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Skin Findings Related to COVID-19, the Review of the Current Literature

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Abstract

COVID-19 is an acute respiratory infection that is caused by SARS-CoV2 and it was declared a pandemic by the World Health Organization in March 2020. Many different skin manifestations such as urticarial lesions, maculovesicular lesions, papulovesicular lesions, MIS-C lesions, purpuric/ petechial lesions, livedoid lesions, and thrombotic-ischemic lesions have been described in this infection. Thus, timely and accurate identification of skin findings might be beneficial in terms of early diagnosis. In addition, the type of lesion gives information about prognosis in some cases. The exact mechanism for the formation of skin lesions is not known, but the immune system activation, the direct cytopathic effect of the virus, the microvascular damage, hypercoagulopathy and complement activation are factors that are thought to play a role in the pathogenesis. Further studies are required in order to systematize the skin findings seen in COVID-19 and to reveal their mechanisms. Furthermore, the COVID-19 pandemic has also induced various skin complications such as pressure sores, dry skin, dermatitis, and contact urticaria due to the use of personal protective equipment (PPE). Besides, the use of PPE might cause exacerbation of skin diseases such as acne, rosacea, seborrheic dermatitis, atopic dermatitis.

Key words: COVID-19, Skin Symptoms, SARS-CoV2, Pandemic.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2 in humans, is going on spreading rapidly and leading to a global health crisis (1). The effects of COVID-19 on the skin can be examined under four headings: skin findings due to lifestyle changes, cutaneous adverse events due to drugs used in the treatment of COVID-19, skin lesions due to COVID-19 and effects of COVID-19 and its treatment on primary skin diseases.

Although new data are being obtained every day, there is still much unknown about the clinical features of the disease, including cutaneous manifestations. SARS-CoV-2, a new strain of the coronavirus family, has been associated with many viral exanthems. Certain adenovirus serotypes, just like SARS-CoV-2, can also be caused by vesicular, maculopapular, or petechial exanthems (2).
A wide range of mucocutaneous findings can be seen in viral diseases. In patients with skin rash and fever, identifying the skin lesions accurately and on time makes a great contribution to the diagnosis. Skin findings seen in COVID-19 can be handled in two main categories as inflammatory exanthems and vascular lesions. Inflammatory exanthems are maculopapular, urticarial, vesicular (chickenpox-like) lesions and MIS-C eruptions. Vascular lesions associated with COVID-19 can be classified as chilblain-like lesions, petechiae / purpuric eruption, and livedoid lesions (3). Some of these lesions, for instance; maculopapular eruptions and urticarial, can also be seen in the course of many other viral diseases, although some appear specific to COVID-19, such as varicella-like lesions (4). Some lesions may precede other symptoms and a careful evaluation of skin findings might be beneficial in terms of early diagnosis and measures to be taken (5, 6). Moreover, it is stated that many lesions might show the way to future complications and disease prognosis (7).

At the beginning of the pandemic, the frequency of skin findings in COVID-19 disease was stated as 0.2% in reports from China (8) However, it is seen that this rate increased up to 20% in later Italian reports (9). In a prospective study conducted in France, the frequency of skin findings in the course of COVID-19 disease was reported as 4.9% (10).

COMMON SKIN MANIFESTATIONS OF COVID-19

Urticarial Lesions

Urticaria; It is a dermatosis with swelling or angioedema or both. Mast cell degranulation plays a role in its physiopathology. There are many triggers in its etiology (11). Viral infections are common causes of urticarial lesions. Different rates of urticarial lesions have been reported in case series published on the skin findings of COVID-19. When the cases in the literature are examined, it has been stated that in the course of COVID-19, urticarial lesions can be seen more frequently in women and also in a wide age range. Casas Galvan et al. reported that they detected urticarial lesions in 73 patients out of 375 (19%) and the lesions were mostly located on the trunk. They found urticarial lesions limited to the palmar region in only a few patients. Urticarial lesions started before the symptoms of COVID-19 in three of these patients, concurrently in 43 of them, and after the symptoms in 25 patients. In addition, the mean lesion duration was found as 6.8 days (12). In the case series of Recalcati et al., 18 patients out of 88 (20.4%) diagnosed with COVID-19 had disease-related skin lesions, while only three of these 18 patients had urticarial lesions and there was no significant relationship between disease severity and presence of urticarial lesions (9). Henry et al. reported a case with limited urticarial lesions to the face and extremities without fever in a female patient with a positive PCR test (13). In contrast, van Damme et al. reported two COVID-19 patients whose initial symptoms were fever and widespread urticarial rash (14). When the cases in the literature are examined, it is seen that the cases are treated with classical treatment protocols (corticosteroid, antihistamine) in acute urticaria.

Although urticarial lesions can be seen in the course of COVID-19 disease, many agents used in the treatment of the disease can also be a trigger of urticaria. In addition, urticarial lesions can be the signs of hyperactivation of the immune system seen in the course of COVID-19, except for drug side effects (15).

During the COVID-19 pandemic, all patients with urticarial rash should be reviewed for the viral pandemic infection, regardless of whether they have additional symptoms or not, in terms of being an early marker of the disease. In this way, a possible infection can be diagnosed at an early stage. With an early diagnosis, it is possible to protect the patient from the complications that might occur later and also to prevent possible transmission by providing the patient’s isolation in the early period.

Maculopapular Lesions

Maculopapular rash is a common skin manifestation that can be caused by many different reasons such as drug side effects, viral infections, and bacterial infections. When it is found with viral and bacterial infections, it usually accompanies symptoms such as headache, muscle pain, fever, and respiratory distress. Hepatitis B, hepatitis C, HIV, infectious mononucleosis, measles, and hand-foot-mouth disease can be mentioned as examples of viral infections that can cause maculopapular rash (16).

It can be said that the most common cutaneous lesion in the course of COVID-19 is maculopapular eruption. In the case series of Casas Galvan et al., 47% of 375 patients
with COVID-19 had maculopapular rash. Itching was reported to be seen in the 56% of the patients with a maculopapular rash. In this study, it was reported that the lesions in some cases were in the form of squamous plaques with perifollicular localization, whereas pityriasis rosea-like lesions were detected in some of the patients. In the same study, it was mentioned that a small number of patients had indurated papules similar to erythema elevatum diutinum or lesions resembling erythema multiforme (12). In the case series published by De Giorgi et al., the incidence of maculopapular eruption in COVID-19 patients was reported as 70% (17). Recalcati et al. described maculopapular eruption in 14 of 18 patients with COVID-19 infection (9). In the literature, the duration of the lesion is seen in a wide range of days, from 2 to 33, in different reports (18–24). While maculopapular rashes in the course of pandemic infection are mostly seen in middle-aged patients, there are also reported cases in young people and children (12, 25). In a large series of cases, maculopapular lesions have been reported to begin concurrently with symptoms of COVID-19, while in a series of fewer cases, lesions have been reported to begin later than symptom onset (27.6-27.85 days) (12, 24–27). The duration of the lesion varies between 4 and 16 days (12, 25).

The histopathology of maculopapular lesions varies according to the duration of the lesion. Moderate epidermal spongiosis, perivascular lymphocytic and eosinophilic infiltrates in the dermis are observed in early lesions, while perivascular lymphocytic infiltration and histiocytes between collagen fibers are found in late lesions (25).

In some studies in the literature, it has been stated that maculopapular rash might be related to the severity of the disease, while the 2% mortality rate of patients with maculopapular rash supports this view (12).

Patients with maculopapular rash can be given corticosteroid and antihistamine treatment, and it is possible to follow them only with treatment for infectious disease. While Avellano Moreno et al. reported that the lesions regressed in 5 days with intravenous corticosteroids and antihistamines, Moray-olive et al. followed the patients without treatment and reported that the average recovery time was 5 days (21, 22).

### Papulovesicular Eruption (Varicella-like)

Vesicle is the term used to describe water-filled bubbles less than 1 cm in diameter seen on the skin. In addition to drug eruptions and primary cutaneous diseases, it can often be seen during the course of various bacterial and viral infections. Varicella, herpes simplex, and virus infections are viral diseases with vesicular lesions (16).

Infection-related vesicular lesions can be localized or widely scattered. The incidence of vesicular lesions in the course of COVID-19 appears to be between 3.77% and 15% in the literature. The reported cases are mostly middle-aged patients and the distribution of the lesions in these patients is mostly limited to the trunk, while a small number of patients have extremity involvement (12, 26, 28–31).

Fernandez-Nieto et al. observed COVID-19 patients and found that lesions in two different patterns, diffuse and localized patterns, could be seen in 24 patients with vesicular lesions. In 18 of these patients, 7-8 mm sized papules, vesicles and pustules, which are Common polymorphic lesions, were seen on the trunk, palms and soles. In other patients, a monomorphic, vesicular eruption with a local pattern, which is 3-4 mm in diameter, mostly involving the trunk, was observed. There is no difference between the two groups in terms of demographic characteristics and severity of COVID-19. In this study, the average age of the patients was 45 and 18 of the patients were female. Lesions developed before the symptoms of COVID-19 in two of the patients, concurrently in three patients, and after the symptoms in 19 patients. The mean latent period was 14 days for these 19 patients, and the mean duration of regression of vesicular lesions is 10 days. Pulmonary involvement was observed in 10 of the COVID-19 patients with vesicular lesions, and only one patient needed an intensive care unit. Mild disease symptoms were observed in the remaining patients (30).

Galvan Casas et al. reported the incidence of vesicular lesions as 9% in a case series of 375 patients. In this study, while monomorphic vesicles were located on the trunk and extremities were observed in most of the patients, larger, tense, serohemorrhagic lesions were observed in a few patients. The average age of the patients was 45.6, and it was reported that 56% of the patients were women. It was observed that the lesions started before the onset of symptoms in 5 patients, after the symptoms in 10 patients, and simultaneously with the symptoms of the disease in
19 patients. While the disease that was observed in these patients was moderate, it was reported that the mean regression time of the lesions was 10.4 days (12).

Recalcati et al. reported varicella-like lesions in one patient out of 18 patients, and Marzano et al. reported varicella-like lesions in 12 patients out of 22 patients diagnosed with COVID-19 and they stated that varicella-like rash could be a specific skin manifestation of COVID-19 disease (9, 31).

In two studies in the literature, it is seen that the histopathological findings of vesicular lesions were examined, and histopathological findings in these studies were found to be compatible with the histopathological findings of viral infection previously described. In the first study, histopathological examination was performed on the lesions of two patients, and moderate acantholysis was reported with intraepidermal vesicles. In the second study, histopathological examination was performed in seven patients and mild epidermal atrophy, basal vacuolar degeneration, basket weave pattern hyperkeratosis, multinuclear hyperchromatic keratinocytes and dyskeratotic cells were reported (30, 31).

There are various speculations regarding the mechanisms of vesicular lesions. Criado et al. stated that the immune system activation seen during the course of infection can also affect the skin. Moreover, in the same study, they also hypothesized that the virus could trigger vesicular lesions by direct cytopathic effect on the endothelium of the dermal vessels (15).

In contrast to urticarial and maculopapular lesions, it is thought that the drugs used in the treatment do not have a role in the etiology of vesicular lesions seen in COVID-19 (30). Vesicular lesions are thought to be associated with intermediate severity of COVID-19 (12,30). Symptomatic treatments such as antihistamines and topical antibiotics are used in the treatment of papulovesicular lesions. Vesicular lesions have been defined as the specific skin lesion of COVID-19 and the recognition of these lesions is very important for the diagnosis of the disease.

Multisystem Inflammatory Syndrome in Children (MIS-C) Lesions

In the early stages of the pandemic, it was thought that serious complications related to COVID-19 were not seen in children. This belief has lost its validity with the reporting of pediatric patients with severe autoimmune and auto inflammatory symptoms similar to Kawasaki disease in the United Kingdom (32). Later, Verdoni et al. reported that the incidence of Kawasaki-like disease increased almost 30-fold and that antibodies against SARS-CoV-2 were found positive in these patients (33). And then this serious disease, named MIS-C, started to be reported from all over the world. Although MIS-C has many common findings overlapping with Kawasaki disease, it can be seen in older children and adolescents compared to Kawasaki disease, and the more frequent cardiac involvement in these cases is the different features of MIS-C from Kawasaki disease (34). Polymorphic eruptions in the form of maculopapular, erythema multiforme-like or diffuse erythroderma, which are among the diagnostic criteria for Kawasaki disease, are similarly observed in MIS-C cases (33). In the case series published by Whittaker et al., it was reported that 30 patients out of 58 diagnosed with MIS-C had erythematous lesions and one patient developed additional purpuric lesions (35). Similarly, in a retrospective study by Miller et al., 31 patients out of 44 diagnosed with MIS-C were reported to have skin findings. Skin findings in these patients were the third most common symptoms after fever and gastrointestinal symptoms (36). In most of the reports, it was stated that patients with MIS-C diagnosis had widespread skin involvement, whereas in the study of Hameed et al., 13 patients out of 35 (37%) with MIS-C had skin findings and these skin lesions could be seen in different patterns, such as extremity, facial or diffuse (37). Although the etiology of Kawasaki disease is largely unknown, it is stated that there is a genetic predisposition on the ground. Similarly, more studies are needed to fully understand the underlying mechanisms in the occurrence of MIS-C disease and its relationship with COVID-19 (38).

Petechial / Purpuric Lesions

Purpuric rashes associated with infection might occur due to the toxic vascular effects of the infection, vascular invasion of the infectious agent or diffuse intravascular coagulation caused by the direct vascular toxic effects of the infection. Petechial / purpura as a skin manifestation associated with COVID-19 has been reported less frequently than other lesions (12).

In a retrospective study of 277 patients with skin lesions diagnosed with COVID-19 in France, petechial / purpuric rash was reported in only 3% of the patients. It has been reported that these lesions might be widespread, acrally
located or limited (26). In another study, it was reported that the lesions were limited to the distal extremities in most patients with petechial rash (29).

While most of the COVID-19 patients with purpuric rash are accompanied by itching, a positive Koebner phenomenon has been reported in the literature in a patient with purpuric rash (39, 40). In two case series including a small number of patients with purpuric rash, it was reported that purpuric lesions started after COVID-19 symptoms (25, 41). De Giorgi et al. reported 13 patients with petechial / purpura and signs of acro ischemia. It has been reported that these lesions are seen in more severe COVID-19 cases and purpuric / acroischemic lesions indicate increased prothrombin time, fibrinogen and D-dimer levels in patients (17). Similarly, in another study, it was reported that 4 patients out of 34 had petechial / purpuric lesions and these patients were middle-aged and severe cases. Interestingly, in two of these four patients, purpuric lesions are accompanied by atypical polymorphic papulovesicular lesions, while in another patient, urticarial lesions are concurrent with purpuric lesions (25).

In a case series of five patients with severe COVID-19 infection, purpuric skin rash was detected in three patients. Histopathological examination was performed in one of these patients with retiform purpura; leukocytoclasia and interstitial and perivascular neutrophilia were found (41). Histopathological features in petechial / purpuric lesions depend on the type of the lesion. Palpable purpura is characterized by basal layer necrosis, small vessel damage with fibrinoid necrosis, neutrophilic infiltration in the vessel walls, leukocytoclasia and erythrocyte extravasation (40, 42). Purpuric patches and retiform purpura is characterized by vascular ectasia, thrombus in deeply located vessels, perivascular and interstitial neutrophilic infiltration with leukocytoclasia and thrombogenic vasculopathy. In addition, diffuse necrosis of the epidermis and adnexal structures is one of the histopathological findings observed in such lesions (41). In addition, complement accumulation was found in both types of lesions (40, 41).

The pathogenesis of petechial / purpura lesions is thought to be pauci-inflammatory thrombogenic vasculopathy. In the immunohistochemistry study by Magro et al., it was observed that the C5b-9 and C4d components of the complement were heavily deposited in the small vessels of both lesional and perilesional skin. These complement components can sometimes be found together with COVID-19 spike glycoproteins (41). Considering the severe clinical conditions of COVID-19 patients with petechial / purpura lesions, it should be considered that the agents used for the disease can also play a role in the etiology of petechiae / purpura lesions.

**Livedoid Skin Lesions**

Livedo reticularis is a reddish-purplish lace-like discoloration of the skin that can be temporary or permanent. The colour change is caused by a decrease in the blood flow of the arterioles that feed the cutaneous capillaries, and the presence of deoxygenated hemoglobin gives the skin a purplish colour. While livedo reticularis that occurs due to the physiological conditions (cold exposure) or idiopathic is named primary, secondary livedo reticularis is used to describe livedoid lesions seen in the course of systematic diseases. Hematological, rheumatic, cardiovascular diseases and infections can cause secondary livedo reticularis (43).

