6% of patients with moderate malnutrition when they were hospitalized. Also, at discharge, the mild malnutrition rate decreased from 21% to 20.5%, the moderate malnutrition rate increased from 5.8% to 7.2%, and the severe malnutrition rate decreased from 4% to 3.8%.

Although it was observed that 107 (86.9%) of 123 patients who were found to have acute or acute on chronic malnutrition during hospitalization continued to have malnutrition at discharge, the malnutrition of 16 (13%) patients improved. Of the patients who did not have acute malnutrition at the time of hospitalization, 4.7% had developed malnutrition by their discharge time.

When we examined the few studies showing the effects of hospitalization on nutritional status, it was seen that malnutrition developed in 24% out of 148 patients who did not have any previous malnutrition in a study in Thailand, and it was shown in another study in England that 23% of the patients underwent nutritional deterioration.[7,20] Ibraheam Kazem et al.[25] found that moderate malnutrition developed in 21% of patients with mild malnutrition during hospitalization, and mild malnutrition developed in 7.2% of patients without malnutrition at admission. It was found that mild malnutrition increased from 12.9% to 15%, moderate malnutrition increased from 14% to 15.6%, and severe malnutrition increased from 6.8% to 7.8% at the time of discharge from the hospital.

The reason why hospitalization posed less risk of malnutrition in our study compared with these other studies might be that there were more patients with moderate and severe malnutrition in other studies compared with our study.

In a study conducted in Türkiye in 2015 comprising 37 centers and 1,513 patients, the prevalence of malnutrition and the length of hospital stays were assessed. It was discovered that patients with malnutrition had longer hospital stays.[24] Similarly, according to Topal and Tolunay[23], those patients with malnutrition spent a longer time in hospital.

The mean LOS was found to be 8.3 days in the present study. When the relationship between LOS and nutritional status was evaluated, the mean LOS was 6.35 days in those patients without malnutrition according to the Gomez classification system, 9.44 days in those with mild malnutrition and 10.85 days in patients with moderate malnutrition, and 15.80 days in patients who had severe malnutrition. This demonstrates that patients with malnutrition spent more time in the hospital than those without malnutrition, and that the length of hospitalization increased as malnutrition severity progressed ($p<0.05$). When the patients were categorized using the Waterlow classification, those who had chronic acute malnutrition stayed in the hospital the longest (11.44 days). Our findings support those in the literature, which revealed that malnutrition lengthened hospital stay.

The present study shows that when treating the primary illness, the assessment of nutritional status is insufficient and hospital-related malnutrition is frequently disregarded. It has been found that a lack of nutritious food can cause problems with growth, development, and health recovery, as well as the effectiveness of medications. This can lead to prolonged hospitalizations and increased mortality and morbidity rates.[23]

As a result, different anthropometric tools for evaluating malnutrition have been suggested. MUAC was recommended because it is an easy, practical, low cost, rapid nutritional assessment method which may be used in patients whose age, height, or weight are not known, and so it can reduce the burden on healthcare workers in emergency situations.[16,26,27]

MUAC is related to arm muscle mass and subcutaneous fat. In undernourished children exhibiting clinical indications of edema, muscle wasting may not be accurately reflected by weight-based indices, potentially producing false-positive or false-negative findings and MUAC more accurately reflects in young children because infants and young children have smaller muscles than adults and MUAC changes little in the first years of life.[26,28] In our study, the frequency of malnutrition under the age of two was 54.2% according to MUAC measurements, and 10.4% of the patients were underweight, and 9.4% were wasted according to the WHO z-score criteria.

According to the MUAC values for those under 5 years, 12% of the malnourished patients did not meet the criteria for malnutrition using the Waterlow classification. The current study showed that MUAC reflects malnutrition in young children better than the other classifications as has been previously reported in the literature.[29,30]

Skinfold thickness measurements are widely used to assess body fat because the measurements are non-invasive, simple and they are sensitive to changes in nutritional status. The two most frequently taken skinfold measurements are at the triceps and subscapular sites.[31] In children, skinfold thickness may be a helpful screening variable. Nevertheless, its precision may be questionable in those children who have severe muscle wasting.[32] In our study, according to the results of TST and SST measurements, malnutrition was detected most frequently at the age of 1.5-2 years, with a total rate of 32.3%. Although TST and SST are good methods to assess body fat as opposed to other anthropometric measurements, they are not adequate indicators of undernutrition.[11]

CONCLUSION

In summary, in this study, the frequency of malnutrition was determined in children according to age groups both at the time of admission to the hospital and at the time of discharge. The frequency of malnutrition is increasing gradually due to insufficient recognition of malnutrition and inadequate treatment during hospitalization. Patients who are malnourished have difficulties receiving treatment, stay longer in hospital and their length of stay increases as their level of malnutrition increases. The development of malnutrition throughout hospitalization in children who do not have malnutrition at the time of hospitalization shows the importance of the assessment of nutritional status. The nutritional status of patients should be assessed with more detailed analyses because checking only the percentiles of a patient's height and weight is not a determining criterion in malnutrition. Another significant issue which attracted attention during this investigation was the lack of a simple and highly accurate calculation method which could be used in all age groups.

MAIN POINTS

- The assessment of nutritional status is important.
- Hospital-related malnutrition is commonly ignored when treating the primary illness because nutritional status screening is insufficient.
- Malnutrition lengthens the hospital stay and increases mortality and morbidity.
- As evaluating merely a patient's height and weight percentiles is not a defining factor in malnutrition, the nutritional condition of patients should be evaluated with more in-depth investigations.
- The problem is the absence of an easy-to-use, almost ideal calculation method which can be used on all age groups.

ETHICS

Ethics Committee Approval: The present study was approved by the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 511, date: 26.05.2015).

Informed Consent: The parents of the children who participated in this study provided written informed permission.

Authorship Contributions

Surgical and Medical Practices: R.K., N.U., Concept: R.K., N.U., A.M.U., Design: R.K., N.U., A.M.U., Supervision: R.K., N.U., A.M.U., Data Collection and/or Processing: R.K., N.U., A.M.U., Analysis and/or Interpretation: R.K., N.U., Literature Search: R.K., N.U., A.M.U., Writing: R.K., N.U., Critical Reviews: R.K., N.U., A.M.U.

DISCLOSURES

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RESEARCH ARTICLE

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Opinions of Obstetricians and Midwives for Vaginal Birth after Cesarean Section: A Qualitative Study in Türkiye

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Abstract

BACKGROUND/AIMS: The most effective strategy to stop the increasing worldwide popularity of cesarean delivery and to break the logic of "once a cesarean, always a cesarean" is "vaginal birth after cesarean (VBAC)". Health professionals are highly influential in women's birth preferences. Therefore, there is an urgent need to focus on the views of midwives and obstetricians about VBAC section. The aim of this study was to investigate the opinions of obstetricians and midwives about VBAC.

MATERIALS AND METHODS: This study adopted two qualitative research approaches, phenomenology and case study. A total of 26 healthcare professionals, including 12 obstetricians and 14 midwives, were interviewed in this study. One-to-one in-depth phone interviews were held with the midwives and obstetricians and these interviews were audio-recorded. The obtained data were written out completely and analyzed thematically. This study aligns with the Consolidated Criteria for Reporting Qualitative Research checklist.

RESULTS: Three main themes and nine sub-themes were obtained in this research. The main themes described are "Healthcare Professional Factors", "Healthcare System Factors", and "Clinical/Pregnant Woman Factors".