Livedoid rashes appear to be less frequently reported during the COVID-19 pandemic compared to other types of rash. Liveoid lesions were found in 6% of the patients in a case series of 375 patients by Galvan casas et al. It is seen that the lesions are mostly located on the trunk, forearm extensor surface, and the dorsal of the hands and feet. In this case series, it is seen that livedoid lesions start simultaneously with the symptoms of COVID-19. In this study, the mean age of patients is 63, the mean duration of the lesion is 9.4 days, and this type of skin lesions are associated with higher mortality rates compared to other lesions (12).

Velasco et al. reported a male patient with livedoid lesions coexisting with COVID-19 symptoms accompanied by acro-ischemia. In the histopathological examination, they found mild necrosis in the upper epidermis, hyaline thrombus in the papillary dermis, neutrophilic infiltration surrounding the occluded blood vessels, and fibrinoid necrosis in larger arterial structures in some regions (44). Magro et al. reported three patients with skin lesions associated with vascular involvement. In the histopathological examination of these patients, perivascular lymphocytic infiltrate and microthrombus without vasculitis were detected in deep dermis venules. They also reported that d-dimer and INR levels were increased in these patients (41).
Although the exact mechanism of livedoid lesions is unknown, several mechanisms have been proposed. One of these theories is the relationship between COVID-19 and hypercoagulability. In a retrospective study of 183 COVID-19 patients, it has been reported that the d-dimer and fibrin degradation products of the cases who died due to this disease were higher and the prothrombin times were longer compared to the others (45). Similarly, patients with livedoid lesions are at higher risk for hypercoagulability, and patients with this lesion have higher mortality rates.

Manalo et al. hypothesized that livedo reticularis is caused by DIC and macrothrombosis in severe disease and by microthrombosis caused by inflammatory cytokines in milder disease (46).

**Thrombotic-Ischemic Lesions**

Infection-related cutaneous thrombotic and ischemic lesions might occur due to the direct vascular invasion of the infectious agent, vascular occlusion, or diffuse intravascular coagulation. These type of lesions are important symptoms of serious infections such as meningococemia, staphylococcal and pneumococcal septicemias (47, 48).

Chilblain lesions, also called pernio, are a localized inflammatory skin finding that causes edema and erythematous-violet discoloration in the extremities. It is triggered by exposure to cold or humid environment. While some cases are seen as idiopathic, they can also be seen in autoimmune diseases such as lupus (49). In some cases, the lesions are associated with Raynaud’s phenomenon and a trigger such as cold exposure or mental stress is thought to cause skin symptoms on the extremities through vasoconstriction (50). Vasoconstriction caused by cold, vasospasm leading to hypoxemia and inflammation are various factors in the formation of these lesions. Other theories are autoantibody-induced endothelial damage and hyperviscosity (49). Considering the increasing incidence of Chilblain-like lesions and their temporal relationship with viral symptoms, the definition of “COVID toes” has come to the fore.

Chilblain-like lesions are lesions that can cause symptoms such as itching, pain or burning, accompanied by vesicles or pustules on an erythematous and edematous background. The incidence of Chilblain-like acral lesions has increased during the COVID-19 pandemic. It has been reported in many case series that chilblain-like lesions can be found in COVID-19. The prevalence of these lesions varies between studies. In an international case series consisting of 505 patients with dermatological findings, 63% of chilblain-like lesions were reported (51). In other studies, the prevalence of chilblain-like lesions ranges from 14.3% to 72% (12, 26, 51–53). These types of vascular lesions have been reported mostly in adolescents and young adults, and the most common location of the lesions is the distal parts of the fingers and toes (12, 26, 30, 51, 52, 54–59). In many case series, it has been reported that the lesions start after the symptoms of COVID-19 and the lesions regress within an average of one to two weeks (12, 51, 54, 55). These types of lesions are an important clue for detecting asymptomatic cases of COVID-19.

In the case series published by Freeman et al., it was reported that in 55% of the cases, chilblain-like lesions were the only symptom of COVID-19 infection and these patients were young and had no additional disease. And in this study, the presence of chilblain-like lesions in COVID-19 was associated with mild disease (51). In the case series of Galvan Casas et al., the frequency of chilblain-like lesions was 19%, the average age of patients with this lesion was 32.5, and the mean duration of lesions was 12.7 days (12).

Different patterns were observed in the histopathological examination performed by Rubio-Muniz et al. They reported that in most of the Chilblain-like lesions, focal vacuolar degeneration in the basal layer, perivascular lymphocytic infiltration in the dermis and regenerative changes in the epidermis were observed. In addition, perivascular neutrophilic infiltration has been reported with epidermal necrosis in some cases (25).

The mechanism of formation of chilblain-like lesions seen in COVID-19 is not fully known. Bouaziz et al. emphasized immune dysregulation, vasculitis, vascular thrombosis and neoangiogenesis in the formation of these lesions. In this study, a large number of chilblain-like lesions were also reported in people who were in close contact with COVID-19 patients who did not have COVID-19 PCR positivity and did not show the general symptoms of COVID-19 infections. Three different hypotheses have been emphasized in the formation of these lesions. Firstly, these lesions might be caused by a confounding factor other than COVID-19. Secondly,
they might develop due to a postviral immunological reaction in asymptomatic forms of COVID-19, and finally, they represent skin involvement of the infection in the COVID-19 patient group showing an unusual immune anti-viral response (3).

**PPE Induced Skin Complications**

Virus-induced or drug-related skin lesions can be seen in patients infected with SARS-CoV-2. In addition, the pandemic has indirectly caused many cutaneous complications with the use of personal protective equipment (PPE). These complications include pressure sores, contact dermatitis, urticaria, dry skin, and exacerbation of pre-existing skin diseases such as seborrheic dermatitis, atopic dermatitis, acne, and rosacea (60). Due to the possible transmission of SARS-CoV-2 from asymptomatic individuals, the widespread use of PPE has become mandatory, especially to reduce infection rates among healthcare professionals and prevent viral spread. Healthcare professionals should protect themselves and their patients from disease transmission by wearing multiple types of PPE such as goggles, face shields, N95 masks, protective gowns and latex gloves. Frequent and long-term use of PPE among healthcare professionals during the COVID-19 pandemic has been associated with various skin complications (61). The fact that impaired cutaneous barriers create a potential gateway for COVID-19 infections and increase contamination is a serious concern with PPE. Masks, goggles, face shields, and gloves exert pressure on areas of contact, create skin abrasion, cause moisture and maceration, and can cause skin damage to the nose bridge, cheeks, forehead and hands. Skin damages caused by PPE include desquamation, erythema, maceration, fissure, papules, and erosions that cause itching and pain (62).

In a cross-sectional questionnaire study conducted by Jiang et al in China, the prevalence of skin lesions caused by the use of PPE in healthcare workers was found to be 42.8% among the 4,306 participants. In this study three types of skin injuries have been identified; pressure ulcers due to the equipment use, skin damage due to moisture, and skin tears. In the same study PPE-related skin lesions were also handled. It has been reported that the prevalence is higher among male physicians, among those who use PPE for more than 4 hours per day, among those over the age of 35, and among the individuals who sweat a lot (61). In another study conducted with 61 healthcare workers who regularly use PPE in China, it was reported that 95.1% of those using N95 masks developed skin lesions due to the use of masks. The most common of these lesions was pressure-related skin damage at the bridge of the nose, while the second most common skin symptom was itching on the face. Moreover, complications related to the use of latex gloves were also detected in 88.5% of the participants. These complications were dry skin, itching, redness, and skin tears. In addition, complications related to the use of protective clothing were also reported in 67% of the participants. The most common of these complications were skin dryness and itching (63).

The most notable of the complications caused by the use of PPE is pressure ulcers. While the most common location of pressure ulcers caused by personal protective equipment is the nose bridge and cheeks (59.65%), they can also be located less frequently in the auricle, forehead, zygoma and chin. It has been reported that 98.84% of pressure ulcers reported in medical personnel are at the stage 1 and stage 2 (61).

The use of barrier films or dressings at pressure points before wearing PPE can reduce such injuries (60, 64, 65). However, the effects of these preventive measures on the ability of PPE to prevent viral spread are not known enough, so it is crucial to be careful about this (65, 66).

Frequent hand washing and intensive use of hand disinfectants during the pandemic caused an increase in the incidence of hand dermatitis both in healthcare workers and in the general population. In addition, frequent washing of hands and keeping them moist in gloves for a long time increases the risk of pseudomonas colonization and infection in the nails. This situation is also important in terms of the risk of transmission to patients in the intensive care unit. The use of regular moisturizing and barrier creams, washing hands with warm water instead of hot water, and reducing the use of alcohol-based hand disinfectants as much as possible provide benefits in terms of preventing hand eczema (62). The American Academy of Dermatology has published recommendations for the prevention and treatment of occupational dermatological problems during the pandemic. Following these recommendations will be beneficial in protecting healthcare professionals from possible skin complications due to the PPE use (67).
DISCUSSION

Among the exanthems that have been mentioned above, maculopapular lesions are the most common, and they are followed by urticarial, vesicular and MIS-C lesions. Maculopapular and urticarial exanthems are typically associated with severe COVID-19 infections and are more common in middle-aged and elderly patients. The time of onset of maculopapular and urticarial lesions varies between studies. These two types of lesions are not helpful in terms of the diagnosis of COVID-19 because these lesions can also occur as a side effect of drugs used in the treatment of infection.

Although the onset of vesicular rash varies, most of them begin after systemic symptoms. It has been reported that it starts before systemic symptoms in very few cases. The mean age of vesicular lesions is 57.44 ± 17.26 years for men and 58.80 ± 15.918 years for women and associated with intermediate severity. This rash type is thought to be the specific rash of COVID-19.

MIS-C is a new, serious disease seen in childhood with a lot of unknown clinical features. Despite the lack of information, published data suggest that most MIS-C patients develop skin symptoms.

Vascular lesions associated with COVID-19 can be categorized as chilblain-like, petechiae / purpura or livedoid. Chilblain-like lesions are very similar to pernio lesions that occur with cold exposure; however, unlike the pernio, these lesions are also seen in warmer weather conditions. Chilblain-like lesions are found on the fingers and toes of young patients and are associated with less severe COVID-19 infections. The onset of chilblain-like lesions is typically after the onset of COVID-19 systemic symptoms. The mean age for chilblain-like lesions ranges from 11-27 in reports and associated with less severe disease.

Petechiae / purpura lesions are more common in middle-aged patients. These lesions have been associated with more severe COVID-19 infection. These lesions can be seen as acral localized, limited to the distal extremities or as diffuse involvement (26, 29). Livedoid lesions are among the rarest skin findings during the pandemic. They mostly occur in elderly patients and have been associated with severe COVID-19 infections (12).

The pathophysiological mechanisms behind the skin symptoms of COVID-19 are not well known, but many theories have been proposed regarding this issue. It is believed that maculopapular and urticarial rashes may occur due to adverse reactions related to drugs used in COVID-19 disease or cytokine storm during the course of the disease (24, 68).

Possible molecular mechanisms of Chilblain-like lesions include immune dysregulation, vasculitis, vascular thrombosis, and neoangiogenesis (3). In the pathogenesis of petechiae / purpuric skin lesions, it is possible to mention about a pauci-inflammatory thrombogenic vasculopathy with dense accumulation of complement components C5b-9 and C4d in the cutaneous microvascular system (41). Also, in the formation of these lesions, cutaneous side effects of the drugs used in the treatment of the disease might be involved.

Livedoid lesions are thought to be due to DIC and macrothrombosis in severe cases and microthrombosis triggered by inflammatory cytokines in milder cases. While vesicular lesions are caused by cytokine storm due to the immune system hyperactivity, there is no definite information about the pathophysiology of MIS-C lesions.

In the covid-19 pandemic, due to the use of PPE and frequent and excessive disinfectants, both primary dermatological problems can develop and exacerbation of existing skin diseases can be seen. This situation once again increases the importance of dermatologists in the pandemic.

Finally, it should be kept in mind that the cutaneous symptoms seen during the pandemic can be a direct effect of the SARS-CoV-2 virus. The possibility of COVID-19 should be carefully evaluated in patients whose skin findings are reported during the pandemic. Given the high mortality rate of the infection, timely and accurate identification of the relevant cutaneous symptoms can play a key role in early diagnosis and treatment. It is clear that more in-depth research is needed to understand the relationship between COVID-19 and the skin.

As a result, different cutaneous symptoms have been described in the COVID-19 pandemic. Although its pathogenic mechanisms are still unclear, it has been stated that hyperactive immune response, complement activation and microvascular damage play a role in the formation of skin findings. On the other hand, the
effects of other infectious agents, patient comorbidities, immune status, concomitant treatments and other still unidentified factors are still the main controversy. Cutaneous findings that can cause suspicion of COVID-19 and identify potentially infectious cases carry dermatologists to an important position in terms of pandemics. Moreover, the role of skin findings associated with COVID-19 as prognostic markers needs to be clarified. However, the literature data show a great heterogeneity in cutaneous manifestations, in their time to occur, and in extracutaneous symptoms associated with skin manifestations. In patients with skin findings and asymptomatic in terms of SARS-CoV-2, skin findings can easily be confused with allergic diseases and other viral diseases. Therefore, clinicians should be aware of the skin involvement in COVID-19 to make an early diagnosis. On the other hand, more histological and clinical studies are required to demonstrate the mechanisms of cutaneous findings.

Declarations
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Carboxyhemoglobin, Methemoglobin and Lactate Levels in Patients with Systemic Inflammatory Response Syndrome

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Abstract

Background: Systemic inflammatory response syndrome (SIRS) is a common, severe inflammatory condition. This condition forms the basis of the definitions of sepsis, severe sepsis, septic shock, and multiple organ failure syndromes. The diagnosis can be made earlier with arterial blood gas analysis, which can provide a lot of information within minutes. This study aimed to determine the value of carboxyhemoglobin (COHb), methemoglobin (metHb), and lactate levels in the prognosis and mortality of patients with SIRS.

Methods: Patients who met the SIRS criteria with the first vital signs and laboratory values and who had arterial blood gas analysis according to the clinician’s decision were included in the study. The demographic characteristics, prognosis and correlation of 1-month mortality rates of patients with baseline COHb, metHb and lactate levels were investigated.

Results: Among non-smoker patients, no significant difference was found between fCOHb values and age, gender, presence of infection, blood pressure, department of hospitalization, and 1-month mortality rates (p>0.05). Also, the relationship between fCOHb values and length of stay in the hospital was not statistically significant (r = -0.013, p = 0.883). Among the patients included in the study; there was no significant difference in metHb values between age groups (p = 0.9941), gender (p = 0.6422), presence of infection (p = 0.1311), blood pressure (p = 0.7711), length of stay in hospital (p = 0.737), inpatient clinics (p = 0.6722) and 1-month mortality (p = 0.8752). Lactate values were found to be correlated with the 1-month mortality of the patients (p = 0.005). Lactate levels were significantly higher in patients who died within 1-month compared to those who survived.

Conclusions: In patients with SIRS, initial COHb and metHb values cannot be considered a predictor for prognosis and mortality. However, lactate values may be useful to predict SIRS mortality even during hospital admission.

Key words: SIRS, Carboxyhemoglobin, Methemoglobin, Lactate.

INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is a common disease encountered in the emergency department (ED) (1, 2). Moreover, arterial blood gas analysis, which is frequently used in ED, can provide valuable data for diagnosis and follow-up (3).

Carbon monoxide (COHb) is formed by binding endogenous or exogenous carbon monoxide (CO) to hemoglobin. Proinflammatory cytokines, bacterial toxins, heme protein, hyperoxia, hypoxia and reactive oxygen radicals increase the levels of hemoxygenase and increase endogenous CO production (4). The asymptomatic increase of methemoglobin (metHb) levels as a result of oxidative stress and inadequate mechanisms for elimination of this stress is being investigated as a marker of early diagnosis and long-term prognosis of many inflammatory conditions. It is known that lipopolysaccharides increase the release of nitric oxide (NO) in sepsis conditions, and this increase in the amount of NO results in hypotension. NO, as an oxidative stress factor, enhances the conversion of hemoglobin to metHb (5-7).

Lactate forms as a result of tissue hypoxia (7-9). Under anaerobic conditions, pyruvate is converted into lactate. In critically ill patients, the amount of lactate increases as a result of oxidative stress (9).