CONCLUSION: As a result of the interviews, in addition to the lack of information about VBAC delivery, various factors which prevent this application from being widespread were determined. Accordingly, with these ideas in mind, there is a need to organize training programs in order to improve healthcare professionals' knowledge and skills about VBAC section. It is recommended to provide the necessary legal regulations and raise awareness on vaginal births after cesarean deliveries.

Keywords: Vaginal birth after cesarean section, obstetrician, midwife, qualitative study

INTRODUCTION

Cesarean section (CS) rates are increasing all around the world. Upon examining CS statistics among the countries of the Organization for Economic Cooperation and Development (OECD), Türkiye ranked first with a CS rate of 54% in 2019. According to the data, Korea has a CS rate of 45%, Poland 38%, Italy 33%, and the USA 32%.[1] The fact that the rate in our country, Türkiye, is 54% in the international records is remarkable in illustrating the subject's importance. In its statement on cesarean delivery rates, the World Health Organization declared that the safe range of cesarean delivery rates of the International Health Community was between 10% and 15% and that exceeding this range was not effective in reducing maternal and neonatal mortality rates.[2] Elective repeat cesarean deliveries (ERCD) are profoundly influential regarding the increase in CS rates.[3] The rates of repeated cesarean deliveries among the OECD countries are between 45.5% and 93.5%.[4] The most effective strategy to stop the increasing worldwide popularity of cesarean deliveries and to break the logic "once a cesarean, always a cesarean" is vaginal birth after cesarean (VBAC).[5-7] The effectiveness of this strategy on reducing the number of cesarean deliveries was

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proven in the previous century with Trials of Labor after Cesarean (TOLAC). VBAC is an invaluable approach for women having been found eligible for TOLAC to experience vaginal birth.[7,8] Finland, Sweden and the Netherlands are developed countries with high VBAC rates ranging from 45% to 55%.[9] In a study conducted with health professionals in these countries, it was stated that it is important to decide on the choice of mode of delivery together with the woman, to support the woman, for midwives and obstetricians to act together, and to adopt a common approach for VBAC.[9] With this in mind, it has been reported in many studies in the literature that health professionals are influential on women's birth preferences.[10-12] For this reason, it is necessary to know the opinions of obstetricians and midwives on this subject.

It was highlighted in a systematic review and meta-synthesis study that the factors affecting the delivery preferences of healthcare professionals should be investigated.[13] Also, the urgency to conduct studies examining the qualitative aspects of the interaction between healthcare professionals and pregnant women, as well as the effects of such interaction on the decision-making process has been reported on in the literature.[14] It was emphasized in another meta-synthesis study that studies on this subject should be conducted in different countries for the promotion of VBAC.[15] The aim of this study was to review midwives' and obstetricians' opinions regarding VBAC.

Research Question

What are the views of obstetricians and midwives on VBAC?

MATERIALS AND METHODS

Study Design

This study was a descriptive qualitative study conducted in order to evaluate the opinions of obstetricians and midwives on VBAC. This study adopted two qualitative research approaches, phenomenology and case study. Qualitative research, which is of the phenomenological type, aims to make general inferences on the experiences of more than one person. Phenomenology, a type of qualitative research, is also a 20th century philosophy defined by the German mathematician and author Edmunnd Husserl. The philosophy of phenomenology, which is frequently preferred in nursing and health sciences, emphasizes the transfer of experience and experiences to daily life. Case studies, on the other hand, are the collection of data under certain themes as a result of obtaining data about a situation in limited times and places in various ways and examining these data in-depth.[16] Case studies, which are a preferred approach in the field of some health sciences such as psychology and medicine, aim to reveal the results of an event.[17] Our research was planned in line with the qualitative research paradigm based on a 32-item Consolidated Criteria for Reporting Qualitative Research, a guide for qualitative studies.

Participants

The research sample consisted of obstetricians and midwives who actively worked in obstetrics services in state hospitals, maternity hospitals, university hospitals, or private hospitals in Türkiye and who were within the sample chosen through a snowball sampling method. A total of 26 healthcare professionals, including 12 obstetricians and 14 midwives, were interviewed in this study.

The study population consisted of obstetricians and midwives working in active obstetric services in state hospitals, obstetrics and gynecology hospitals, university hospitals or private hospitals in Türkiye. According to the 2020 Turkish Statistical Institute, a total of 59,040 midwives and 171,259 physicians were working in Ministry of Health, university or private hospitals.[18] According to 2018 data from the Ministry of Health, General Directorate of Health Services, Department of Manpower, 5,608 of the physicians working were gynecologists or obstetricians.[19] In this study, the purposeful sampling method, which is one of the most widely used non-probability sampling strategies, was applied.[17] The research sample consisted of obstetricians and midwives working in any of the above-mentioned health institutions. By using the "theoretical sampling" approach to determine the sample size, the data collection process was completed at the stage when the concepts and processes which could be the answer to the research question started to repeat (saturation point). Considering similar studies, it was predicted that this number would be at least 12-15 for each group (obstetricians and midwives) and this number was reached in the study as expected.[12]

Data Collection

The data were collected through in-depth, one-to-one interviews with healthcare professionals using a semi-structured interview form developed by the researchers and evaluated by an expert committee (obstetrician lecturer, midwife lecturer).

The questionnaires to introduce the participants were prepared separately for obstetricians and midwives. The introductory questionnaire includes nine questions for obstetricians and seven questions for midwives.

In this study, a semi-structured interview form was used to collect qualitative data. In order to obtain the opinions of obstetricians and midwives on VBAC, the form consists of open-ended questions and includes a total of four questions with two sub-items each.

The questions in the semi-structured questionnaire were prepared in line with the opinions and suggestions of the obstetrician and midwife faculty members in a meeting held with the expert committee. The data were collected by phone calls made via WhatsApp. The researcher conducted all interviews from home due to coronavirus disease-2019. Appointments were made with obstetricians and midwives working at the clinic. Appointment days and times varied according to the availability of the health professionals.

After receiving permission for recording, the interviews were audio-recorded. The research data were collected using an introductory questionnaire prepared separately for obstetricians and midwives and a semi-structured interview form prepared for both groups. The introductory questionnaire form had nine questions for obstetricians and seven questions for midwives. There were a total of four questions with two sub-items in the form consisting of open-ended questions in order to get the opinions of obstetricians and midwives about VBAC. The interviews lasted 15-20 minutes due to the workload of the obstetricians and midwives working at clinics during the pandemic. Data were collected between January and July, 2021.

Ethical Procedures

This research was approved by the Ege University Scientific Research and Publication Ethics Committee (approval number: 09/05-676, date: 15.10.2020). An informed consent form was read to the healthcare professionals at the start of their interview. Their consent was obtained

at the beginning of the audio interview by asking them to declare to "have read, understood, and accepted the informed consent form." The midwives are referred to as "MW 1, MW 2 etc.", and the obstetricians are referred to as "OBS 1, OBS 2 etc.". During the collection of the data, the rules in the Helsinki Declaration were followed.

Statistical Analysis

Initially, one-to-one, in-depth interviews were conducted with the obstetricians and the midwives. The interviews were recorded as audio recordings. The raw transcripts of the recordings were transcribed into the Microsoft Word program. The accuracy of the data in the Microsoft Word document was checked by repeatedly listening to the recordings. A categorization matrix was created in line with the purpose of this study. The data were presented for an expert opinion. All data were examined in terms of content in accordance with the categories, and it was re-evaluated as to whether the data conformed to the categorization and then it was coded. The data were collected under the themes determined by the program MAXQDA 2020, and an evaluation was accordingly made between the coded data and the researcher's notes in accordance with an expert opinion. Following these stages, the data were visualized.[20]

Rigor

This research had limitations related to validity and reliability, which is a concern in all qualitative research.