The aim of this study was to investigate the clinical value of COHb, metHb and lactate in order to predict prognosis and mortality, obtained by the first arterial blood gas analysis in patients diagnosed with SIRS in ED.

MATERIALS AND METHOD

At the Gazi University Clinical Research Ethics Committee on 13.04.2015, ethical approval was obtained with the decision number 160.

This study was designed as a prospective clinical study, with patients admitted to ED of a university hospital between April 2015 and June 2015. Patients older than 18 years, who were diagnosed as SIRS with vital signs and laboratory data taken at the time of admission to the ED, whose arterial blood gas samples were taken immediately after admission, were included in the study. Among patients admitted to ED of Gazi University Faculty of Medicine:

- Patients under the age of 18
- Patients whose informed consent could be obtained from themselves or their legal relatives
- Patients whose blood samples had technical laboratory errors
- Patients who had congenital methemoglobinemia and those exposed to agents causing toxic methemoglobinemia
- Patients with epileptic seizures or previously diagnosed with epilepsy
- Patients who were using biguanides as oral antidiabetic were excluded.

Moreover, patients who were smokers and patients with carbon monoxide intoxication were excluded from the statistics about COHb.

Data Collection

Data collection started on the date of 01.04.2015 and ended on 30.06.2015. Demographic characteristics of patients, vital signs, laboratory values, diagnoses, source of infection (if present), result of ED visiting, referred clinic (if the patient was admitted), length of stay in hospital and 1-month mortality rates were recorded. Before data collection, written consent was obtained from patients or legal guardians.

Blood Gas Analysis

Arterial blood gas samples taken from the patients were analyzed with the blood gas analyser (ABL800 BASIC®) within ED.

Statistical Analysis

Research data were uploaded to the computer using “SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc., Chicago, IL)”. The conformity of variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk Test). As a statistical method, Mann-Whitney U Test was used for determining the statistical significance of the two independent groups for the variables not normally distributed; Kruskal Wallis Test was used for three independent groups. Bonferroni correction was performed to determine the source of the difference when there was a significant difference between the three independent groups. The relationship between the variables was evaluated by the Spearman’s Test. The level of statistical significance was accepted as p<0.05.
RESULTS

One hundred forty-nine patients were evaluated. Three of these patients declined to participate in the study. There were deficits in 4 patients’ data. One patient was excluded from the study because he was brought to the ED as cardiopulmonary arrest and the vital signs were unstable. After the exclusion of eight patients, 141 patients were included in the study. Of the 141 patients, ten patients were active smokers, so they were excluded from COHb evaluations. Analyses on COHb values were performed with the remaining 131 patients. Data of vital signs and laboratory results were recorded for diagnosis of SIRS (Table 1).

Table 1. Vital signs and laboratory values of patients

<table>
<thead>
<tr>
<th>(n: 141)</th>
<th>Number</th>
<th>%</th>
<th>(n: 141)</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>Leukocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>33</td>
<td>23.4</td>
<td>Leukocytosis (&gt;12000/µL)</td>
<td>87</td>
<td>61.7</td>
</tr>
<tr>
<td>Tachycardic (&gt;90)</td>
<td>105</td>
<td>74.5</td>
<td>Leukopenia (&lt;4000/µL)</td>
<td>43</td>
<td>30.5</td>
</tr>
<tr>
<td>Bradycardic (&lt;60)</td>
<td>3</td>
<td>2.1</td>
<td>Immature band forms (&gt; 10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>11</td>
<td>7.8</td>
</tr>
<tr>
<td>Temperature</td>
<td>Blood Pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthermic (&gt;38°C)</td>
<td>30</td>
<td>21.3</td>
<td>Normotensive</td>
<td>66</td>
<td>46.9</td>
</tr>
<tr>
<td>Normal (36-38°C)</td>
<td>111</td>
<td>78.7</td>
<td>Hypotensive (systolic &lt;90 mmHg or systolic blood pressure drops at least 40 mmHg)</td>
<td>48</td>
<td>34.0</td>
</tr>
<tr>
<td>Hypothermic (&lt;36°C)</td>
<td>0</td>
<td>0</td>
<td>Hypertensive (systolic &gt;140 mmHg)</td>
<td>27</td>
<td>19.1</td>
</tr>
<tr>
<td>Tachypnea or Hypocarbia</td>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>34</td>
<td>24.1</td>
<td>Acidosis (&lt;7.35)</td>
<td>30</td>
<td>21.3</td>
</tr>
<tr>
<td>Tachypnea or hypocarbia</td>
<td>107</td>
<td>75.9</td>
<td>Alkalosis (&gt;7.45)</td>
<td>41</td>
<td>29.1</td>
</tr>
<tr>
<td>Tachypnea (&gt;20/ min)</td>
<td>59</td>
<td>41.8</td>
<td>Normal (7.35-7.45)</td>
<td>70</td>
<td>49.6</td>
</tr>
<tr>
<td>Hypocarbia (PaCO2&lt;32 mmHg)</td>
<td>73</td>
<td>51.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemic (&lt;95%)</td>
<td>84</td>
<td>59.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&gt;95%)</td>
<td>57</td>
<td>40.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The median of COHb fraction (fCOHb) value at the time of admission was 1.1% (min: 0-max: 4.8); the median value of fraction of metHb (fmetHb) was 0.7% (range: 0.1 - 4.0) and the median value of lactate was 1.6 mmol / L (range: 0.3 - 20.0) (Table 2).

Table 2. Initial arterial blood gas analysis; fCOHb, fmetHb, lactate

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fCOHb (%)</td>
<td>1.28±0.73</td>
<td>1.1 (0-4.8)</td>
</tr>
<tr>
<td>fmetHb (%)</td>
<td>0.89±0.66</td>
<td>0.7 (0.1-4.0)</td>
</tr>
<tr>
<td>Lactate (mmol / L)</td>
<td>2.11±2.15</td>
<td>1.6 (0.3-20.0)</td>
</tr>
</tbody>
</table>

SD: Standard deviation

Among 141 patients, 64.5% (n:91) have had at least one focal infection, while in 35.5% (n:50) a focal infection could not be found. Among the 91 patients with focal infections; 56% (n:51) had lower respiratory tract infections, 29.6% (n:27) had urinary tract infections, 6.5% (n:6) had gastroenteritis, 4.3% (n:4) had cellulitis, 4.3% (n:4) had intracranial infection, 3.2% (n:3) had infective endocarditis, 1% (n:1) had cryptic tonsillitis.

The mean value of the length of stay in hospital was 9.28 ± 10.69 days and the median value of the length of stay in hospital was 7 days (range: 0.5 - 70). When the 1-month mortality rate of these patients was evaluated, it was determined that 14.9% (n:21) died within one month following their admission to the ED.

A statistically significant relationship was found between fCOHb values and the result of ED visit (p: 0.004). Post-hoc binary comparisons revealed significant differences between “referral to another hospital and left ED”, “discharge and left ED” and “death in ED and left ED.” Patients who left ED had a higher fCOHb value in comparison to referred patients, discharged patients and patients who died in ED. On the other hand, statistical analyses did not exhibit a significant relationship between fCOHb values and age, gender, the status of infection, blood pressure, place of admission, department of hospitalization, and 1-month mortality rates (p>0.05) (Table 3).
Table 3. Distribution of COHb values between selected demographic features, vital signs, result of ED visit, place of admission and 1-month mortality

<table>
<thead>
<tr>
<th>(n: 131)</th>
<th>fCOHb n</th>
<th>Median (min-max)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>58</td>
<td>1.2 (0.3-3.7)</td>
<td>0.572&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>66-80</td>
<td>46</td>
<td>1.0 (0-3.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>27</td>
<td>0.9 (0.2-3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74</td>
<td>1.1 (0-3.7)</td>
<td>0.487&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>1.0 (0.1-3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Status of Infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of infection cannot be found</td>
<td>47</td>
<td>1.0 (0.5-3.7)</td>
<td>0.802&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sepsis</td>
<td>56</td>
<td>1.2 (0-2.8)</td>
<td></td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>28</td>
<td>1.0 (0.3-3.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>62</td>
<td>1.0 (0.1-3.7)</td>
<td>0.912&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypotensive (systolic &lt;90 mmHg or systolic blood pressure drops at least 40 mmHg)</td>
<td>44</td>
<td>1.1 (0.3-3.4)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive (systolic &gt;140 mmHg)</td>
<td>25</td>
<td>1.0 (0-2.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Result of ED Visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>35</td>
<td>0.9 (0.3-3.4)</td>
<td>0.004&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Admitted to hospital</td>
<td>76</td>
<td>1.1 (0-3.0)</td>
<td></td>
</tr>
<tr>
<td>Referral to another hospital</td>
<td>6</td>
<td>0.6 (0.5-2.1)</td>
<td></td>
</tr>
<tr>
<td>Left ED</td>
<td>8</td>
<td>1.8 (0-9-3.7)</td>
<td></td>
</tr>
<tr>
<td>Death in ED</td>
<td>6</td>
<td>0.8 (0.1-1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Place of Admission (n: 76)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward</td>
<td>42</td>
<td>1.0 (0-2.8)</td>
<td>0.245&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>34</td>
<td>1.2 (0.5-3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Department of Hospitalization (n: 76)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal clinics</td>
<td>71</td>
<td>1.1 (0-3.0)</td>
<td>0.871&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Surgical clinics</td>
<td>5</td>
<td>1.2 (0.8-2.6)</td>
<td></td>
</tr>
<tr>
<td><strong>1-month Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exitus</td>
<td>20</td>
<td>1.2 (0.1-2.3)</td>
<td>0.918&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alive</td>
<td>111</td>
<td>1.0 (0-3.7)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Kruskal Wallis Test; <sup>b</sup>Mann-Whitney U Test

Among 131 non-smoker patients, the relationship between fCOHb values and length of stay in hospital were not found to be statistically significant (r: -0.013, p: 0.883) (Figure 1).

Figure 1. Relationship between fCOHb values and length of hospital stay

Among 141 patients included in the study; there was no significant relationship between metHb values and age (p:0.9941), gender (p:0.6422), status of infection (p:0.1311), blood pressure (p:0.7711), length of stay in hospital (p:0.737), place of admission (p:0.6722) and 1-month mortality (p:0.8752) (Table 4, Figure 2).

Figure 2. Relationship between MetHb values and length of hospital stay

There was a significant relationship between lactate values and 1-month mortality rates of the patients (p:0.005).
Lactate levels were significantly higher in patients who died within 1-month compared to those who survived. However, there were no significant differences between lactate levels and age, genders, the status of infection, blood pressure, the result of ED visit, length of stay in the hospital, and place of admission (p>0.05) (Table 4, Figure 3).

Table 4. Distribution of MetHb and lactate values between selected demographic features, vital signs, results of ED visiting, place of admission and 1-month mortality

<table>
<thead>
<tr>
<th></th>
<th>MetHb</th>
<th></th>
<th>Lactate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (min-max)</td>
<td>P</td>
<td>Median (min-max)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>0.7 (0.1-3.6)</td>
<td>0.994\textsuperscript{a}</td>
<td>1.6 (0.3-7.0)</td>
<td>0.799\textsuperscript{a}</td>
</tr>
<tr>
<td>66-80</td>
<td>0.7 (0.1-4.0)</td>
<td>1.6 (0.5-20.0)</td>
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</tr>
<tr>
<td>&gt;80</td>
<td>0.7 (0.1-2.4)</td>
<td>1.6 (0.8-6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.7 (0.1-4.0)</td>
<td>0.642\textsuperscript{b}</td>
<td>1.7 (0.3-20.0)</td>
<td>0.629\textsuperscript{b}</td>
</tr>
<tr>
<td>Female</td>
<td>0.7 (0.1-2.5)</td>
<td>1.6 (0.5-12.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Status of Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of infection cannot be found</td>
<td>0.8 (0.2-3.6)</td>
<td>0.131\textsuperscript{a}</td>
<td>1.6 (0.6-7.0)</td>
<td>0.373\textsuperscript{a}</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.7 (0.1-4.0)</td>
<td>1.6 (0.3-20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>0.7 (0.2-2.4)</td>
<td>1.9 (0.5-6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>0.7 (0.1-4.0)</td>
<td>1.8 (0.4-20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotensive (systolic &lt;90 mmHg or systolic blood pressure drops at least 40 mmHg)</td>
<td>0.75 (0.2-2.5)</td>
<td>0.771\textsuperscript{a}</td>
<td>1.8 (0.5-6.1)</td>
<td>0.380\textsuperscript{a}</td>
</tr>
<tr>
<td>Hypertensive (systolic &gt;140 mmHg)</td>
<td>0.8 (0.4-2.5)</td>
<td>1.6 (0.6-3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Result of ED Visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>0.7 (0.2-2.3)</td>
<td>0.659\textsuperscript{a}</td>
<td>1.6 (0.5-3.7)</td>
<td>0.119\textsuperscript{a}</td>
</tr>
<tr>
<td>Admitted to hospital</td>
<td>0.7 (0.1-4.0)</td>
<td>1.6 (0.3-20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral to another hospital</td>
<td>0.5 (0.4-1.6)</td>
<td>1.6 (1.1-5.0)</td>
<td></td>
<td></td>
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<tr>
<td>Left ED</td>
<td>0.8 (0.1-3.6)</td>
<td>1.9 (1.1-7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death in ED</td>
<td>0.7 (0.3-2.5)</td>
<td>2.8 (1.7-12.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Place of Admission (n=84)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward</td>
<td>0.7 (0.1-4.0)</td>
<td>0.672\textsuperscript{b}</td>
<td>1.4 (0.3-20.0)</td>
<td>0.105\textsuperscript{b}</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>0.7 (0.1-2.6)</td>
<td>1.7 (0.8-6.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Department of Hospitalization (n=84)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal clinics</td>
<td>0.7 (0.1-4.0)</td>
<td>0.298\textsuperscript{a}</td>
<td>1.6 (0.3-20.0)</td>
<td>0.419\textsuperscript{a}</td>
</tr>
<tr>
<td>Surgical clinics</td>
<td>0.9 (0.5-1.8)</td>
<td>1.9 (1.1-3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1-month Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exitus</td>
<td>0.7 (0.3-4.0)</td>
<td>0.875\textsuperscript{b}</td>
<td>2.0 (0.9-20.0)</td>
<td>0.005\textsuperscript{b}</td>
</tr>
<tr>
<td>Alive</td>
<td>0.7 (0.1-3.6)</td>
<td>1.6 (0.3-7.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Kruskal Wallis Test; \textsuperscript{b}Mann-Whitney U Test
Figure 3. Relationship between lactate values and length of hospital stay

DISCUSSION

COHb and metHb in this study were not sufficiently correlated to determine prognosis in patients with SIRS. On the other hand, lactate levels in SIRS patients were valuable and significant to predict prognosis.

In a study by De Siqueira et al., which was performed on 200 healthy individuals to determine COHb reference values, COHb average was found as 1.00 ± 0.75% (10). Mean COHb values in 131 non-smoker patients were found similarly in our study. However, it should be taken into account that normal values in the literature are values from healthy control groups. In this study, we only included patients with SIRS who were not active smokers. Our results about mean and median COHb percentages were close to reference values in the literature, but these data for SIRS patients in our study should not be referred to when discussing reference values in healthy individuals.

We evaluated the COHb values of 131 patients to investigate whether COHb could provide a prediction for the clinical course and mortality of patients. Among 131 patients, those who left ED with their own decision were found to have significantly higher COHb values than those discharged from ED, referred to another hospital, and died in ED. This difference could be explained by the fact that patients who left ED had worse clinical conditions than those who were discharged. However, we do not think that this statistically significant difference will be useful in clinical practice.

In Moncure et al.’s study, severe sepsis patients admitted to intensive care units were found to have higher COHb values compared to those who were normotensive (11). However, in the same study, COHb levels did not differ significantly depending on whether there was a focus of infection. Moreover, mortality was not found to be associated with COHb levels (11). In our study, we evaluated COHb values of 131 non-smoker patients and analyzed the difference with regard to sepsis or severe sepsis. However, there were no significant COHb elevations in sepsis or severe sepsis patients compared to patients without infection or between sepsis and severe sepsis patient groups. In the same study by Moncure et al., blood gas samples were taken multiple times from patients during the intensive care unit’s follow-up period (11). In our study, the result that COHb values did not express a significant difference may be attributed to the single blood gas sample taken, only at the time of admission. Hunter et al.’s study, performed with blood samples from 32 surgical intensive care unit patients, revealed that COHb values were significantly increased in critically ill patients (12). However, the definition of “critically ill patients” in that study was not distinguished by SIRS but by intensive care scoring (12). There was no significant difference in COHb values of patients hospitalized in intensive care units and non-intensive care units in our study. Also, in our study, COHb values of patients hospitalized in the intensive care unit were not found to be correlated with negative clinical outcomes, unlike the study of Hunter et al. (12). It might also be the result of the fact that our study was designed with a single blood gas sample analysis, which was taken at the time of admission. On the other hand, higher numbers of patients were included in our study, compared to studies of Moncure et al. and Hunter et al. (11, 12). Although a higher number of patients provides more reliable results, only initial COHb values were considered in our study may be a limitation.