For validity, these limitations were tried to be overcome by defining the characteristics of the research sample, environment and processes in detail at a level which could be compared with other samples, obtaining as much unbiased and in-depth information from the participants as possible, and obtaining confirmation of the information provided.

For reliability, the individuals who were data sources in this study were clearly identified, the interviews were audio recorded, and detailed information on data collection and analysis methods was provided in the research report.[17]

RESULTS

As for the socio-demographics of the participants, a total 26 healthcare professionals from 12 different provinces, including 14 midwives and 12 obstetricians participated in this study. The age range of the participants varied between 23 and 47 years. The midwives had different work experiences ranging from 1 to 29 years, while the obstetricians had expertise from 2 to 7 years. Of the midwives and obstetricians who agreed to participate in this study, 13 were actively working in public hospitals, 6 in maternity hospitals, 2 in private hospitals, and 5 in university hospitals with 19 of them having VBAC experience. The socio-demographic characteristics of the interviewed midwives and obstetricians are shown in Table 1.

The findings are presented in three main categories: "Healthcare Professional Factors", "Healthcare System Factors", and "Clinical/ Pregnant Woman Factors" (Figure 1).

Main Theme 1: Healthcare Professional Factors

The theme of Healthcare Professional Factors was divided into three sub-themes: "Status of Recommending VBAC", "Unplanned" and "Impact on Opinion after VBAC Experience".

Sub-Theme 1: Status of Recommending VBAC

Healthcare professionals who declared that they did not recommend VBAC explained their reasons for not recommending it. Healthcare professionals usually stated that they did not recommend VBAC due to possible complications, inadequate equipment in their hospital, the presence of past surgical operations, the fear of childbirth in women, the lack of enough studies on VBAC and inter-pregnancy intervals of less than twelve months.

"Honestly, I do not recommend it because of the possible complications" [MW12].

"I do not recommend it because the hospital has limited equipment. There is no blood bank in the hospital. There is no on-call anesthesia team or obstetrician in the hospital. That is why I do not recommend it" [OBS3].

"I do not recommend it as there are too few studies on this subject" [MW8].

"I do not recommend it if inter-pregnancy has an interval of less than two years" [MW5].

Other health professionals explained why they recommend VBAC. Healthcare professionals declared that they could recommend VBAC to appropriate pregnant women after evaluating the women in terms of factors such as the inter-pregnancy interval, vaginal examination findings, and chronic diseases. In addition, they also talked about the advantages of vaginal delivery.

"The women I recommend VBAC to are those with a cesarean delivery history with an interval of at least two years, having no problem relating to the mother or her pelvic structure. If I do not see any problems relating to this delivery, then I have them opt for VBAC" [OBS9].

"If there are four to five years between inter-pregnancy, I recommend VBAC" [OBS6].

"I recommend VBAC. Because vaginal birth has certain advantages for both the mother and her baby. It enhances the bond between the mother and her baby. It has both medical and psychological benefits. Also, it avoids cesarean delivery-related traumas" [MW4].

Sub-Theme 2: Unplanned

Healthcare professionals stated that their VBAC experiences were mostly unplanned, and they had to use the vaginal birth method as the dilatation and effacement processes had been completed:

"Generally, VBAC is unplanned. The pregnant woman comes with a cervix dilation of eight to nine centimeters and childbirth occurs" [MW6].

Sub-Theme 3: Impact on Opinion after VBAC Experience

The midwives' opinions were positively affected after VBAC experiences, while obstetricians who are against VBAC, on the other hand, stated why they were still against VBAC.

"Women who prefer a caesarean section in their first birth do not need to have a caesarean section again. All women have a chance of vaginal delivery" [MW6].

Table 1. Socio-demographic characteristics of the participants

Participants	Hospital	Gender	Age	City	Work experience (years)	VBAC experience
Midwife 1	Maternity hospital	Female	29	Ankara	8	Yes
Midwife 2	Maternity hospital	Female	35	Ankara	12	No
Midwife 3	Maternity hospital	Female	46	Ankara	28	Yes
Midwife 4	State hospital	Female	23	Ankara	1	No
Midwife 5	Maternity hospital	Female	42	Ankara	17	No
Midwife 6	Maternity hospital	Female	38	Ankara	19	No
Midwife 7	State hospital	Female	47	Bursa	29	No
Midwife 8	Maternity hospital	Female	28	İzmir	6	No
Midwife 9	University hospital	Female	24	Kocaeli	2	Yes
Midwife 10	University hospital	Female	38	İzmir	15	No
Midwife 11	State hospital	Female	43	Balıkesir	9	Yes
Midwife 12	State hospital	Female	30	Manisa	8	Yes
Midwife 13	State hospital	Female	26	Manisa	4	Yes
Midwife 14	State hospital	Female	30	Manisa	12	Yes
Obstetrician 1	State hospital	Female	34	İzmir	6	Yes
Obstetrician 2	State hospital	Female	32	Edirne	2	Yes
Obstetrician 3	State hospital	Female	31	Gümüşhane	5	Yes
Obstetrician 4	Private hospital	Female	31	İstanbul	2	Yes
Obstetrician 5	University hospital	Female	33	İzmir	2	Yes
Obstetrician 6	State hospital	Female	36	Eskişehir	7	Yes
Obstetrician 7	State hospital	Female	34	İstanbul	6	Yes
Obstetrician 8	University hospital	Female	35	Diyarbakır	3	Yes
Obstetrician 9	Private hospital	Male	36	İstanbul	4	Yes
Obstetrician 10	State hospital	Male	30	İzmir	2	Yes
Obstetrician 11	State hospital	Male	36	Sivas	3	Yes
Obstetrician 12	University hospital	Female	37	İzmir	7	Yes

VBAC: Vaginal birth after cesarean.

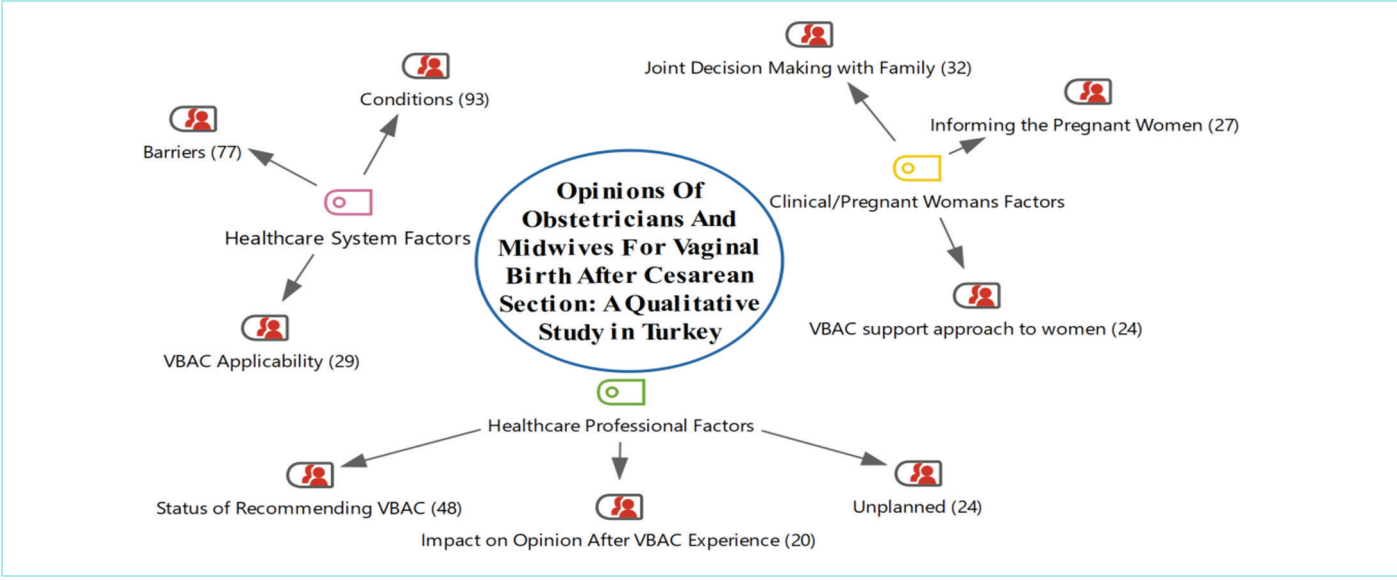

Figure 1. Codes of themes of the opinions of obstetricians and midwives for vaginal delivery after cesarean section.
VBAC: Vaginal birth after cesarean.