Moreover, a group of patients in our study was discharged from ED. This clinical difference between patient groups and the evaluation of the blood gas measurements only at the time of admission might be the reason for the result that COHb values could not be associated with length of stay in hospital and 1-month mortality in SIRS patients. According to our results, COHb levels in blood gas samples taken at admission are not a prognostic marker for length of stay in hospital and 1-month mortality, for patients diagnosed with SIRS with initial vital signs and laboratory values.
MetHb has been associated with the diagnosis and severity of various inflammatory conditions (7, 13). Schuerholz et al. retrospectively evaluated metHb values of 655 internal intensive care patients and revealed that septic patients had higher metHb values at the time of admission to the intensive care unit, which was significantly more prominent compared to non-septic patients and significantly correlated with the changing Sequential Organ Failure Assessment (SOFA) scores (7). Ohashi et al. evaluated 14 septic patients in the intensive care unit and reported that metHb values are higher in those patients compared to 31 non-septic patients hospitalized within the same intensive care unit (14). In this study, we also compared metHb values between patients with and without an infection, but we did not find a significant increase of metHb in the septic group. In the present study, the number of patients who had been discharged from ED in a shorter time period was more than the other studies; therefore, the septic patient group in the study, which had a higher rate, was found to have a better prognosis. This difference may be the reason metHb values were not significantly higher in septic patients in our study. Ohashi et al. had evaluated metHb with the data obtained by serial measurements during the recovery period of sepsis (14). However, when we evaluated metHb values obtained from arterial blood gas analysis at the time of admission, we could not find a significant relationship between the length of stay in hospital and 1-month mortality in patients with SIRS. Our study was the first, investigating the relationship between SIRS and metHb in terms of taking ED patients into consideration and evaluating only blood gas values at the time of admission. Both our literature search and the results of our study showed that metHb was not useful for predicting the prognosis or mortality of patients with SIRS.

It is well-known that many different causes of tissue hypoxia lead to elevated lactate levels over a short period of time (15). SIRS, which is known to be a severe inflammatory process, is an important cause of hypoxic stress. Mikkelsen et al. reported a significant relationship between the 28-day mortality of patients with severe sepsis or septic shock and the first blood gas lactate levels in their study, with 830 patients admitted to the ED in two years (16). Our study was similar to that of Mikkelsen et al., as evaluating initial blood gas values of ED patients. Moreover, in addition to the results of Mikkelsen et al., we found that the lactate levels were also indicative for 1-month mortality in all patients with SIRS and sepsis, not only for patients with severe sepsis and septic shock. Although fewer patients were included, as patients with SIRS who were not hypotensive were included, our study results may be useful for clinicians for a larger patient group than Mikkelsen et al.’s study. Singer et al. performed serial lactate measurements while monitoring 258 sepsis patients followed in the ED, and according to their study, high lactate levels were clearly associated with poor prognosis (8). This study has a smaller number of patients than Singer et al., and we only included those who were fulfilling the SIRS definition and evaluated lactate levels obtained only from initial arterial blood gas analysis. Therefore, our study was able to support the results of Singer et al.’s study in a wider diagnostic spectrum, with less laboratory analysis. In a systematic review by Kruse et al., whether lactate levels at the time of admission were a marker for mortality was investigated. Accordingly, Kruse et al. emphasized that elevated lactate levels at the time of admission were related to patients’ mortality. In that review, patients whose lactate values were higher than 2.5 mmol / L in arterial blood gas analysis was reported to have significantly higher mortality rates (19). In our study, higher lactate levels in patients diagnosed as SIRS were significantly associated with 1-month mortality. Higher lactate levels in patients who died within 1 month were significantly higher than those who survived. Thus, lactate levels give the physicians an opinion about mortality in patients with SIRS, even at the time of admission.

In conclusion, it was found that COHb and MetHb values measured in the arterial blood gas samples during admission to the ED were not useful in predicting prognosis or mortality in patients with SIRS. On the other hand, lactate levels were associated with mortality in SIRS, even at admission to ED.

**Declarations**

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

At the Gazi University Clinical Research Ethics Committee on 13.04.2015, ethical approval was obtained with the decision number 160.
REFERENCES


Mean Platelet Volume and Red Cell Distribution Width Values in Patients with COVID-19 Admitted to Intensive Care Units or Wards from Emergency Department

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Abstract

Background: Mean platelet volume (MPV) and red cell distribution width (RDW) values are components of complete blood count (CBC) which is a routine, cheap and fast test used in the evaluation of patients admitted to the emergency department (ED). The present study aimed to investigate RDW and MPV values in patients with Novel Coronavirus Disease 2019 (COVID-19) admitted to intensive care units (ICU) or wards from the ED.

Methods: A retrospective data analysis of patients who were admitted to Ankara City Hospital ICUs and wards with the diagnosis of COVID-19 was performed. Group 1 included patients admitted to ICUs and Group 2 included those admitted to wards.

Results: A total of 127 patients were admitted with a COVID-19 diagnosis. Mean age in Group 1 and Group 2 were 46±17 and 41±14, respectively. The number of patients admitted to ICU (Group 1) was 46 (36.2%), and the number of patients admitted to wards (Group 2) was 81 (63.7%). Of all patients, 122 patients (96.06%) were discharged and 5 patients (3.9%) died. RDW values in Group 1 was higher than those in Group 2 (p<0,001). Similarly, MPV was higher in Group 1 than Group 2 (p<0,001).

Conclusion: In patients with COVID-19, RDW and MPV values are higher in those admitted to ICU than patients admitted to wards from the ED.

Key words: Complete Blood Count, COVID-19, Mean Platelet Volume, Intensive Care Units, Red Cell Distribution Width.
INTRODUCTION

Novel Coronavirus Disease 2019 (COVID-19) was initially announced in Wuhan city of Hubei State, China as pneumonia with unidentified origin on December 31, 2019 by World Health Organization (WHO) China Country Office (1). The outbreak immediately spread to countries out of China and WHO declared COVID-19 as pandemic on March 11, 2020 (1). COVID-19 has a severe course particularly in patients with chronic conditions or immunodeficiency and is associated with increased mortality (2). As vaccine trials are ongoing, new mutants of the virus are identified (3). Early diagnosis and treatment plays a key role in the management of COVID-19 viral infection with high transmission and fatality rates. WHO recommended Real Time-Polymerase Chain Reaction (RT-PCR) as definitive method for detection of COVID-19, however it is not helpful for assessment of disease severity (4, 5). Several various biochemical and inflammatory markers were shown to be associated with the severity of COVID-19 (6).

Platelets (PLTs) play a substantial role in the recognition of injured endothelium, aggregation around site of injury, clot formation and also interaction with leukocytes for the initiation of inflammation (7-9). Certain proinflammatory molecules such as cytokines, chemokines and interleukins are stored in granules located in PLT and then released following activation. Mean platelet volume (MPV) value is an important indicator of PLT activation and has been shown to increase in states of infection and inflammation in previous reports (7-9). Moreover, increase in MPV values were shown to be associated with mortality in COVID-19 patients (10).

Red blood cell distribution width (RDW) is an indicator of heterogeneity in erythrocyte volume (11). Measurement of RDW is traditionally used in the differential diagnosis of anemia. Furthermore, RDW was shown to be a powerful predictor of morbidity and mortality in various patient populations (11). Increase in RDW value was shown to be correlated with the severity of COVID-19 (12).

Components of CBC including RDW and MPV values were evaluated.

Complete blood count tests, including RDW and MPV values, are easily accessible and measurable. They are also cheap routine blood tests providing rapid results for the evaluation of patients in emergency departments (ED). The present study aimed to investigate the use of RDW and MPV values for guidance in the decision of admitting patients with COVID-19 to ICUs or wards from the ED.

MATERIALS AND METHODS

The study was approved by the Ethical Committee of Ankara City Hospital (Date: 09/12/2020, No: E1-20-854).

The present study was conducted in Ankara City Hospital, a tertiary care healthcare facility located in Ankara, Turkey. The study was approved by the Ethical Committee of Ankara City Hospital. Retrospective analysis of patients presenting to the ED and admitted to ICU or wards after being diagnosed with COVID-19 via RT-PCR test or chest computed tomography findings consistent with COVID-19 pneumonia, between March 20, 2020 and April 10, 2020 was performed. All of the patients were over 18 years old. COVID-19 diagnosis of patients with chest CT findings compatible with COVID-19 was settled by consultation of the ED physician, radiologist, infectious disease specialists and ICU physicians. Patients diagnosed with COVID-19 via RT-PCR test or chest CT were excluded in the presence of chronic conditions (diabetes, myocardial infarction, etc.).

Patients were divided into two groups as patients admitted to ICU (Group 1) and those admitted to wards (Group 2). Group 1 included patients with severe pneumonia defined by WHO criteria (severe pneumonia adolescent or adult: fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 ≤ 93% on room air (13)) and admitted to ICUs. Group 2 included patients admitted to wards who lack severe pneumonia criteria or recommendation for admission to ICU by an infectious diseases specialist.

Demographic characteristics, Complete Blood Count (CBC) results, RDW and MPV values measured in the ED presentation of each patient were obtained from the hospital medical records system. The reference ranges in our hematology laboratory are as follows: Red Blood Cell (RBC), 4-5.65 x10^12/L; RDW, 11.5-16 %; Hemoglobin (Hb), 12.5-17.2g/dL; White Blood Cell (WBC) count: 3.6-10.5 x10^9/L; PLT, 160-400 x10^9/L; and MPV, 6-10 fL.

RT-PCR detection kit (SARS-CoV-2 (2019-nCoV) qPCR Detection Kit, Bioeksen R&D Technologies Ltd. Turkey) was used for COVID-19 diagnosis.

Components of CBC including RDW and MPV values of patients in both groups were evaluated.

Statistical Analyses

Continuous variables were presented as mean ± standard deviation and median (interquartile quartiles). Normality
was tested by calculation of skewness and kurtosis for all continuous variables. Unpaired t test was used to compare normally distributed continuous variables between two independent groups. Mann–Whitney U test was used to test non-normally distributed continuous variables. A p value of <0.05 was considered significant for all tests. Statistical Package for the Social Sciences (SPSS version 11.0, SPSS Inc., Chicago, IL, USA) was used.

RESULTS

During the study period, 271 patients were diagnosed with the COVID-19 disease and admitted to the hospital (128 patients to ICUs, 143 patients to wards). Of those, 144 patients (53.1%) with chronic diseases were excluded from the study. The remaining 127 patients were evaluated. The number of male patients was 71 (55.9%). Mean age was 46±17 years in Group 1 and 41±14 in Group 2, the difference was statistically significant (p: 0.013), (Table 1). The number of patients in Group 1 was 46 (36.2), and it was 81 (63.7%) in Group 2. The number of discharged patients in the entire study population was 122 (96.06%) and five patients died (3.9%), all of which were patients admitted to ICUs (Group 1).

Table 1. Study group characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (Patients admitted to ICUs)</th>
<th>Group 2 (Patients admitted to wards)</th>
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</tr>
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<tbody>
<tr>
<td>Patient age (years)</td>
<td>46 ± 17</td>
<td>41 ± 14</td>
<td>0.013*</td>
</tr>
<tr>
<td>WBC (109/L)</td>
<td>6.5 (9.6-4.6)</td>
<td>6.35 (7.6-5.2)</td>
<td>0.031*</td>
</tr>
<tr>
<td>RBC (1012/L)</td>
<td>4.44 ± 0.91</td>
<td>4.89 ± 0.48</td>
<td>0.005*</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.3 (14.8-11.1)</td>
<td>14.1 (15.2-13.2)</td>
<td>0.006*</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>15.9 (14.6-16.7)</td>
<td>13 (14-12.6)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>PLT count (109/L)</td>
<td>175 ± 90</td>
<td>256 ± 61</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>9.49 ± 1.31</td>
<td>8.10 ± 0.93</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

*p values indicate differences between ICU and non-ICU patients. p < 0.05 was considered statistically significant. Continuous variables were presented as mean ± standard deviation and median (interquartile quartiles). Hb; Hemoglobin, ICU; Intensive Care Unit, MPV; Mean Platelet Volume, PLT; Platelet, RBC; Red Blood Cell, RDW; Red Blood Cell Distribution Width, WBC; White Blood Cell.

WBC count in Group 1 (median: 6.5, range: 9.6-4.6) was higher than Group 2 (median: 6.35, range: 5.2-7.6), and it was statistically significant (p: 0.031). RBC count in Group 1 patients (mean: 4.44 ± 0.91) was lower than Group 2 (mean: 4.89 ± 0.48, p: 0.005). Hb values were lower in Group 1 patients (median: 13.3, range: 11.1-14.8) than those in Group 2 (median: 14.1, range 13.2-15.2, p: 0.006) (Table 1).

RDW value in patients in Group 1 (median: 15.9, range: 14.6-16.7) was significantly higher than patients in Group 2 (median: 13, range 12.6-14, p<0.001). PLT count of patients in Group 1 (median: 15.9, range: 14.6-16.7) was lower than those in Group 2 (median: 13, range: 12.6-14, p<0.001). MPV value in patients in Group 1 (mean 9.49 ± 1.31) was higher than those in Group 2 (mean: 8.10 ± 0.93 fL, p<0.001).

DISCUSSION

The severity of the disease in COVID-19 was shown to be associated with increasing age (14). In the present study patients admitted to ICUs (Group 1) were older than patients admitted to wards (Group 2). However, mean age in both groups were younger than 50 years old. Median age of patients with severe and non-severe COVID-19 in the study by Zhenga et al. was similar with the present study (15). Despite the limited number of patients, it is widely accepted that COVID-19 is more common in middle-aged patients and the prognosis of the disease may be poor even in the absence of comorbid conditions in this patient population.

Moderate increase in WBC count values in patients with severe COVID-19 and a significant increase in WBC count values in patients who died due to COVID-19 disease were reported (6, 16). Similarly, the present study detected increased WBC count values in patients with severe COVID-19 who were admitted to ICUs than those admitted to wards.

RDW was shown to be a useful predictor of morbidity and mortality in a wide range of conditions including sepsis, pneumonia and other respiratory diseases (6, 11, 17-19). Severe COVID-19 was shown to be associated with decreased Hb and hematocrit values while RDW was correlated with the severity of COVID-19 (10). On the other hand, another study pointed out a significant decrease in Hb related with increased pro-inflammatory cytokines in patients with severe and critical COVID-19 (20). In consistence with the above-mentioned findings, the present study also detected decreased RBC and Hb count and increased RDW in patients with COVID-19.
who were admitted to ICUs. Increase in RDW value was shown to be associated with the inflammatory response thus indicating decreased life turnover of blood cells in peripheral circulation and increased production in bone marrow (14, 21-23). Various pathophysiological mechanisms might have played a role in the decrease of RBC and Hb values while RDW is increased in severe COVID-19 cases including a gradual increase in anemia driven by immune injury leading to bone marrow suppression. Compensatory efforts including hyperplasia in erythrocyte cell series and release of immature red blood cells to peripheral circulation might have resulted in the RDW increase (12, 19).

Previous reports demonstrated that prognosis in patients with various diseases who require admission is associated with decreased PLT and increased MPV values (6, 7, 9, 24, 25).

Decreased PLT count was reported to be one of the most common laboratory findings in COVID-19 and associated with increased mortality and disease severity suggesting its use as a prognostic parameter (15, 20, 26, 25). Besides, MPV value is an important indicator of PLT activation that has been shown to increase in states of infection and inflammation in previous reports (7-9). Güçlü et al. reported that a decrease in the number of PLT and an increase in MPV were associated with mortality in COVID-19 patients (10). Furthermore, the present study also demonstrated decreased PLT and increased MPV values in COVID-19 patients admitted to ICU. PLTs play a dynamic role in COVID-19 as they also do in the inflammatory response to many viral diseases. Thus, one can use alterations in PLT parameters for escalating treatment strategies and decision making for admission to ICUs (28, 29).