"It did not change my opinion. We can see how thin the lower segment got because of the previous cesarean deliveries. I believe it has a high probability of a uterine rupture caused by contractions. The VBAC experience did not give me much except anxiety" [OBS2].

Main Theme 2: Healthcare System Factors

The theme of Healthcare System Factors was divided into three sub-themes: "Conditions", "Barrier" and "VBAC Applicability".

Sub-Theme 1: Conditions

Health professionals stated that women should be informed in detail about VBAC, the pregnant woman should be followed up regularly before delivery, and the reason for the previous caesarean section should be known. They stated that it would be an advantage if the woman had a history of vaginal delivery. Health professionals have stated that VBAC can be done in fully equipped centers. They also have talked about the importance of having the experience of performing VBAC.

"The family should be well informed. It should not be the 'It is so popular to have a vaginal birth' kind of awareness. They should know all the risks" [OBS1].

"The pregnant women must not have any cesarean indications under any circumstances. The reason for the previous cesarean should be well investigated" [MW10].

"The fact that the patient had a previous vaginal birth may be seen as a simple factor since it will facilitate the labor progression" [OBS3].

"There should be a neonatal intensive care unit at the hospital where we can immediately supply the necessary blood products which should be provided" [MW9].

"There should be an on-call anesthesia expert and obstetrician in the hospital. We should be able to process the pregnant woman to a cesarean within minutes" [OBS1].

"VBAC may be recommended by physicians as the experience and expertise develop in Türkiye" [OBS11].

Sub-Theme 2: Barriers

The healthcare professionals stated some barriers to VBAC. These factors include malpractice lawsuits filed against them in cases of any complications, CS indications, insufficient experience, workload, lack of time, the status of women in society, pregnant women lacking information about VBAC, and the fear of vaginal delivery. The healthcare professionals participating in this study specified that the most common barrier to VBAC was the risk of uterine rupture. Midwives have criticized the fact that obstetricians always prefer ERCD.

"The experts have hesitations because of malpractice suits. A legal regulation should be made about this" [OBS5].

"We do not have enough experience" [OBS6].

"It is a little about the status of women in society. The people here avoid taking women to hospital by valuing them, and therefore the pregnancies cannot be followed up. That is why we know the problems we will encounter" [MW9].

"I think the patients are not adequately informed about this. This inevitably causes an increase in cesarean rates" [MW12].

"The pregnant women do not want vaginal birth because of the fear of normal birth and their anxiety about it" [OBS11].

"Even a small membrane bleeds in cases of ruptures. Both baby and mother may be dead within minutes or even seconds. I think both are equally very valuable. VBAC is like a gamble" [OBS1].

"We act according to the obstetrician's decision. The obstetrician's choice of birth is important" [MW7].

Sub-Theme 3: VBAC Applicability

The obstetricians and midwives had a disagreement on VBAC applicability in our country. They predominantly declared that the VBAC applicability was low in the current healthcare system.

"I do not find public hospitals appropriate at all. Because only one physician is on call. It can be very difficult to even keep up with normal patients. Much closer follow-up and more experienced midwives are required for VBAC" [OBS7].

"It can be applied if desired. Why not? The delivery room is a place open to development" [MW14].

"I think it may be applied in the current healthcare system. Most public hospitals have these opportunities. My current hospital also has these opportunities" [OBS2].

Main Theme 3: Clinical/Pregnant Woman Factors

The theme of Clinical/Pregnant Woman Factors was divided into three sub-themes: "Joint Decision Making", "Informing the Pregnant Women", "VBAC approach to women".

Sub-Theme 1: Joint Decision Making with the Family

The healthcare professionals, in general, specified the requirement for a joint decision with the woman and her family on the delivery preference:

"A joint decision should be made by clearly talking about all of the risks. It should not be a unilateral decision" [MW8].

"I want every woman to be sure of her birth choice. It's not good to force people to do things" [OBS1].

Sub-Theme 2: Informing the Pregnant Women

The healthcare professionals who encountered women with previous cesareans and their families said they only provided information if the women asked about VBAC.

"I explain if the pregnant woman asks. However, I do not suggest VBAC" [OBS4].

"If the conditions are OK, every time, I ask if they are considering VBAC" [OBS9].

Sub-Theme 3: VBAC Support Approach to Women

Some of the midwives and obstetricians participating in this study declared that they support VBAC. Some, on the other hand, have

stated that they do not support VBAC and will refer pregnant women to another medical institution.

"If there are no complications and most importantly, if the woman wants it, I support VBAC. Of course, by informing about the benefits and risks" [MW4].

"I support VBAC and explain all of the risks completely to the pregnant women. I have not experienced anything negative yet" [OBS9].

"I inform the pregnant women of the possible risks. I explain that I do not recommend VBAC. If the woman wants VBAC, I suggest that the pregnant woman talks to another doctor who will undertake this risk" [OBS2].

DISCUSSION

Most of the obstetricians and midwives participating in this study stated that they had VBAC experience. However, health professionals stated that they did not plan VBAC and that they had to have vaginal delivery to women who had previously had a CS. However, it has been reported that women who want VBAC in the Netherlands are followed up by their obstetrician throughout their pregnancy and care services are provided by midwives, obstetricians and assistant doctors in the hospital.[9] In Sweden, it is known that VBAC is recommended for pregnant women who have had a previous CS and have no complications.[9]

The reason why the results of this study are different from the literature can be said to be because of the higher rates of VBAC in other countries, where health professionals have experienced VBAC many times and as a result of gaining experience, they prefer VBAC in a planned manner without hesitation.

Those midwives who had previously experienced VBAC who participated in this study were positively affected. However, obstetricians stated that VBAC did not add anything to them other than causing anxiety. After the VBAC experience in the literature, the opinions of the obstetricians were divided into two. While one of the obstetricians with VBAC experience stated that they chose ERCD to avoid negative results, another obstetrician shared his sadness that he could not perform VBAC because his patient wanted a CS and he lost his patient due to a cesarean complication.[12] Looking at the results, it can be seen that midwives are more in favor of vaginal delivery compared to obstetricians. The reason why obstetricians prefer CS is that they think that the negativities which may occur at the time of birth will put them in a difficult situation. In this situation, it is thought that VBAC rates can be increased significantly with the support of obstetricians.

The obstetricians and midwives participating in this study stated that women should be given detailed information about complications. Similarly, in a study conducted in Ireland, Italy and Germany, health professionals were of the opinion that VBAC should be offered to women as a birth choice and it emphasized the importance of informing the woman about VBAC in detail and impartially while discussing the possible risks.[12,21] It is extremely important that the woman and her family be made aware of VBAC, which is one of their birth preferences, and that they decide on their own will. Obtaining the consent of the woman is also extremely valuable for the obstetrician and midwife in order to perform their profession without fear.

The obstetricians and midwives mentioned that the conditions in the hospital should be improved in order to perform VBACs. Panda et al.[13] mentioned that TOLAC is not preferred due to insufficient hospital conditions. In addition, similar to the results of this study, it is considered important for health professionals to experience VBAC in the literature.[21] Therefore, it is thought that it is extremely important for midwives, who follow pregnant women in the prenatal period and provide one-on-one counseling, to receive the necessary training and gain experience in order to offer VBAC as a birth preference to pregnant women.

Similar to the results of this study, health professionals consider the risk of uterine rupture as the biggest barrier to VBAC.[12] According to this result, this barrier can be removed with the development of tools which can predict the risk of uterine rupture and the development of scales which can evaluate the suitability of women for VBAC.

The obstetricians and midwives participating in this study stated that they were disturbed by malpractice lawsuits and that they could not take any risks in order to avoid being exposed to such lawsuits. In the study of Firoozi et al.[22], it was stated that health professionals moved away from VBAC because they did not want to take legal responsibility.[22] In line with the results of the studies, it can be seen that obstetricians and midwives want to feel safe in cases of any problems during VBAC. In this situation, it is extremely important to develop health policies to support health professionals and to support them in their implementation of VBAC.

In this study, the obstetricians and midwives stated that they did not have enough time to inform the pregnant woman because the hospitals were very busy. Similarly, in a study conducted in Australia, health professionals stated that the current system is not suitable for VBAC and they did not have enough time to inform the patients about the harms and risks.[10] There is a need to increase the number of health professionals and well-equipped health institutions in order to provide quality health services to every pregnant woman and also to provide the necessary training.

While studies conducted at the international level do not mention the woman's right to speak and their status in society as a possible barrier to VBAC, attention should be drawn to women's rights to speak in society in Türkiye. Midwives criticize the value given to women by their spouses/mothers-in-law and also the public attributed the inability of women to be followed up regularly to the pressure exerted on these women and stated this as being a barrier to VBAC. In another study conducted in Türkiye, it was also mentioned that the family and relatives of the woman were influential in the decision of birth preference.[23] Therefore, it is thought that it is important to follow up and inform the woman with her family throughout the pregnancy period in terms of making a joint decision in the birth preference.

CONCLUSION

There is a need to organize training programs in order to improve healthcare professionals' knowledge and skills regarding VBAC. The provision of delivery preferences to women and the development of policies regarding joint decision-making by healthcare professionals and pregnant women on the mode of delivery can increase the rates of VBAC. There is a need to improve hospital conditions so that emergency intervention can be provided in unplanned situations during labor,

and there is a need to strengthen healthcare professionals, and to implement laws and regulations supportive of VBAC. VBAC must be offered to pregnant women by healthcare professionals as a delivery choice. Healthcare professionals should support the participation of all pregnant women in this training. It is recommended to increase qualitative and quantitative research on the subject, and conduct evidence-based research.

MAIN POINTS

- The lack of knowledge about vaginal birth after cesarean section and other various factors such as malpractice prevented the application from being widespread.
- Obstetricians have concerns about vaginal birth after cesarean delivery.
- Midwives believe that vaginal birth after caesarean section is a chance for women who have already had a caesarean section.
- Conditions in hospitals should be improved so that vaginal delivery is preferred after cesarean section.
- Health policies that support obstetricians and midwives are needed.

ETHICS

Ethics Committee Approval: This research was approved by the Ege University Scientific Research and Publication Ethics Committee (approval number: 09/05-676, date: 15.10.2020).

Informed Consent: An informed consent form was read to the healthcare professionals at the start of their interview.

Authorship Contributions

Surgical and Medical Practices: N.Ü.B., E.Ç.T., Concept: N.Ü.B., E.Ç.T., Design: N.Ü.B., E.Ç.T., Data Collection and/or Processing: N.Ü.B., Analysis and/or Interpretation: N.Ü.B., E.Ç.T., Literature Search: N.Ü.B., E.Ç.T., Writing: N.Ü.B.

DISCLOSURES

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

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RESEARCH ARTICLE

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Assessment of Autonomic Dysfunction with the COMPASS-31 Test and Its Relationship with Disease Activity, Cardiovascular Risk, Anxiety, and Depression in Patients with Sjögren's Syndrome

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Abstract

BACKGROUND/AIMS: Primary Sjögren's syndrome (pSS) is a chronic, auto-immune, multisystemic inflammatory disease and this chronic inflammation may cause risk factors for autonomic dysfunction (AD) and/or cardiovascular risk. This study aimed to determine the frequency of AD in pSS patients using Composite Autonomic Symptom Score-31 (COMPASS-31) and also the relationship between disease activity and cardiovascular risks and AD, as well as to compare the symptoms of AD with healthy study participants.

MATERIALS AND METHODS: This was a cross-sectional study. The research cohort was comprised of 42 patients diagnosed with pSS and 42 healthy controls. AD was evaluated with the COMPASS-31 questionnaire. Cardiovascular risk was assessed with the 10-year Framingham Risk Score (FRS) algorithm. Body mass index, dyslipidemia, and metabolic syndrome (MetS) were recorded. In the pSS group, disease activity was evaluated with European League against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) and European League against Rheumatism Sjögren's Syndrome Patient Reported Index (ESSPRI). Additionally, the Numerical Rating Scale and Hospital Anxiety and Depression Scale (HADS) were recorded.

RESULTS: Patients with pSS had a significantly higher mean total COMPASS-31 score than the controls (58.5 vs. 50.0; p=0.040). In sub-domain analysis, pSS patients exhibited significantly higher mean scores in the pupillomotor domain than controls (13.5 vs. 9.0; p=0.002). MetS (10 vs. 2; p=0.023), the mean 10-year FRS (6.0 vs. 2.0; p=0.012), HADS depression score (9.5 vs. 5.0; p=0.001) and HADS anxiety score were higher in those patients with pSS (11.3 vs. 6.7; p<0.001). COMPASS-31 was not correlated with ESSDAI or ESSPRI (p=0.128, p=0.0.66 respectively). The FRS and HADS depression score were evaluated as being effective on the COMPASS-31 score (p=0.535, p=0.465 respectively).

CONCLUSION: An increased prevalence of AD, cardiovascular risk, MetS, depression, and anxiety levels in patients with pSS was found in this study. The total COMPASS score did not correlate with disease activity. The COMPASS-31 questionnaire showed a relationship between cardiovascular risk and HAD depression symptom levels.

Keywords: Autonomic dysfunction, Sjögren's syndrome, COMPASS-31, cardiovascular risk, depression and anxiety

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INTRODUCTION

Sjögren's syndrome (SS) is an auto-immune, multisystemic inflammatory disease, characterized by decreased lacrimal and salivary gland functions. In addition, systemic involvement is common. The most affected organs are the lungs, kidneys, bladder, lymph nodes, gastrointestinal system, peripheral and central nervous system and the cardiovascular system.[1,2]

The autonomic nervous system (ANS) regulates physiological and involuntary functions in the body, such as secretion by glands, heart rate, and the control of respiration.[3] The prevalence of cardiovascular involvement was demonstrated to be approximately 61.6% in subjects with Primary Sjögren's syndrome (pSS) compared to 29.7% in healthy controls.[4] Autonomic dysfunction (AD) may be responsible for increased cardiovascular risk in pSS. In cardiovascular events, reduced heart rate is a major sign of AD.[5] In one study, AD, which was common among patients with pSS, was linked with systemic disease activity.[6] PSS is an inflammatory disease with a high inflammatory load, high levels of C-reactive protein, tumor necrosis factor-alpha, and interleukin-6 or autoantibodies against the ganglionic acetylcholine receptor which may cause AD.[7,8] These inflammatory cytokines, autoantibodies, vasculitis, and DMARDS which are used for treatment also play a role in AD and cardiovascular diseases (CVD) in pSS.