Considering all the results obtained in the present study and referred previous studies, one can assume that increased RDW and MPV values in COVID-19 indicate initiation of PLT activation and severe inflammation in patients admitted to ICUs, even in their initial presentation to the ED.

The main limitation of the current study was the retrospective design in a single center. Besides, patients’ data regarding the time period between symptom onset and ED presentation were missing. The sample size was not large enough due to the exclusion of patients with comorbid conditions, which may interact with CBC parameters.

In conclusion, RDW and MPV values were higher in those admitted to ICUs than patients admitted towards in patients with COVID-19. RDW and MPV values could be indicative of the severity of COVID-19 infection and the prognosis of the disease.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study was approved by the Ethical Committee of Ankara City Hospital (Date: 09/12/2020, No: E1-20-854).

REFERENCES


Factors Affecting the Nutritional Habits of Cerebral Palsy Patients

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Abstract

Background: Cerebral palsy (CP) is a motor control and postural disorder. Feeding problems in children with CP increase the risk of morbidity and mortality by leading to malnutrition and growth retardation. In this study, we aimed to investigate the factors affecting the dietary habits of patients with CP.

Methods: Patients with CP who participated in the rehabilitation program in Medipol University Department of Physical Medicine and Rehabilitation were included in the study. The dietary habits of the patients were evaluated and biceps, triceps, and subscapular skin thickness, mid-upper arm circumference was measured. Beck depression inventory (BDI) was filled in by all mothers. The study included 29 patients with CP (16 males and 13 females with a mean age of 3.9 ± 3.1).

Results: No correlations were found between biceps, triceps and subscapular skin thickness, mid-upper arm circumference, maternal depression level, and eating habits. There were statistically significant correlations between the gross motor functional classification system (GMFCS) and saliva (r=0.396, p=0.008), reflux (r=0.142, p=0.046), constipation (r=0.361, p=0.044), gas presence (r=0.483, p=0.008), and mid-upper arm circumference (r=0.483, p=0.008).

Conclusion: These results indicate that nutritional problems increase as the level of functional disability increases.

Key words: Cerebral Palsy, Dietary, Skin Thickness, Nutritional Problems.

Cite this article as: Korkmaz MÇ, Ağırman M, Ay E. Factors affecting the nutritional habits of cerebral palsy patients. Arch Curr Med Res. 2021;2(2):93-97
INTRODUCTION

Cerebral palsy (CP), the result of a nonprogressive injury that develops in utero process, during birth process or during the first 3 years of life, is a motor control and postural disorder (1). The average incidence rate is reported to be 2–3 of 1,000 live births (2). In addition to motor control disorder, children with CP may experience mental health issues, epileptic seizures, and gastrointestinal illnesses; oromotor, sucking, chewing, dental, drooling, vision, hearing, and genitourinary problems can also accompany the disease (3). Feeding problems in children with CP increase the risk of morbidity and mortality by leading to malnutrition and growth retardation (4).

Although the expected lifetime of CP patients varies according to the child’s functional level, the most important determinants are mobility and nutrition (5). Other health problems resulting from nutritional difficulties include malnutrition, esophagitis, recurrent chest infections and progressive lung disease. Most children with CP at risk for these problems are spastic quadriplegic and dystonic (6). Stallings et al. reported that the development of children with diplegic or hemiplegic CP is directly related to their nutritional status and recommended that they be followed periodically (7).

Another study conducted with children who have spastic quadriplegic CP demonstrated that developmental criteria correlated significantly with nutritional levels (8). The diagnosis of nutritional disorders as well as specific treatment, prevention of malnutrition, and complications related to nutritional problems are very important. In this study, we aimed to investigate the factors affecting the dietary habits of patients with CP.

MATERIALS AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the Istanbul Medipol University Non-Interventional Ethics Committee (Date: 14.02.2018; Decision Number: 115).

Patients with CP who participated in the rehabilitation program in Medipol University Department of Physical Medicine and Rehabilitation were included in the study. The parents of all participants were informed about the purpose of the study and the procedures and informed consents were obtained. The demographic data of participants were recorded in patient follow-up forms. Body weights and heights were measured, and the patients were questioned regarding their diet and the number of meals consumed per day.

Issues such as loss of appetite, nausea, vomiting, diarrhea, difficulty in chewing, recurrent pneumonia, prolonged feeding times; mouth sores, excess saliva, and gas complaints were addressed. Biceps, triceps, and subscapular skinfold thicknesses were measured with a caliper. The patient’s elbow was flexed at 90° in the triceps skinfold thickness measurement, and the midpoint between the acromion and olecranon protrusions was marked. After the marked location was held with thumb and index finger, the measurement was completed with a caliper. The biceps skinfold thickness was measured from the anterior side of the arm to the acromion bone border and from the midline of the antecubital fossa. For the measurement of subscapular skinfold thickness, a mark was placed at the inferior corner of the scapula, and a measurement was made to the body at an angle of about 45°. For the measurement of the subscapular skinfold thickness, a mark was placed at the inferior corner of the scapula, and a measurement was made to the body at an angle of about 45°. To measure the mid-upper arm circumference, the patient’s elbow was flexed to 90°, and the midpoint between the acromial overhang and the olecranon projection was marked and measured with a tape measure. The Gross Motor Functional Classification System (GMFCS) was used to determine the level of gross motor function. The five-level GMFCS is a functionality-based system developed to standardize the assessment of the gross motor function of children with CP (Table 1). At level 1, the patient can be mobilized inside and outside the home without the help of an auxiliary device; at level 5, mobilization is severely restricted even if using an auxiliary device. The Beck Depression Inventory (BDI) was completed by the mothers of all the participants. Developed by Beck et al. (1978), the BDI comprises 21 items. The depression score is assumed to increase as the level of depression increases (9).

Table 1. Gross motor function classification system (GMFCS) general headings for each level

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Walks without Limitations</td>
</tr>
<tr>
<td>2</td>
<td>Walks with Limitations</td>
</tr>
<tr>
<td>3</td>
<td>Walks Using a Hand-Held Mobility Device</td>
</tr>
<tr>
<td>4</td>
<td>Self-Mobility with Limitations; May Use Powered Mobility</td>
</tr>
<tr>
<td>5</td>
<td>Transported in a Manual Wheelchair</td>
</tr>
</tbody>
</table>
Statistical Analysis

Descriptive values were made using the average, standard deviation, and percentage (%) rates using IBM SPSS 21 (IBM Corp., Armonk, NY, USA). Relations were assessed by Spearman’s correlation analysis. P < 0.05 was considered statistically significant.

RESULTS

The study included 29 patients with CP (16 males and 13 females with a mean age of 3.9 ± 3.1). Of the 29 patients, 14 had quadriplegic CP, 7 had diplegic CP, and 8 had hemiplegic CP (Table 2). The patients’ GMFCS scores reflected the following percentages: 17.2% at level 1, 10.31% at level 2, 27.6% at level 3, 20.7% at level 4, and 24.1% at level 5. In addition, 86.2% of the patients were using at least one orthosis. Based on their eating habits, 69% of the participants had a good appetite, and 31% had a poor appetite. The patients’ numbers of meals per day were as follows: 13.8% had three or fewer meals, 72.4% had three to six meals, and 13.8% had more than six meals.

Table 2. Demographic and clinical characteristic of patient

<table>
<thead>
<tr>
<th>Demographic and Clinical characteristic of Patient</th>
<th>n: 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/ Female</td>
<td>16/13</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>3.9 ± 3.1</td>
</tr>
<tr>
<td>Quadriplegic cerebral palsy</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>Diplegic cerebral palsy</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Hemiplegic cerebral palsy</td>
<td>8 (28%)</td>
</tr>
</tbody>
</table>

Moreover, 13.8% of the patients experienced nausea, 17.2% experienced frequent vomiting, 6.9% experienced reflux, 20.7% had gas, 37.9% had constipation, and 34.5% had saliva problems (Table 3). At the time of the study, 31% of the patients were receiving supplemental vitamins. No correlations were found between biceps, triceps, and subscapular skin thickness, mid-upper arm circumference, maternal depression level, and eating habits. There were statistically significant correlations between GMFCS and saliva (r=0.396, p=0.008), reflux (r=0.142, p=0.046), constipation (r=0.361, p=0.044), gas presence (r=0.483, p=0.008), and mid-upper arm circumference (r= 0.483, p=0.008).

Table 3. Percentage of nutritional problems in 29 cerebral palsy patients

<table>
<thead>
<tr>
<th>Nutritional problem*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>37.9%</td>
</tr>
<tr>
<td>Saliva</td>
<td>34.5%</td>
</tr>
<tr>
<td>Gas</td>
<td>20.7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13.8%</td>
</tr>
<tr>
<td>Reflux</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

*More than one nutritional problem was detected in 9 patients.

DISCUSSION

In this study, nutritional problems were found in patients with CP and are listed in order of frequency as follows: constipation, saliva, gas, vomiting, nausea, and reflux. It was observed that these problems increased as the motor functional status worsened. Constipation is a common problem in patients with CP and is caused by impaired bowel motility, irregular muscle contractions, dysfunction of rectal sphincter control, inactivity, and inadequate fluid and fiber intake. In children with CP, the colonic transit time in the left colon and rectum has been shown prolonged. In one study, 74% of children with CP had chronic constipation (10). The present study found that constipation was the most common gastrointestinal problem (37.9%). Gastroesophageal reflux (GERD) is a common problem in children with CP. Spasticity of the intraabdominal muscles, increased intra-abdominal pressure due to constipation, extended periods in the supine position, and delayed gastric emptying due to impaired gastrointestinal function and motility may trigger reflux (11).

Chronic GERD can cause esophagitis, which may lead to loss of appetite as well as aspiration (12). Problems of development and coordination of the muscles around the mouth may cause drooling, difficulty in feeding, and speech problems (13). The risk of aspiration is high for children having CP with oropharynx, larynx, or tracheal motor coordination. Children with CP often develop silent aspiration, which is defined as the passage of food downstream of the vocal cords without clinical signs or symptoms (14). Due to motor impairment, most patients with CP are dependent on others for their nutritional activities.
In children with CP, problems such as prolonged feeding times, malnutrition, aspiration of excess saliva resulting in coughing and obstruction are frequently encountered. Nutritional difficulties, growth, and growth retardation due to these problems negatively affect the lives of both children and their families. A questionnaire administered to parents can be useful in terms of the screening, detection, and treatment of children at risk for malnutrition (15-16). Studies have shown that the parents of patients with CP find it stressful to attend to the nutritional needs of their children and that they spend significant amounts of time feeding their children during the day (15-17).

In our study, 13% of the participants required more than six meals per day. The time spent on nutrition, although exhausting for families, may not always lead to satisfactory results (17). In some families, the feeding times of children are shorter due to stress, and this can lead to malnutrition, which in turn may cause the children to experience developmental delays (16). In a study conducted in Turkey, depression and quality of life in mothers of healthy children and of those with CP having similar demographic characteristics were compared. In order to evaluate The Beck Depression Inventory (BDI) and the Nottingham Health Profile (NHP) were used. The NSP subgroup scores and BDI scores were significantly higher in the mothers of children with CP. In this study, no correlations were found between the GMFCS level, the BDI, and the NHP (18). Studies have found growth retardation in children with CP (19-20). In patients with CP, motor dysfunction may also be associated with oromotor dysfunction; thus, feeding is impaired (21).

Children with CP are at high risk of malnutrition. Acute and chronic malnutrition can be seen due to a limited calorie intake (16). In our study, we measured skinfold thickness with a skinfold caliper to evaluate the nutritional status of the participants. Skinfold measurements are used to determine subcutaneous and body fat levels. Triceps skinfold thickness is an important predictor of low-fat deposition and malnutrition in patients with CP (22).

Triceps skinfold measurements are used to evaluate short-term storage in total body fat stores, and subscapular skinfold measurements are used to show long-term energy deposits (7). A study by Sullivan et al. indicated that mid-upper arm circumference measurement was a good predictor of nutritional status (23).

In our study, we examined the relationship between the nutritional status of children with CP and maternal depression. We evaluated the biceps, triceps, subscapular skinfold thickness with a skinfold caliper and measured the mid-upper arm circumference. In our study, there were no correlations between biceps, triceps, subscapular skinfold thickness, mid-upper arm circumference measurement, mothers’ depression levels, and feeding habits of children with CP. This finding may be related to the number of patients included in the study or the lack of a significant relationship between these values, as the dietary habits and issues were not indicative of malnutrition. In a study examining the anthropometry and body composition of children with CP, serum leptin and protein values, mid-upper arm and hip circumferences, and subscapular skinfold thickness were measured. In patients with more severe motor loss, the fat content of skinfold thickness and serum ferritin levels were found to be lower than those with mild involvement (24). Similarly, in our study, there were statistically significant differences between the GMFCS levels of the patients and the mid-upper arm circumference.

In conclusion, nutritional problems are frequently encountered in patients with CP. Some of these problems are directly related to the level of functional disability. Children with CP should be evaluated in terms of nutrition and malnutrition. Based on our study findings, we suggest that increasing the patients’ functional gains with rehabilitation therapies will reduce their nutritional problems.

**Declarations**

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the İstanbul Medipol University Non-Interventional Ethics Committee (Date: 14.02.2018; Decision Number: 115).
REFERENCES


Investigation of the Effect of Pentoxifylline and Tocopherol on Osseous Healing Following Tooth Extraction in Bisphosphonate-Administered Rats

Ezgi Tuncay¹, Mustafa Öztürk², Ayşenur Nergiz Tanıdır³, Burcu Şengüven⁴, Özge Tuğçe Paşaoğlu⁵

Abstract

Background: The incidence of medication-related osteonecrosis of the jaw has increased with the widespread use of bisphosphonates. Present study aimed to evaluate the effect of pentoxifylline and/or tocopherol alone or in combination, on bisphosphonate-induced osteonecrosis in tooth extracted rat jaw.

Methods: 24 rats were randomly assigned to 4 groups and each animal received intraperitoneal zoledronic acid injection 0.06 mg/kg/week for 3 weeks. Following the zoledronic acid application, the lower right first molars of the rats were extracted on day 22. Starting from the day of tooth extraction animals received intraperitoneal pentoxifylline and/or tocopherol injections. Fourteen days later all rats were sacrificed. RANKL and osteoprotegerin (OPG) in blood were measured, and mandibles were examined histologically. When the inter-group differences were evaluated, the Kruskal Wallis-H Test and the Chi-square analysis were used.

Results: Each groups’ serum RANKL, OPG and RANKL/OPG levels did not reveal any statistically significant differences. There were no statistically significant differences in terms of bone necrosis, abscess formation, inflammation, osteoblastic/osteoclastic activity, bone cellularity and epithelial integrity.

Conclusions: Pentoxifylline and/or tocopherol injections alone or in combination did not have any statistically significant effect on the jaw following tooth extraction in bisphosphonate-induced rat animal model.

Key words: Bisphosphonates-Associated Osteonecrosis of the Jaw, Pentoxifylline, Tocopherol.

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INTRODUCTION

Bisphosphonates are a class of drugs that have been widely used since the end of the 20th century in the treatment of systemic diseases such as osteoporosis, Paget’s disease, multiple myeloma, cancers with bone metastases and hypercalcemia due to malignancy (1). The primary biological effect of all bisphosphonates occurs by inhibiting the bone resorption process through inhibitory activity on osteoclasts. Thus, bisphosphonates disrupt the mechanism of bone regeneration (2).

In the beginning, the side effects of these drugs were known to be acute phase responses, gastrointestinal and renal side effects. Another side effect of this drug was first reported by Marx in 2003, as osteonecrosis of the jaw (3). This condition was named “Medication-Related Osteonecrosis of the Jaw (MRONJ)” in 2014 according to the declaration issued by the Association of American Oral and Maxillofacial Surgeons (AAOMS) (2). AAOMS defines it as intraorally exposed bone, after treatment with anti-resorptive agents, persistent over a period of 8 weeks and no history of radiation therapy or metastases in the jaws (4).

The current treatment of MRONJ, reported by AAOMS, is based on eliminating or reducing the complaints of the patients. However, the expected results may not be obtained with this treatment protocol. Therefore, apart from the medical and/or surgical treatments of MRONJ, new methods and agents, which are thought to influence the bone and soft tissue healing in the positive direction, are being investigated (2, 5).