In clinical practice, it is hard to identify the AD in pSS. Various invasive and non-invasive examinations are performed in the detection of pathologies caused by ANS. For this purpose, various scores have been developed to be used in the detection of ANS problems, using information received from the patient without the need for invasive interventions. However, due to the open-ended questions contained in these evaluations, their large number of questions, the complexity of the scoring algorithms, and the low intelligibility of the questions, it is hard to use these scales in daily practice. The composite Autonomic Symptom Score-31 (COMPASS-31) test was produced with the aim of achieving a more easily applicable test.[9] COMPASS-31 is widely applicable, up-to-date, practical, and autonomic symptoms and functions are evaluated by the individuals themselves. COMPASS-31 in patients has been used for diabetes mellitus (DM), systemic sclerosis, and other inflammatory diseases.[10,11]

This study aimed to evaluate the frequency of AD in patients assessed by COMPASS-31 and its relationship with disease activity and cardiovascular risks, and fatigue in patients with pSS, as well as to compare symptoms of AD with healthy control participants.

MATERIALS AND METHODS

The research cohort comprised 42 pSS patients (42 females; mean age: 44.6±7.5 years) and 42 healthy participants (42 females; mean age: 43.8±9.7 years). 2016 ACR/EULAR classification criteria were used to diagnose pSS. Healthy participants attending the physical medicine and rehabilitation outpatient clinic for routine physical examination or hemogram measurements were enrolled as the control group. This cross-sectional study was carried out with the permission of the Hitit University Çorum Erol Olçok Training and Research Hospital Ethics Committee (approval number: 2023-128, date: 01.11.2023) and all protocols involving human subjects were conducted in strict accordance with the ethical guidelines outlined by the institutional and/or the national research governing body, as well as the Declaration of Helsinki.

We calculated the study's sample size based on the study by Tecer et al.[12] The type 1 error was 0.05 and the test power was 0.80, the minimum sample size was calculated as 27 patients in each group using the G*Power version 3.0.10 program.

Female subjects over 18 years of age were included. Those patients with a history of concomitant rheumatic disease, severe CVD such as heart failure, myocardial infarction or arrhythmia, vasculitis, DM, pregnancy, lactation, malignancy, peripheral or central nervous system diseases, and kidney or lung failure were excluded. The control group had the same exclusion criteria. The anthropometric measurements, blood lipids, and fasting glucose levels of the patients were recorded. The drugs they used were investigated. All evaluations were carried out by the same physician.

In the pSS group, disease activity was evaluated with European League against Rheumatism Sjögren's Syndrome Patient Reported Index (ESSPRI) and European League against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI).

ESSPRI is a patient-reported outcome which measures pain, dryness, and fatigue on a 0-10 numerical scale (0: no symptoms and 10: worst possible symptoms). An ESSPRI score of ≥5 is defined as high disease activity and a score of <5 is defined as low disease activity.[13]

ESSDAI evaluates twelve different systems. Its subdomains are glandular, articular, cutaneous, constitutional, pulmonary, lymphadenopathy, renal, muscular, hematological, peripheral nervous system, central nervous system, and biological. Total scores over seven indicate an active disease and total scores of 0-7 indicate a mild disease.[14]

The Hospital Anxiety and Depression Scale (HADS) was used to assess the anxiety and depression levels in the participants. This patient-completed questionnaire compromises two subscales: HADS anxiety and HADS depression. Both subscales consist of seven questions and each question is scored from 0 to 3. Lower scores indicate lower levels of anxiety and depression.[15]

Pain was assessed with the Numerical Rating Scale. Patients rate their pain from no pain (0 points) to the worst pain (10 points).[16]

For the assessment of AD in both groups, COMPASS-31 was used. COMPASS-31 is a test which is based on widely applicable, up-to-date, easy-to-apply, and scientific approaches in which the autonomic symptoms and functions are evaluated by the individuals themselves. It consists of 31 multiple-choice questions in 6 autonomic areas, including the orthostatic, vasomotor, secretomotor, gastrointestinal, bladder function, and pupillomotor areas. The total score was measured from the sum of all of the domains from 0 (normal) to 100 (the most severe AD).[9]

For the assessment of cardiovascular risks, anthropometric measurements (height, weight), blood pressure, waist circumference (WC), and hip circumference (HC) were measured. Blood pressure was measured noninvasively with a cuff sphygmomanometer. The waist-hip ratio was calculated as waist-to-HC. WC was measured from the midpoint of the lateral iliac points and the lowest rib and the HC was measured from the greater trochanters. Based on reports on the Turkish population, WC ≥90 cm in females is defined as as abdominal obesity.[17] Body mass index (BMI) was noted in kilograms/square meter (kg/m^2), dividing weight by the square of height. Patients were classified as obese if their BMI was ≥30 kg/m^2, based on the guidelines of the National

Institutes of Health Expert Panel.[18] Smoking status was recorded as current, former, or never.

The 10-year risk of CVD was evaluated using the Framingham Risk Score (FRS) algorithm, which assesses the main risk of heart failure, coronary artery disease, and peripheral arterial disease by incorporating the traditional CVD risk factors [age, sex, total cholesterol, high-density lipoprotein (HDL), blood pressure, smoking, and DM], in which a score of <10% indicates low, 10-19% indicates intermediate, and ≥20% indicates high risk.[19]

Metabolic syndrome (MetS) was assessed via five parameters, according to the American Heart Association/National Heart, Lung, and Blood Institute criteria: (1) abdominal obesity (WC >90 cm for females); (2) the presence of hypertension (DBP >85 mmHg and/or SBP >130 mmHg) or the use of anti-hypertensive therapy; (3) triglyceride level ≥150 mg/dL or being under hypertriglyceridemia treatment; (4) HDL level <50 mg/dL or being treated for reduced HDL; and (5) fasting plasma glucose level ≥100 mg/dL or being treated for high glucose levels.[20] Three positive parameters out of these five led to a diagnosis of MetS.

Statistical Analysis

IBM SPSS Statistics Standard Concurrent User V 26 was used in order to evaluate the data. Descriptive statistics are given as the number (n), percentage (%), mean ± standard deviation, median, and interquartile range values. The Shapiro-Wilk normality test was used to check the normal distribution of the numerical variables. The Levene test was used to check the homogeneity of the variances. Comparisons of two groups for numerical variables were performed with the t-test in Independent samples in cases of normal distributions of the data, and the Mann-Whitney U test in cases of non-normal distributions. Chi-square tests (Pearson, Continuity correction, Fisher's exact) were used in order to compare groups with categorical variables. In cases where the chi-square test results were found to be significant, the differences between the categories were evaluated with two Bonferroni corrected ratio z-tests. Relationships between numerical variables were evaluated with Spearman's correlation. In order to determine the effective factors on the COMPASS-31 total score, multiple linear regression analysis was used. A value of $p<0.05$ was considered statistically significant.

RESULTS

This study was conducted on 42 patients with pSS and 42 healthy controls. The comprehensive clinical features of all of the subjects are presented in Table 1. The patient (44.6±7.5) and the control groups (43.8±9.7) were similar in terms of age (p=0.737) and BMI (p=0.053).

Those patients with pSS had a significantly higher mean total COMPASS-31 score than the controls (58.5 vs. 50.0; p=0.040). In sub-domain analysis, pSS patients exhibited significantly higher mean scores in the pupillomotor domain than the controls (13.5 vs. 9.0; p=0.002) (Table 2).

As shown in Table 3, 15 patients in the pSS group and 3 patients in the control group had MetS and this was statistically significant (p=0.023). The mean 10-year FRS was 6.0 in those patients with pSS and 2.0 in the controls, which was statistically significant (p=0.012). HAD depression scores (9.5 vs. 5.0; p=0.001) and HAD anxiety scores (11.3 vs. 6.7; p<0.001) were higher in those patients with pSS.

Table 1. Demographic and clinical characteristics of pSS patients and controls

	Healthy	pSS	p-value
Age	43.8±9.7	44.6±7.5	0.737†
BMI kg/m²	25.22±4.07	27.21±4.92	0.053†
Job, n (%)			
Housewife	2 (4.8)	34 (80.9)	<0.001‡
Worker	27 (95.2)	8 (19.1)	
Educational level, n (%)			
Middle school	0 (0.0)[a]	35 (80.9)[b]	
High school	15 (35.7)[a]	3 (9.6)[b]	<0.001‡
University	27 (64.3)[a]	4 (9.5)[b]	
Smoking status, n (%)			
Smoker	15 (35.7)	5 (11.9)	
Never smoked	25 (59.5)	31 (73.8)	0.051‡
Ex-smoker	2 (4.8)	6 (14.3)	
Disease duration, (months)	-	90.0 (110.0)	-
ESSDAI	-	2.0 (2.0)	-
ESSPRI	-	21.5 (10.0)	-

Numerical data are given as mean ± standard deviation or median (interquartile range) values, †: Independent samples t-test, ‡: Chi-square test, [a,b]: Superscripts indicate differences between groups in each rows. There was no statistically differences between groups with the same superscripts. BMI: Body mass index, ESSDAI: European League against Rheumatism Sjögren's Syndrome Disease Activity Index, ESSPRI: European League Against Rheumatism Sjögren's Syndrome Patient Reported Index, pSS: Primary Sjögren's syndrome.

Table 2. Comparison of COMPASS-31 scores by groups

	Groups		
	Healthy	pSS	p-value
Total score	50.0 (22.7)	58.5 (14.5)	**0.040&**
Orthostatic sub-score	4.0 (6.0)	7.0 (6.0)	0.918&
Vasomotor sub-score	2.0 (5.0)	4.0 (4.0)	0.316&
Secretomotor sub-score	8.0 (2.0)	9.0 (3.0)	0.624&
Gastrointestinal sub-score	20.0 (14.0)	22.0 (12.5)	0.165&
Bladder sub-score	3.0 (2.0)	3.0 (2.0)	0.621&
Pupillomotor sub-score	9.0 (7.5)	13.5 (4.0)	**0.002&**

Numerical data are given as median (interquartile range) values, Mann-Whitney U test. COMPASS-31: Composite Autonomic Symptom Score-31, pSS: Primary Sjögren's syndrome.

Table 3. Comparison of other variables according to groups

	Groups		
	Healthy	pSS	p-value
Framingham risk score	2.0 (7.5)	6.0 (5.7)	**0.012&**
HAD depression score	5.0 (3.5)	9.5 (5.7)	**0.001&**
HAD anxiety score	6.7±2.4	11.3±4.5	**<0.001†**
Waist circumference	79.2±8.2	90.1±11.7	**<0.001†**
Hip circumference	101.7±7.2	107.6±9.7	**0.012†**
Metabolic syndrome, n (%)	3 (7.1)	15 (35.7)	**0.023‡**

Numerical data are given as mean ± standard deviation or median (interquartile range) values, †: Independent samples t-test, &: Mann-Whitney U test, ‡: Chi-square test. pSS: pSS: Primary Sjögren's syndrome, HAD: Hospital anxiety and depression score.

According to Table 4, there was a relatively positive correlation between COMPASS-31 total scores and the FRS and the HAD depression scores in the pSS group. Vasomotor scores had a moderate positive correlation with the FRS and a weak positive correlation with HC. There was a moderate positive correlation between the gastrointestinal scores and the HAD depression scores. There was a moderate positive correlation between the bladder scores and the FRS. AD was not correlated with age, disease duration, smoking status, or disease activity.

According to Table 5, there was no significant correlation between AD as assessed with COMPASS-31 scores and job, education, or smoking status. The total scores and gastrointestinal scores of those with MetS were statistically higher than those of patients without MetS (p=0.049, p=0.009, respectively).

FRS, HAD depression scores and MetS variables with a p-value of <0.25 were included in the multiple linear regression model in comparisons with the COMPASS-31 total scores in Table 4, 5. The final model was reached using the backward elimination method. In the final model, the HADDEP variable was evaluated as effective on the COMPASS-31 total score [coefficient (95% confidence internal), 1.630 (0.601-2.659), adjusted r^2=0.262; p=0.003].

DISCUSSION

As far as we know, this was the first study in which AD was evaluated using COMPASS-31, comparing pSS individuals with healthy ones in the Turkish population, and also investigating its relationship with cardiovascular risk and disease activity. There are few studies investigating the relationships between pSS and AD in the literature.[6,21,22]

Table 4. Comparison of COMPASS-31 Scores with other numerical variables in patients with pSS

	COMPASS-31 (rho)						
	Total score	**Orthostatic**	**Vasomotor**	**Secretomotor**	**Gastrointestinal**	**Bladder**	**Pupillomotor**
Age	0.011	0.001	0.183	-0.084	0.219	-0.150	-0.085
BMI	-0.061	-0.198	0.080	-0.112	-0.147	0.189	-0.175
Disease duration	0.270	0.268	0.214	-0.148	0.142	0.042	0.113
Numeric rating scale	-0.022	0.126	0.171	-0.141	-0.089	-0.070	-0.034
ESSDAI	0.128	-0.094	0.099	-0.224	0.090	-0.150	0.232
ESSPRI	0.066	0.095	0.367	-0.261	0.042	-0.056	0.119
Framingham risk score	**0.535****	0.056	**0.460***	-0.173	0.355	**0.442***	0.227
HADS-D score	**0.465***	0.153	0.274	-0.156	**0.458***	0.149	0.341
HADS-A score	0.198	0.251	0.007	-0.331	0.303	0.216	0.275
Waist circumference	0.174	0.068	0.264	-0.336	-0.016	0.277	-0.104
Hip circumference	0.131	-0.049	**0.377***	-0.372	0.076	0.215	-0.175

rho: Spearman's rank correlation coefficient, *p<0.05; **p<0.01, BMI: Body mass index, ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index, ESSPRI: European League Against Rheumatism Sjögren's Syndrome Patient Reported Index, HADS-D: Hospital depression score, HADS-A: Hospital anxiety score.