The aim of this study was to prove the preventive effect of pentoxifylline and tocopherol on bisphosphonate-related osteonecrosis following tooth extraction in bisphosphonate-administered rats.

MATERIALS and METHODS

Ethics Committee Approval and the Study Setting

This study was conducted in accordance with Gazi University Animal Experiments Local Ethics Committee Presidency Permission No. 66332047-604.01.02/139-17808, date: 05.08.2013.

The experimental phases of our study were carried out at the Gazi University Experimental Research Center and Animal Laboratory (GUERCAL), the biochemical evaluations were performed at GUERCAL, and the histopathological evaluations were performed at Gazi University Faculty of Dentistry, Department of Oral Pathology.

The Characteristics of the Experimental Animals Used in the Study and the Optimized Criteria

In our study, 24 Wistar female healthy albino rats (200-250g) were used, which were obtained from GUERCAL. During the study, the care for the animals was provided at GUERCAL. Maintenance care for all animals was given in the same room by placing 6 rats in each cage. The rats were kept in a room with a 12-hour light and dark cycle, at 21-24°C, and 40-45% humidity. During the study, the rats were fed with standard dry pellet diet and water.

Zoledronic acid (ZA) 4 mg/5ml intravenous (IV) infusion (Novartis Pharma AG, Switzerland), which is one of the nitrogen-containing bisphosphonate group of drugs, was used to create animal models with MRONJ in the study.

Surgical Protocol

All rats in the study received an intraperitoneal injection of ZA at 0.06 mg/kg per week for 3 weeks. On the 22nd day, mandibular right first molar tooth extraction was performed using the Bien Elevator (Medisporex CE 7811, Sialkot) and Deciduous Tooth Bayonet (Jensen JP-1 JDK111 CE, North Haven) in each of the subjects that had been prepared for surgery, by the same physician.

Study Groups

Following the teeth extraction, 24 rats were randomly divided into four groups, with six rats in each group. The subgroups and the distribution of the type of injections and the doses after the extraction were as follows (Table 1):
Table 1. Grouping of experimental animals

<table>
<thead>
<tr>
<th>Group</th>
<th>Bisphosphonates application prior to tooth extraction</th>
<th>The applicable agent after tooth extraction</th>
<th>Rat numbers in the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Intraperitoneal Zoledronic Acid</td>
<td>Intraperitoneal Saline Solution</td>
<td>6</td>
</tr>
<tr>
<td>Group B</td>
<td>Intraperitoneal Zoledronic Acid</td>
<td>Intraperitoneal Alpha-Tocopherol</td>
<td>6</td>
</tr>
<tr>
<td>Group C</td>
<td>Intraperitoneal Zoledronic Acid</td>
<td>Intraperitoneal Pentoxifylline</td>
<td>6</td>
</tr>
<tr>
<td>Group D</td>
<td>Intraperitoneal Zoledronic Acid</td>
<td>Intraperitoneal Pentoxifylline and Alpha-Tocopherol</td>
<td>6</td>
</tr>
</tbody>
</table>

Group A (Control Group): The rats in this group received daily intraperitoneal injections of isotonic NaCl solution.

Group B (Tocopherol Group): The rats in this group received daily intraperitoneal injections of 20 mg/kg/day of tocopherol (300 mg intramuscular ampule; Aksu Pharmaceutical, Turkey) for 14 days.

Group C (Pentoxifylline Group): The rats in this group received daily intraperitoneal injections of 50 mg/kg/day of pentoxifylline (100 mg/5 ml IV ampule; Berksam Pharmaceutical Trade. Inc., Turkey) for 14 days.

Group D (Tocopherol and Pentoxifylline Group): The rats in this group received daily intraperitoneal injections of 50 mg/kg/day of pentoxifylline and 20 mg/kg/day of tocopherol for 14 days.

**Blood Sample Collection and Sacrification**

The euthanasia procedure was performed on the 36th day when the experiment had been completed.

The blood samples were evaluated biochemically. A 3 ml sample of blood was collected in a sterile glass tube with clot activator, and without waiting, it was centrifuged at 3000 rpm for 10 minutes (Selecta Centronic-BL, J.P. SELECTA S.A., Barcelona). After centrifugation, the plasma portion was moved into 1.5 ml eppendorf tube to be evaluated with the ELISA kit (Rat OPG-RANKL Eliza Kit, Elabscience Biotechnology Co. Ltd., Japan).

After euthanasia, mandibular bone blocks where the tooth extraction was performed were removed for the extraction sockets to be examined histopathologically. The obtained bone blocks were kept in biopsy containers filled with 10% formaldehyde (Figure 1).

**Biochemical Method**

Cell-free plasma was obtained separately from all subjects. The parameters were studied as suggested by the manufacturer with ELISA kits (Rat OPG-RANKL Eliza Kit, Elabscience Biotechnology Co. Ltd., Japan).

**Histopathological Method**

The samples obtained after sacrifice were fixed for 24-72 hours in 10% buffered formalin solution. Subsequently,
decalcification in 10% formic acid was provided. Sagittal plane section samples of 4-5 µm thickness were obtained from the tissues for routine hematoxylin-eosin staining to the adhesive slides (Surgipath, X-tra Adhesive Microslides, Illinois, USA). The sections were evaluated under the light microscope Leica DM 4000 B (Leica Microsystems GmbH. Wetzlar, Germany).

Presence of necrotic bone, bone cellularity, osteoblastic/osteoclastic activity, microorganism presence, presence of abscess and the density of inflammatory cell infiltration were evaluated in the hematoxylin-eosin stained sections from the mandibular bone blocks (Figure 2).

Figure 2. Histological sections of extracted sockets are shown for each group with each groups letter (Hematoxylin-eosin, x200)

The inflammatory cells were counted in the defect (also healing) field in the hematoxylin-eosin sections. The inflammation density was scored with a four-graded system reported by Hirshberg et al (6).

Statistical Analysis

The data obtained in this study were analyzed using the SPSS 20 software package.

The Shapiro Wilk's test was used in the case of normal distribution of the variables, due to the number of units. The significance level was accepted as 0.05 when the results were interpreted (When $p<0.05$, the variables were considered not to have come from normal distribution, and when $p>0.05$, the variables were considered to have come from normal distribution).

When the inter-group differences were evaluated, the Kruskal Wallis-H Test was used in the case of variables not coming from normal distribution. The Chi-square analysis was used to evaluate the relationship of the nominal variables between the groups. The results were interpreted as 0.05 being accepted as the significance level.

RESULTS

Biochemical Results

The blood samples from the control and experimental groups were analysed using an ELISA kit; and RANKL, OPG and RANKL/OPG values were measured. (Table 2, Figure 3).

Table 2. Absolute RANKL, OPG and RANKL/OPG serum levels of each rat in each group is provided with in the table

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal Number</th>
<th>RANKL (pg/ml)</th>
<th>OPG (pg/ml)</th>
<th>RANKL/OPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>1</td>
<td>9.61</td>
<td>19.76</td>
<td>0.49</td>
</tr>
<tr>
<td>Group A</td>
<td>2</td>
<td>11.01</td>
<td>18.57</td>
<td>0.59</td>
</tr>
<tr>
<td>Group A</td>
<td>3</td>
<td>3.74</td>
<td>27.14</td>
<td>0.14</td>
</tr>
<tr>
<td>Group A</td>
<td>4</td>
<td>8.66</td>
<td>16.67</td>
<td>0.52</td>
</tr>
<tr>
<td>Group A</td>
<td>5</td>
<td>10.00</td>
<td>14.29</td>
<td>0.7</td>
</tr>
<tr>
<td>Group A</td>
<td>6</td>
<td>9.05</td>
<td>17.14</td>
<td>0.53</td>
</tr>
<tr>
<td>Group B</td>
<td>7</td>
<td>6.26</td>
<td>16.67</td>
<td>0.38</td>
</tr>
<tr>
<td>Group B</td>
<td>8</td>
<td>5.70</td>
<td>15.24</td>
<td>0.37</td>
</tr>
<tr>
<td>Group B</td>
<td>9</td>
<td>4.64</td>
<td>24.76</td>
<td>0.19</td>
</tr>
<tr>
<td>Group B</td>
<td>10</td>
<td>3.52</td>
<td>19.05</td>
<td>0.18</td>
</tr>
<tr>
<td>Group B</td>
<td>11</td>
<td>3.91</td>
<td>15.48</td>
<td>0.25</td>
</tr>
<tr>
<td>Group B</td>
<td>12</td>
<td>4.36</td>
<td>15.71</td>
<td>0.28</td>
</tr>
<tr>
<td>Group C</td>
<td>13</td>
<td>5.81</td>
<td>55.48</td>
<td>0.1</td>
</tr>
<tr>
<td>Group C</td>
<td>14</td>
<td>4.36</td>
<td>18.33</td>
<td>0.24</td>
</tr>
<tr>
<td>Group C</td>
<td>15</td>
<td>4.25</td>
<td>17.14</td>
<td>0.25</td>
</tr>
<tr>
<td>Group C</td>
<td>16</td>
<td>4.36</td>
<td>16.43</td>
<td>0.27</td>
</tr>
<tr>
<td>Group C</td>
<td>17</td>
<td>3.74</td>
<td>17.62</td>
<td>0.21</td>
</tr>
<tr>
<td>Group C</td>
<td>18</td>
<td>3.63</td>
<td>15.24</td>
<td>0.24</td>
</tr>
<tr>
<td>Group D</td>
<td>19</td>
<td>14.62</td>
<td>15.48</td>
<td>0.96</td>
</tr>
<tr>
<td>Group D</td>
<td>20</td>
<td>7.71</td>
<td>16.43</td>
<td>0.47</td>
</tr>
<tr>
<td>Group D</td>
<td>21</td>
<td>3.58</td>
<td>15.24</td>
<td>0.23</td>
</tr>
<tr>
<td>Group D</td>
<td>22</td>
<td>13.85</td>
<td>25.24</td>
<td>0.55</td>
</tr>
<tr>
<td>Group D</td>
<td>23</td>
<td>4.53</td>
<td>21.67</td>
<td>0.21</td>
</tr>
<tr>
<td>Group D</td>
<td>24</td>
<td>4.30</td>
<td>22.14</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Histological Results

In all rats, in order to assess the healing process of the tooth extraction socket on the 14th day, eight variables such as necrotic bone presence, necrotic bone/total bone ratio, presence of abscess, level of inflammation, epithelial integrity, bone cellularity, and the presence or absence of osteoclastic and osteoblastic activity were evaluated. (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
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In the defect field, hypercellular woven-trabecular new bone trabeculae accompanied by connective tissue composed of cell-rich active-swollen fibroblasts anastomosing with each other, with prominent osteoblastic columns were observed. Osteoclastic activity was observed in only one sample (Table 3).

Necrotic bone trabeculae were often observed in the superficial part of the defect field. It was observed that, generally, these constituted a very small part of the defect field.

Inflammation was not prominent in most of the samples. Only a few samples revealed intense abscess formation with acute inflammatory cell infiltration rich in neutrophils (Table 3). In general, mononuclear inflammatory cell infiltration, which can be considered within the normal range, was noticed in the samples.

No evidence of foreign body reaction was observed in the samples.

No significant difference was observed between the groups in terms of the amount of bone filling/bone quality, intensity of the inflammation or necrotic bone density. In one single rat (D6), a large area of bone necrosis between the trabeculae was observed. This image resembled a real bisphosphonate-related osteonecrosis.

**Statistical Results**

No statistically significant difference was determined in the histopathological (necrotic bone presence, bone cellularity, osteoclastic-osteoblastic activity, inflammation, abscess presence and necrotic bone/total bone percentage) and biochemical evaluation (RANKL, OPG, RANKL/OPG values).

**DISCUSSION**

In recent years, an increase in the number of patients diagnosed with MRONJ, which is related to the use of bisphosphonates has been observed in the public. The presence of MRONJ significantly affects the patient's quality of life. However, there is no certain standard therapy for MRONJ or a specific protocol to reduce the development of MRONJ in the literature (7). Hence, the pathophysiology and the treatment of MRONJ should be clearly understood (8). Many studies have been conducted for the treatment of MRONJ in recent years (9), #3. In our study, we aimed to evaluate whether substances, we believe to reduce the risk of MRONJ, have any effect on bone healing in an experimental MRONJ model histopathologically and biochemically. To date, there are a few controlled studies conducted in this field with this subject.

In many experimental animal studies with experimental MRONJ models, rats were generally the preferred animals. ZA is one of the most potent amino bisphosphonates used intravenously, which is frequently associated with development of osteonecrosis. Therefore, the risk of MRONJ is higher in patients using ZA and it is one of the most commonly used bisphosphonates in experimental MRONJ studies (8, 10). In various studies using MRONJ models, ZA was administered to rats in doses of 0.25mg/kg subcutaneously, 0.04mg/kg IV and 0.02 mg/kg IV (11, 12). Since there was no precise dose protocol for ZA in rats and it would be inappropriate to apply higher doses of ZA to animal subjects compared to humans, because the drug has a cumulative effect. ZA application protocol for human patients is 4 mg/mL of ZA (IV) per month for a 70 kg person. Dose adjustments for rats were made according to human doses and it was decided that the drug be administered intraperitoneally instead of IV.

In many studies conducted to form an experimental MRONJ model, to increase the possibility of MRONJ formation, tooth extraction is the preferred surgical procedure. In Marx et al.’s study, it was reported that in 119 MRONJ patients, 68% was in the mandible, 28% in the maxilla and 4% in both jaws (13). In this study, because the study conditions were suitable and in parallel to the above-mentioned studies, right mandibular 1st molar tooth of all rats were extracted to increase the rate of MRONJ formation.

In Takami et al.’s study, it was reported that phosphodiesterase inhibitors such as pentoxifylline prevent the intracellular cAMP breakdown. They induce osteoclast formation in the mouse bone marrow, stimulate calvarial osteoblasts and trigger the secretion of RANKL and OPG cytokines in calvarial osteoblasts (14). In a study by Horiuchi et al., where the effects of parathyroid hormone and pentoxifylline on new bone formation was assessed, it was found that pentoxifylline increases new bone formation by increasing the BMP-2 (15). In another study conducted by Aydin et al. with a fracture model in rats, it was reported that 50mg/kg/day of pentoxifylline accelerated fracture healing in the
early healing period (16). There are antioxidant defense mechanisms in cells and the extracellular fluid that try to defuse the cytotoxic oxygen radicals. In humans, one of the substances that help prevent the damage of oxidants on the cell membrane is tocopherol, which is a type of vitamin E that has antioxidant property (17). In a study by Turk et al., a fracture model was formed in rats and 20mg/kg/day tocopherol was administered intraperitoneally to the study group. The fracture healing in rats, which were sacrificed on the 60th day, was evaluated, and the healing of the fractures in the study group were observed to be significantly better. Therefore, tocopherol was reported to have benefits in the early and late bone healing processes in clinical cases (18). Today, pentoxifylline is used with tocopherol in the treatment of osteoradionecrosis. These two drugs show a potent antifibrotic effect together. Studies have reported that the combination of pentoxifylline and tocopherol significantly decreases the chronic damage caused by radiotherapy (19). Epstein et al. published a case series of jaw osteonecrosis in six patients, due to use of ZA, ibandronic acid and alendronate. To treat these patients, in addition to antimicrobial therapy, oral 400 mg/day pentoxifylline and 400 mg/day tocopherol were prescribed. At the end of a 10-month follow-up, it was reported that the exposed bone surfaces shrank by 76% and all of the patients’ complaints decreased (19). In a case report published by Magremanne et al., a jaw necrosis due to bisphosphonate use at stage 3 in the left lower jaw was detected. In addition to antimicrobial treatment, the patient was prescribed 400 mg pentoxifylline and 500mg tocopherol twice a day. After about 12 months, it was reported that the patient’s complaints of paresthesia and pain had disappeared and the mucosal healing was completed (20). Studies on osteoradionecrosis and treatment of MRONJ in the literature have demonstrated that pentoxifylline and/or tocopherol may be useful in the treatment of jaw necrosis due to drugs. Considering the data obtained in previous studies on the subject, the present study evaluated the preventive effect of pentoxifylline and/or tocopherol on MRONJ formation.

New proteins, named RANKL, RANK and OPG, which have been defined in recent years, were presented as a series of cytokines connected to the TNF family, which is responsible for bone formation (21). RANKL and OPG are the major regulators of the molecular mechanism in osteoclast development and function. Both parameters may be used as genetic, immunohistochemical and serum indicators in in-vivo and in-vitro studies related to bisphosphonates (22). In this study, serum RANKL, OPG and RANKL/OPG values were used for biochemical evaluation to assess the systemic effects of pentoxifylline and tocopherol on bone metabolism.

Sonis et al. reported in their study that at the end of the surgical procedure following subcutaneous 0.075 mg/kg ZA administration on rats, 60% of the rats developed jaw necrosis. Biet al. found no jaw necrosis after tooth extraction following intraperitoneal 0.125 mg/kg ZA administration (11). Huja et al. administered 0.1 mg/kg ZA per week for 9 weeks and no surgical procedure was performed. Although the specified ZA dose was much higher than the dose used in humans, no osteonecrosis was observed in the mice in the experiment group (23). Recreo et al. performed upper jaw 3rd molar tooth extraction in the experiment group following 0.1 mg/kg ZA administration 3 times a week for 9 weeks intraperitoneally. Osteonecrosis occurred in the extraction field in the experiment group, while in the group without tooth extraction, no osteonecrosis was reported (11). Considering the previous studies, the ZA dose, duration of use, injection type, and the presence of surgical procedure were all observed to affect the risk of MRONJ formation. In some studies in which high dose of ZA was administered, no osteonecrosis formation was observed; whereas in our study and in the similar studies mentioned above, osteonecrosis was observed even with low doses.

Although statistically insignificant, the histological findings in the osteonecrosis models formed in previous studies revealed similar results with our study. The necrotic bone trabeculae with empty lacunae containing no osteocytes were mostly observed in areas close to the surface of the defect. In the pentoxifylline study groups, lower rates of abscess formation and inflammation were determined. Therefore, we believe that application of pentoxifylline reduces the formation of these findings and reduces the risk of osteonecrosis.

RANKL and OPG play a major role in regulating the maturation and differentiation of osteoclasts (24). Bisphosphonates particularly affect the osteoclasts; therefore, they affect the RANKL-RANK-OPG metabolism. Thus, clarification of the effect of RANKL and OPG release on MRONJ development and the definition of the agents that increase or decrease the release of these two factors are very important for MRONJ and for other studies about MRONJ treatment. Mercatali et al. assessed the RANK,
RANKL and OPG values of 49 follow-up cancer patients who used IV ZA for 12 months. At the end of 12 months, the mean RANKL value decreased by 22%, the mean OPG value increased by 96%, and the RANKL/OPG ratio decreased by 56%. ZA is believed to affect the RANKL, RANK and OPG release due to its osteoclastic activity reducing effect (25). In our study, no significant difference was found between the groups in terms of serum RANKL, OPG, RANKL/OPG values (p>0.05 Kruskal-Wallis H Test). Considering the inhibitory effect of bisphosphonate use on RANKL release, the lower RANKL values obtained in groups B, C and D compared to group A resulted in the opinion that pentoxifylline and/or tocopherol injection reduces RANKL expression or has no effect on its stimulation. The lower RANKL values in the study groups resulted in the opinion that osteoclast activation, differentiation and apoptosis are lower, and thus, bone resorption is higher in the control group. In addition, considering the increasing effect of bisphosphonate use on OPG release, it is believed that with the lower OPG values found in groups B and C compared to group D may be caused by pentoxifylline and/or tocopherol application, which may have decreased the effect of bisphosphonates on OPG values and risk of MRONJ formation. Bisphosphonate application is known to decrease the RANKL/OPG ratio. Thus, the RANKL/OPG ratios of group B, C and D being less than group A, led to the conclusion that pentoxifylline and/or tocopherol injection has no effect on increasing the total bone mass.

Although there are studies in recent years associated with the effects of bisphosphonate use on RANKL and OPG release, there are no studies evaluating the effects of agents or surgical procedures that may have possible benefits on MRONJ treatment and RANKL and OPG values. Therefore, our study is the first in the literature about this topic.

Given these results, even with the low dose of ZA applied to rats intraperitoneally, with the human ZA dose taken as reference, osteonecrosis fields histologically compatible with MRONJ were detected. Furthermore, although application of pentoxifylline and/or tocopherol in the model of MRONJ formation risk, compared with the control group, statistically made no difference at all, when we analyzed the histopathological and biochemical data we observed differences between the groups. In particular, pentoxifylline and/or tocopherol injections were observed to positively affect the OPG. The limiting factors of this study were as follows: when the model was created for MRONJ formation in the study groups, only one bisphosphonate type and dose was selected, and only a given single dose option for pentoxifylline and/or tocopherol administration was used. All animals were sacrificed at the same time so the bone healing parameters in different time periods could not be evaluated. In order to further assess the information on preventive and/or therapeutic effects of pentoxifylline and/or tocopherol in MRONJ; more extensive experimental and clinical trials are needed with the mentioned limitations overcome. Also, new bone formation should be assessed with 3-dimensional radiographic methods, as well as histopathological and histomorphometric evaluation.

Declarations
This research was supported by Scientific Research Projects of Gazi University with project number 03/2014-02. There is no conflict of interest.
This study was conducted in accordance with Gazi University Animal Experiments Local Ethics Committee Presidency Permission No. 6632047-604.01.02/139-17808, date: 05.08.2013.

REFERENCES


The Influence of Body Mass Index on Lower Extremity Vein Diameters at Different Levels in Healthy Population

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Abstract

Background: To investigate changes in the size of the deep and superficial venous systems associated with body mass index (BMI), gender, age, in patients without venous insufficiency including the effects of posture.

Methods: Healthy individuals who had no previous diagnosis of venous insufficiency were evaluated with an ultrasound device with a duplex option. The left and right deep and superficial venous systems were scanned both supine and upright positions by the same two radiologists. All clinical findings, BMI and age were recorded for each subject.

Results: Two-hundred ninety-eight patients were included in the study. The patients' mean age and BMI were 49.94 ±13.19 years (range 19-76), BMI was 24.91±4.0 kg/m² (range 18-38) respectively. The difference between upright and supine positions vein diameters were statistically significant (p<0.01). There were no significant differences between overweight and normal participants in terms of femoral and saphenous vein diameters (p>0.05). The proximal diameter of the great saphenous vein was significantly lower in overweight patients (Table 2). When the patients were analyzed according to BMIs the right femoral vein diameters, the diameters of proximal part and distal two parts of the right great saphenous vein, and left proximal small saphenous vein diameters were significantly higher in patients whose BMI values were between 35-39.99 (obese-class II) (p<0.001).

Conclusions: In conclusion we found both lower limbs’ vein diameters were significantly larger in upright position either superficial and deep systems, however the relationship between age and BMI was not significant. Further longitudinal studies are needed to clarify the influence of anatomic variances in subjects with obese healthy veins.

Key words: Chronic Venous Disease, Risk Factors, Age, Obesity, Lower Extremity, Vein Diameter.

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INTRODUCTION

Chronic venous disease (CVD) is one of the most common disorders in many countries. The etiology is probably multifactorial. Obesity has been suggested as one of the risk factors for CVD, or an aggravating factor rather than the primary cause of CVD (1, 2).

Obesity can significantly affect the development of metabolic syndrome with a cluster of cardiovascular risk factors (3). It is thought to predispose individuals to venous stasis, which is a trigger of both deep vein thrombosis and CVI (4, 5).

The venous system of the lower extremity is anatomically divided into a deep and superficial system, but functionally it is accepted as one unit. Both systems communicate with each other by means of perforating veins and through the confluence of the great and small saphenous vein (6). Determination of the physiological adaptations of vein size and volume increase associated with the standing position has been insufficiently described. The details of the anatomy of the venous system are particularly relevant and have recently become even more significant because of the surgical interest in this vein as an approach to each in situ bypass procedure; hence, accurate knowledge of this system has provided a major advance in the simplification of such procedure (7).

In this study, we aimed to investigate changes in the size of the deep and superficial venous systems associated with body mass index (BMI), gender, age, in patients without venous insufficiency including the effects of posture.

MATERIALS AND METHODS

The study protocol was approved by the Acıbadem University, Ethics Committee (Date: 26.07.2018, No: 2018-11/9). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who were employed at the hospital gave informed consent to the study protocol. Healthy individuals who had no previous diagnosis of venous insufficiency were included in our study. While the patients were being evaluated, they were questioned whether they had any complaints in the lower limb or not. Complaints such as pain, numbness, itchiness, heaviness, burning and cramps were recorded. Measurements were done in the mid-day (9:30-15:00). The left and right deep and superficial venous systems were scanned both in supine and upright position by the same two radiologists. All clinical complaints, body mass index (BMI) and age were recorded for each subject. BMI was calculated as the patient’s weight (kg) /height (m²). Classifications for BMI were used according to the NIH and the World Health Organization (WHO) for White, Hispanic, and Black individuals. BMIs were classified as: severely underweight - BMI less than 16.5 kg/m², underweight - BMI under 18.5 kg/m², normal-weight - BMI greater than or equal to 18.5 to 24.9 kg/m², overweight – BMI greater than or equal to 25 to 29.9 kg/m², obesity – BMI greater than or equal to 30 kg/m², obesity class I – BMI 30 to 34.9 kg/m² , obesity class II – BMI 35 to 39.9 kg/m², obesity class III – BMI greater than or equal to 40 kg/m² also referred to as severe, extreme, or massive obesity (8, 9).

The patients with symptoms on the right or left sides were excluded and the participants with symptoms in both lower extremities were enrolled in the study.

The superficial system, great saphenous vein was evaluated as a) sapheno-femoral junction (SFJ) distal to terminal valve (2 cm), b) mid-thigh c) knee level d) midleg (below medial trochanter 10 cm), e) 1 cm proximal to medial malleolus. Small saphenous vein was evaluated as 1) sapheno-popliteal junction 1 cm distal 2) mid leg 3) 1 cm proximal to medial malleolus. Deep venous system was measured as (a) femoral vein (FV) proximal to the orifice of the great saphenous vein (b) the proximal section of the FV about 1–2 cm distal to the orifice of the deep FV and (c) the distal section of the FV about 20 cm distal to the orifice of the deep FV were used for scanning (7).

The ultrasound machine (Loqic S8, GE, NewYork, USA) with a 38 mm linear transducer (6–13 MHz) and the duplex option was used. The mean diameter for each measuring position was calculated by assessing both minimum and maximum diameter (cross measurement) with B-mode sonography. Besides their estimated anatomical location, veins were identified by being compressed by brief transducer pressure and through differentiation with color duplex sonography. The diagnosis of reflux was based on the detection of reverse flow induced by Valsalva’s maneuver of the ½ proximal limb and by augmentation maneuver of the ½ distal lower extremity. Reflux longer than 0.5 s for the great saphenous vein and longer than 1 second for the femoral vein was considered as insufficiency. Eighteen patients were excluded because of pathological reflux. Intraobserver variation was tested under same conditions for five subjects. Interobserver variation was tested for six subjects by re-measuring the FVD in raw digital ultrasound images) with the analyze-tool image processing program.
Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of variables. The suitability of univariate data to normal distribution was evaluated by Kolmogorov-Smirnov test and Shapiro-Wilk Francia test. Mann-Whitney U test was used with Monte Carlo simulation technique in comparing two independent groups to quantitative data. For the comparison of duplicate measurements of dependent quantitative variables, Wilcoxon Signed Ranks Test was used with Monte Carlo simulation. Kendall's tau-b test was used to examine the correlations of variables with each other. Quantitative variables are mean ± SD in tables. (standard deviation), Median (Percentile 25% / Percentile 75%) and Median (Minimum / Maximum), while categorical variables were shown as n (%). Variables were examined at a 95% confidence level, and a p value of less than 0.05 was considered significant.

RESULTS

Two-hundred ninety-eight patients (173 female, 125 male) were included into the study. The patients mean age was 40.94 ±13.19 years (range 19-76). The mean height and weight of the patients were 167.41± 9.16 cm and 70.04 ± 13.24 kg respectively. The mean BMI was 24.91±4.0 kg/m² (range 18-38). The median diameter of the middle position (proximal FV) distal to the orifice of the deep FV of right and left limbs measured 9 mm and 10 mm in supine position (range: 8-10 mm) and 13 mm (range 11-15) and 12 mm in upright position respectively. A mean diameter increases of 33% for the right limb and 20% for the left limb in upright position. The distal level (distal FV) diameters of right and left limbs were 6 mm and 5.6 mm in supine position and 7 mm and 6.5 mm in upright position which means an increase of 16% and 18% respectively. The difference between upright and supine positions’ vein diameters were found statistically significant (p<0.01). Diameters of the femoral vein and the great saphenous vein of both lower limbs in the different levels of all studied subjects were summarized in Table 1.

Table 1. Both extremities comparison of the vein diameters at supine and upright position

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<td>Med (Q1 / Q3)</td>
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<td></td>
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<td>13 (11 / 15)</td>
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<td>Femoral Vein-2</td>
<td>7.5 (6.5 / 8.5)</td>
<td>10 (8.8 / 12)</td>
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<tr>
<td>Femoral Vein-3</td>
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<td>7 (6 / 9)</td>
<td>&lt;0.001</td>
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<td>5.7 (5.2 / 6.4)</td>
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<td>5.2 (4.8 / 6)</td>
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<td>12 (9.8 / 14)</td>
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<tr>
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<td>9 (7.5 / 11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Femoral Vein-3</td>
<td>5.6 (5 / 6.8)</td>
<td>6.5 (5.5 / 8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Great Saphenous Vein-1</td>
<td>5.1 (4.8 / 5.5)</td>
<td>5.2 (4.7 / 5.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Great Saphenous Vein-2</td>
<td>4.5 (4.3 / 4.9)</td>
<td>4.6 (4.2 / 5)</td>
<td>0.031</td>
</tr>
<tr>
<td>Great Saphenous Vein-3</td>
<td>4.1 (3.7 / 4.4)</td>
<td>4.1 (3.6 / 4.5)</td>
<td>0.145</td>
</tr>
<tr>
<td>Great Saphenous Vein-4</td>
<td>3.5 (3.2 / 3.8)</td>
<td>3.55 (3 / 4)</td>
<td>0.479</td>
</tr>
<tr>
<td>Great Saphenous Vein-5</td>
<td>2.8 (2.6 / 3.2)</td>
<td>3 (2.5 / 3.5)</td>
<td>0.446</td>
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<td>Small Saphenous Vein-1</td>
<td>3.4 (3 / 3.8)</td>
<td>3.42 (3.3 / 3.6)</td>
<td>0.018</td>
</tr>
<tr>
<td>Small Saphenous Vein-2</td>
<td>2.8 (2.3 / 3.2)</td>
<td>2.9 (2.7 / 3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small Saphenous Vein-3</td>
<td>2.1 (1.7 / 2.6)</td>
<td>2.2 (2.2 / 2.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Wilcoxon Signed Ranks Test (Monte Carlo), Med.: Median, Q1: Percentile 25%, Q3: Percentile 75%
There were no significant differences between overweight and normal participants in terms of femoral vein diameters at supine position (p>0.05). The proximal diameter of the great saphenous vein was significantly lower in overweight patients (Table 2). When the patients were analyzed according to BMI levels, the right femoral vein diameters, the diameters of proximal level and distal two level of the right great saphenous vein and left proximal small saphenous vein diameters were significantly higher in patients whose BMI values were between 35-39.99 (obese-class II) (p<0.001) (Table 3).