Table 5. Comparison of COMPASS-31 scores with categorical variables

	n	Total score	Orthostatic	Vasomotor	Secretomotor	Gastrointestinal	Bladder	Pupillomotor
Job								
Housewife	34	60.0 (14.0)	6.0 (6.0)	4.0 (4.0)	9.0 (3.0)	22.0 (13.0)	3.0 (1.0)	14.0 (5.0)
Worker	8	56.0 (17.0)	7.0 (5.0)	5.0 (3.5)	9.0 (2.0)	22.0 (10.5)	5.0 (2.0)	13.0 (1.5)
p*		0.727	0.215	>0.999	0.684	0.483	0.560	0.413
Education								
Middle school	35	61.0 (15.0)	6.0 (6.0)	2.0 (4.0)	9.0 (3.0)	22.0 (14.0)	3.0 (1.0)	14.0 (5.0)
High school + university	8	56.0 (13.0)	7.0 (4.0)	5.0 (2.0)	8.0 (3.0)	22.0 (7.0)	5.0 (1.5)	13.0 (1.5)
p*		0.908	0.483	0.521	0.264	>0.999	0.239	0.413
Smoking status								
Never smoked	31	61.0 (15.5)	6.0 (6.0)	2.0 (4.0)	9.0 (3.0)	20.0 (14.5)	3.0 (1.5)	14.0 (4.0)
Smoker or ex-smoker	11	56.0 (13.0)	7.0 (6.0)	5.0 (4.0)	9.0 (4.0)	22.0 (3.0)	4.0 (2.0)	13.0 (2.0)
p*		0.640	0.640	0.568	0.717	0.917	0.296	0.101
Metabolic syndrome								
No	27	54.5 (18.0)	4.0 (5.3)	2.0 (3.0)	9.0 (3.0)	19.0 (11.3)	3.5 (2.5)	14.0 (5.5)
Yes	15	63.0 (10.3)	7.5 (3.3)	5.5 (5.0)	7.5 (4.0)	26.0 (4.8)	3.0 (1.3)	13.0 (4.0)
p*		**0.049**	0.072	0.080	0.286	**0.009**	0.332	0.832

Numerical data are given as median (interquartile range) values, *: Mann-Whitney U test.

As a result of this study, it could be seen that those patients with pSS had significantly higher AD, cardiovascular risk, MetS, depression, and anxiety levels. The total COMPASS score was not correlated with disease activity. The FRS, and the HAD depression scores were independent predictors of COMPASS scores and AD.

When patients have pSS, clinicians are primarily interested in their clinical symptoms and inflammation levels. The evaluation parameters which are used are mostly based on symptoms such as dry mouth, dry eyes, and inflammation markers in the blood. However, in these patients, the increased frequency of AD symptoms and increased cardiovascular risks due to existing inflammations are at least as important as the disease itself. Since pSS is a chronic disease, these risks increase over the years. Therefore, as in all rheumatic diseases, it is important to investigate AD and CVS in pSS with a fast, easy, inexpensive, and non-invasive method in outpatient clinic conditions. Thus, high-risk patients can be quickly identified and referred with relevant diagnoses for treatment.

An association had been found between AD and pSS in previous studies.[6,23] The results of our study were similar to a previous study where patients with pSS had a significantly higher mean total COMPASS-31 score than the controls.[23] In a cohort study of Koreans, AD was higher in pSS and no correlation was found between AD and secretomotor function as was the case in our study.[24] Similarly, as in the previous study, there were significantly higher mean scores in the pupillomotor domain than in the controls.[22] It was difficult to say whether the eye-related findings in pSS are due to the disease itself or to AD. Therefore, in future studies, patients can be classified according to the severity of ocular and oral symptoms, and AD can also be investigated in these subgroups.

Parreau et al.[25] found a relationship between symptoms of the gastrointestinal system and ESSPRI, but not with ESSDAI. ESSPRI and ESSDAI do not include any questions about gastrointestinal symptoms in pSS. In COMPASS-31, there are questions to evaluate gastrointestinal system problems. In this study, unlike the previous study, GIS symptoms were not high and not correlated with disease activity.[24] However, the patients were not questioned regarding any medications used for their GIS symptoms. The GIS symptoms of the patients in the study group may have already been treated.

In this study, no significant correlation was found between AD and age, disease duration, smoking status, or disease activity. The total COMPASS score did not correlate with disease activity as assessed by ESSDAI or ESSPRI. Different results were obtained in studies investigating the relationships between disease activity and COMPASS scores. In a large study in the United Kingdom with 317 patients, the total COMPASS scores correlated with disease activity.[6] In another study with a limited number of patients, Stojanovich et al.[23] could not find a correlation with disease activity as our study did. The patient group was small in this study as was the case with Stojanovich et al.[23] Larger studies with larger patient groups may help to determine this relationship.

Since rheumatologic diseases are long-term, they affect patients' sleep patterns, social relationships, and quality of life. Therefore, the anxiety and depression levels of these patients may be affected. Since this study wanted to evaluate patients with pSS as a whole, we also wanted to investigate the anxiety and depression levels of these patients. In this study, multivariate analysis demonstrated that the HADS depression scores were key independent predictors of COMPASS-31 scores. Also, those patients with higher gastrointestinal COMPASS-31 subdomain scores positively correlated with the HADS depression scores. HADS anxiety scores were also higher in the study group. It suggests that AD may contribute to symptoms of depression and anxiety in pSS patients. A previous study showed there was a correlation between AD symptoms and anxiety levels.[21] However, this study evaluated depression and anxiety symptoms using HADS, and patients with pSS should be evaluated in more detail regarding their psychological state.

In this study, MetS is more common in pSS (35.7%) as was also seen in a previous study (MetS=39.4%).[26] In this study, the COMPASS-31 total score and the gastrointestinal subdomain were higher in those patients with MetS. Gezer et al.[27] also found a relationship between the COMPASS-31 secretomotor subdomain and MetS in another rheumatologic disease, psoriatic arthritis. This suggests that chronic inflammation plays a role in MetS. More detailed studies are needed in order to assess which pathophysiology is responsible.

Some prediction tools are available to detect cardiovascular risks in patients with pSS, for example, heart rate variability or cardiovascular reflex tests.[28,29] In 2021, the EULAR recommended the use of prediction tools such as FRS in pSS.[30] There is a correlation between AD and FRS and 10-year FRS positively correlated with the total COMPASS scores and also with the vasomotor and bladder subgroups in this study. Another study found that FRS was elevated independently of subclinical atherosclerosis.[31] Although patients with diabetes, severe CVD, stroke, kidney, and liver dysfunction which can affect the ANS were excluded, a positive association was found with AD and cardiovascular risk. If diabetic patients were included in this study, the prevalence of MetS, and the 10-year FRS would probably have been higher. This is so important because, in daily practice during the routine examination of patients with pSS, CVD and ADs can be ignored. However, COMPASS-31, a simple validated questionnaire, may indicate risks for CVD and patients can be referred to the relevant specialists. In addition, early detection of cardiovascular involvement helps initiate appropriate treatment. It also helps to prevent the severe consequences of ANS dysfunctions, such as sudden clinical death or arrhythmias. Davies and Ng[32] suggested that there is an interaction between the ANS and the immune system, and because of this interaction, new treatments for ANS are promising in rheumatic diseases.

Study Limitations

This study had a limited number of patients and only women were included. DM and severe CVD were excluded due to their direct effect on ANS. However, many factors can affect ANS, such as hypertension, hyperlipidemia, or many drugs. This study evaluated AD with a questionnaire, while a reflex test or heart rate variability were not used.

CONCLUSION

In this study, patients with pSS had significantly higher levels of AD, cardiovascular risk, MetS, depression, and anxiety levels. The COMPASS-31 questionnaire showed a relationship between AD, cardiovascular risk, and also HAD depression symptom levels. No correlation between disease activity and the COMPASS-31 score was observed.

MAIN POINTS

- Autonomic dysfunction (AD) and cardiovascular disease risk are higher in those patients with primary Sjögren syndrome.

- COMPASS-31 is a simple validated questionnaire which may indicate risks for AD in patients with pSS.
- Early diagnosis of AD helps to prevent the severe consequences of ANS and helps to initiate the appropriate treatment.

ETHICS

Ethics Committee Approval: This cross-sectional study was carried out with the permission of the Hitit University Çorum Erol Olçok Training and Research Hospital Ethics Committee (approval number: 2023-128, date: 01.11.2023).

Informed Consent: It was obtained.

DISCLOSURES

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