Table 2. The comparison of vein diameters and complaints at upright position

<table>
<thead>
<tr>
<th>Upright Position</th>
<th>Gender</th>
<th>Right Femoral Vein-1</th>
<th>Right Great Saphenous Vein-1</th>
<th>Right Small Saphenous Vein-1</th>
<th>Left Femoral Vein-1</th>
<th>Left Great Saphenous Vein-1</th>
<th>Left Small Saphenous Vein-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.370</td>
<td>5.6 (5.2 / 6.3)</td>
<td>4 (3.4 / 4.5)</td>
<td>5.2 (4.6 / 5.5)</td>
<td>3.4 (3.3 / 3.7)</td>
<td>12 (10.5 / 14)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.079</td>
<td>5.9 (5.3 / 6.4)</td>
<td>4.2 (3.5 / 4.5)</td>
<td>5 (4.8 / 5.5)</td>
<td>3.4 (3.3 / 3.6)</td>
<td>12 (9.6 / 14)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.154</td>
<td>0.295</td>
<td>0.566</td>
<td>0.292</td>
<td>0.328</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>12.5 (10 / 14)</td>
<td>5.6 (5.1 / 6.3)</td>
<td>4.3 (3.4 / 4.6)</td>
<td>5.5 (5 / 5.6)</td>
<td>3.4 (3.3 / 3.6)</td>
<td>11 (9.5 / 13)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>0.154</td>
<td>0.375</td>
<td>0.003</td>
<td>0.596</td>
<td>0.106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without pain</td>
<td>0.002</td>
<td>0.518</td>
<td>0.853</td>
<td>0.043</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with pain</td>
<td>0.089</td>
<td>0.147</td>
<td>0.222</td>
<td>0.455</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without heaviness</td>
<td>13 (12 / 15)</td>
<td>5.5 (5.2 / 6.3)</td>
<td>4 (3.3 / 4.5)</td>
<td>5.2 (4.6 / 5.5)</td>
<td>3.4 (3.3 / 3.6)</td>
<td>12 (9.4 / 13)</td>
<td></td>
</tr>
<tr>
<td>Patients with heaviness</td>
<td>0.078</td>
<td>0.236</td>
<td>0.020</td>
<td>0.262</td>
<td>0.358</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without burning</td>
<td>0.021</td>
<td>0.056</td>
<td>0.526</td>
<td>0.108</td>
<td>0.027</td>
<td>0.121</td>
<td></td>
</tr>
<tr>
<td>Patients with burning</td>
<td>0.024</td>
<td>0.078</td>
<td>0.236</td>
<td>0.020</td>
<td>0.262</td>
<td>0.541</td>
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</tr>
<tr>
<td>Patients without itchiness</td>
<td>13 (12 / 14)</td>
<td>5.7 (5.2 / 6.4)</td>
<td>4.1 (3.5 / 4.5)</td>
<td>5.2 (4.7 / 5.5)</td>
<td>3.4 (3.3 / 3.6)</td>
<td>12 (10.5 / 14)</td>
<td></td>
</tr>
<tr>
<td>Patients with itchiness</td>
<td>0.005</td>
<td>0.382</td>
<td>0.082</td>
<td>0.793</td>
<td>0.665</td>
<td>0.358</td>
<td></td>
</tr>
</tbody>
</table>

Mann Whitney u test (Monte Carlo), Med.: Median, Q1: Percentile 25%, Q3: Percentile 75%
Table 3. The comparison of vein diameters according to BMI

<table>
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<tr>
<th></th>
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<th></th>
<th></th>
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</tr>
</thead>
<tbody>
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<td>Femoral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein 1</td>
<td>13 (10 / 14)</td>
<td>13 (11 / 14)</td>
<td>13 (12 / 15)</td>
<td>15 (13 / 17)</td>
<td>17 (17 / 17)</td>
</tr>
<tr>
<td>Vein 2</td>
<td>10 (9 / 10)</td>
<td>10 (8 / 11)</td>
<td>10 (8 / 11)</td>
<td>13 (11 / 15)</td>
<td>15.5 (13 / 16)</td>
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<tr>
<td>Vein 3</td>
<td>7 (6 / 8)</td>
<td>7 (6 / 9)</td>
<td>7 (6 / 9)</td>
<td>12 (8 / 12)</td>
<td>12 (11 / 12)</td>
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<tr>
<td>Great Saphenous</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein 1</td>
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<td>5.65 (5.2 / 6.3)</td>
<td>5.7 (5.2 / 6.4)</td>
<td>6 (5.3 / 6.8)</td>
<td>7.5 (6.8 / 7.5)</td>
</tr>
<tr>
<td>Vein 2</td>
<td>5.2 (4.8 / 5.7)</td>
<td>5.15 (4.8 / 5.8)</td>
<td>5.2 (4.7 / 6)</td>
<td>5.5 (5 / 6)</td>
<td>5.6 (5.2 / 6.2)</td>
</tr>
<tr>
<td>Vein 3</td>
<td>4.6 (4.5 / 5.4)</td>
<td>4.8 (4.5 / 5.4)</td>
<td>4.8 (4.3 / 5.5)</td>
<td>4.5 (4.5 / 5.5)</td>
<td>5.5 (3.6 / 5.5)</td>
</tr>
<tr>
<td>Vein 4</td>
<td>4.4 (4 / 5)</td>
<td>4.25 (4 / 4.9)</td>
<td>4.3 (4 / 5.1)</td>
<td>4 (3.8 / 4.2)</td>
<td>3.5 (3 / 3.5)</td>
</tr>
<tr>
<td>Vein 5</td>
<td>4 (3.5 / 4.5)</td>
<td>3.8 (3.5 / 4.5)</td>
<td>4 (3.5 / 4.5)</td>
<td>3.5 (3.2 / 3.8)</td>
<td>3 (2.5 / 3)</td>
</tr>
<tr>
<td>Small Saphenous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein 1</td>
<td>3.8 (3.4 / 4.7)</td>
<td>4.2 (3.5 / 4.5)</td>
<td>3.9 (3.6 / 4.4)</td>
<td>4 (3.5 / 4.5)</td>
<td>4.5 (3.3 / 4.5)</td>
</tr>
<tr>
<td>Vein 2</td>
<td>2.9 (2.5 / 3.5)</td>
<td>3.2 (2.6 / 3.6)</td>
<td>3.1 (2.6 / 3.5)</td>
<td>3.6 (3 / 4)</td>
<td>4 (2.8 / 4)</td>
</tr>
<tr>
<td>Vein 3</td>
<td>2.5 (1.7 / 2.6)</td>
<td>2.35 (1.8 / 2.8)</td>
<td>2.4 (1.8 / 2.6)</td>
<td>3 (2.5 / 3)</td>
<td>3.25 (2.5 / 3.5)</td>
</tr>
<tr>
<td>Femoral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein 1</td>
<td>11 (7.9 / 12)</td>
<td>12 (9 / 13)</td>
<td>12 (10.4 / 14)</td>
<td>17 (13 / 18)</td>
<td>14 (14 / 14)</td>
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<tr>
<td>Vein 2</td>
<td>7.5 (6 / 9)</td>
<td>8.35 (7.5 / 10)</td>
<td>9 (7.6 / 10.5)</td>
<td>15 (11 / 15)</td>
<td>13 (12 / 13)</td>
</tr>
<tr>
<td>Vein 3</td>
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<td>6.5 (5.5 / 7.5)</td>
<td>6.5 (5.5 / 7.7)</td>
<td>12 (8 / 13)</td>
<td>10 (9 / 10)</td>
</tr>
<tr>
<td>Great Saphenous</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein 1</td>
<td>5.4 (5 / 5.7)</td>
<td>5.1 (4.5 / 5.5)</td>
<td>5.2 (4.8 / 5.5)</td>
<td>5.4 (5 / 5.5)</td>
<td>5.05 (4.5 / 5.3)</td>
</tr>
<tr>
<td>Vein 2</td>
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<td>4.5 (4 / 4.9)</td>
<td>4.6 (4.2 / 5.1)</td>
<td>5 (4.4 / 5)</td>
<td>4.65 (4 / 5)</td>
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<tr>
<td>Vein 3</td>
<td>4.3 (3.6 / 4.7)</td>
<td>4.1 (3.5 / 4.5)</td>
<td>4.1 (3.5 / 4.6)</td>
<td>4 (4 / 4.3)</td>
<td>4.25 (3 / 4.5)</td>
</tr>
<tr>
<td>Vein 4</td>
<td>3.9 (3.2 / 4.2)</td>
<td>3.5 (3 / 4)</td>
<td>3.8 (3 / 4)</td>
<td>3.5 (3.3 / 3.7)</td>
<td>3.45 (2.5 / 3.7)</td>
</tr>
<tr>
<td>Vein 5</td>
<td>3.1 (2.7 / 3.8)</td>
<td>2.9 (2.5 / 3.5)</td>
<td>3 (2.6 / 3.5)</td>
<td>3 (3 / 3.2)</td>
<td>3 (2 / 3)</td>
</tr>
<tr>
<td>Small Saphenous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein 1</td>
<td>3.4 (3.3 / 3.8)</td>
<td>3.4 (3.3 / 3.6)</td>
<td>3.4 (3.3 / 3.6)</td>
<td>3.8 (3.3 / 3.8)</td>
<td>4.15 (3.3 / 4.5)</td>
</tr>
<tr>
<td>Vein 2</td>
<td>2.9 (2.6 / 3.3)</td>
<td>2.8 (2.6 / 3.1)</td>
<td>2.9 (2.7 / 3.1)</td>
<td>3.2 (2.8 / 3.5)</td>
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<td>2.3 (2.1 / 2.5)</td>
<td>2.4 (2.1 / 2.5)</td>
<td>2.5 (2.2 / 2.5)</td>
<td>3 (2.5 / 3.5)</td>
</tr>
</tbody>
</table>

Kruskal-Wallis H Test (Monte Carlo); Post Hoc Test: Dun’s Test, Med.: Median, Q1: Percentile 25%, Q3: Percentile 75%

For the analysis of the correlation between vein diameters and BMI, age and gender, the explanation factor (r2) of Kendall’s tau-b test was applied and a very weak correlation between these values was observed. Thus, it did not represent any statistical relevance (Table 4).
Table 4. Correlations statistics of vein diameters and demographic data

<table>
<thead>
<tr>
<th>n:298</th>
<th>Supine position</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>BMI</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Right</td>
<td>Femoral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein 1</td>
<td>0.113</td>
<td>0.006</td>
<td>-0.052</td>
<td>0.212</td>
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</tr>
<tr>
<td>Vein 2</td>
<td>0.146</td>
<td>&lt;0.001</td>
<td>-0.076</td>
<td>0.068</td>
<td>0.001</td>
</tr>
<tr>
<td>Vein 3</td>
<td>0.131</td>
<td>0.002</td>
<td>-0.088</td>
<td>0.035</td>
<td>0.109</td>
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<td>Great Saphenous</td>
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<td></td>
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</tr>
<tr>
<td>Vein 1</td>
<td>0.087</td>
<td>0.032</td>
<td>0.089</td>
<td>0.028</td>
<td>0.165</td>
</tr>
<tr>
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<td>0.096</td>
<td>0.019</td>
<td>0.11</td>
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</tr>
<tr>
<td>Vein 3</td>
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<td>0.127</td>
<td>0.154</td>
<td>0</td>
<td>0.061</td>
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<tr>
<td>Vein 4</td>
<td>0.03</td>
<td>0.465</td>
<td>0.254</td>
<td>&lt;0.001</td>
<td>-0.001</td>
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<tr>
<td>Vein 5</td>
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<td>0.682</td>
<td>0.266</td>
<td>&lt;0.001</td>
<td>0.001</td>
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<td>Left</td>
<td>Femoral</td>
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</tr>
<tr>
<td>Vein 1</td>
<td>0.074</td>
<td>0.07</td>
<td>-0.017</td>
<td>0.676</td>
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<tr>
<td>Vein 2</td>
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<td>0.046</td>
<td>-0.053</td>
<td>0.193</td>
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<td>0.208</td>
<td>-0.102</td>
<td>0.012</td>
<td>0.135</td>
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<td></td>
</tr>
<tr>
<td>Vein 1</td>
<td>0.055</td>
<td>0.174</td>
<td>0.048</td>
<td>0.239</td>
<td>0.033</td>
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<td>Vein 2</td>
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<td>0.054</td>
<td>-0.004</td>
<td>0.919</td>
<td>0.033</td>
</tr>
<tr>
<td>Vein 3</td>
<td>0.052</td>
<td>0.196</td>
<td>0.005</td>
<td>0.909</td>
<td>-0.007</td>
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<td>0.432</td>
<td>0.055</td>
<td>0.174</td>
<td>-0.005</td>
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<td>0.049</td>
<td>0.224</td>
<td>0.073</td>
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</table>

Kendall’s tau-b Test, r: Correlation Coefficient

DISCUSSION

In this study, no relationship was found between BMI, age, and gender in terms of the diameters of the lower extremity venous system. Both lower limbs’ vein diameters were significantly larger in upright position either superficial, or deep veins. We found higher diameters in class II obese patients.

Although much research has been conducted on subjects with venous disease, little is known about the hemodynamics of normal limbs (10). Several epidemiologic studies evaluated strong evidence to the hypothesis that obesity is a risk factor for chronic venous insufficiency and venous thrombo-embolism (11-13). Data about the association between obesity and CVD, as well as between obesity and severity of CVD are inconsistent (1, 2). Kügler et al. showed that increased body weight significantly correlates with higher venous pressure in lower extremities. Elevated venous pressure in obese subjects without any known venous pathology can be explained by several possible mechanisms. One is increased intra-abdominal pressure caused by the abdominal fat (14). The study conducted by Amélia et al revealed non-significant changes of great saphenous vein diameters in obese patients compared to lean subjects. The authors also emphasized that age is not necessarily associated directly with an increase in venous diameter of the deep and superficial venous system. The age-related increase in BMI was the most important determinant for an increase in diameter of veins in the standing position (15).
In this study we attempted to pierce out that there were significantly higher diameters (mm) of great saphenous and femoral veins at upright position in both lower limbs compared to corresponding levels in the supine position. In line with our results, Kröger et al observed that the cross-sectional area (CSA) of the femoral vein and great saphenous vein as well as the volume increase in the standing position compared to the supine position (6). Orthostatic stress promotes translocation of thoracic blood volume into the compliant venous system of the legs, buttock, and pelvis (16, 17). This rapid fluid shift reduces central blood volume and represents a substantial cardiovascular stress, as reflected in reflex increases in heart rate and sympathetic nerve activity (18).

A previous study reported that venous diameter in the upright position is significantly higher in obese subjects compared with non-obese subjects (17). In healthy people, there is usually no difference in vein diameter between the right and left leg whereas varicose veins are frequently more extended on one limb (19).

In our study, we found higher diameters in right femoral vein, proximal part and distal two levels of the right great saphenous vein and left proximal small saphenous vein diameters in class II obese patients. Wallenberg et al. found femoral vein diameter was significantly greater in obese compared with non-obese participants (20). This could be interpreted as a result of elevated intraabdominal pressure transmitted to the femoral veins and leading to vein wall distension. Increased stasis and reduced forward flow velocity might be a consequence.

The possible effect of obesity on the initiation of varicose veins and the effect that obesity has on the severity of venous reflux and the complications of venous insufficiency must be viewed differently. According to Bonn study, obesity was not a risk factor for varicose veins but was a risk factor for oedema and skin changes of chronic venous insufficiency (21). Therefore, in our study, we questioned symptoms with the hypothesis that there might be a relationship between BMI and symptoms like oedema or skin changes however we found no relationship between BMI and clinical symptoms.

Our study sample is too limited to stratify venous flow impairment for categories of BMI. Furthermore, an inference is not possible about venous velocities in patients with moderate overweight (BMI, 25-30 kg/m²) subjects. Our data only indicate that an impairment of lower limb venous outflow is observed in class II obese individuals, but not whether this translates into an increased risk for venous thromboembolism or chronic venous insufficiency. This link has recently been reported by larger, event-driven cohort studies (22-27). However, other factors such as ambulatory activity, ankle-joint function, and gait pattern might be involved as well.

The non-blinded manner of data assessment by doppler ultrasound must be considered a shortcoming in our study protocol. Blinding the observer in our study setting was impossible, and measurements were strictly standardized to overcome this. This standardization and the applied exclusion criteria were also needed to minimize the effect of other factors that might affect venous flow, such as movement, posture or respiration pattern. We found no differences between the right and the left leg regarding doppler ultrasound hemodynamic parameters. Nevertheless, our data indicate that a simple, non-invasive assessment by DU imaging is sufficient to detect differences in flow patterns with respect to obesity, although there was no matching for age between obese and non-obese individuals. While it seems unlikely we cannot rule out this as a possible confounder.

In conclusion we found both lower limbs’ vein diameters were significantly larger in the upright position either superficial and deep systems and impairment of lower limb venous outflow is observed in class II obese individuals however the age and BMI relations were not significant. In our opinion, the measurement of the lower extremity venous diameters from different levels and evaluation of the obese individuals according to categorized BMI distinguishes our study from others.

Further longitudinal studies are needed to clarify the influence of anatomic variances in subjects with healthy populations.

Declarations
The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.
The study protocol was approved by the Acıbadem University, Ethics Committee (Date: 26.07.2018, No: 2018-11/9). The study was conducted in accordance with the principles of the Declaration of Helsinki.

REFERENCES

Comparison of Suture-Button Versus Hook-Plate Fixation for Acromioclavicular Joint Injuries

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Abstract

Background: This retrospective study aimed to compare the clinical and radiological results of clavicular hook plate fixation versus suture-button fixation of acromioclavicular joint (ACJ) dislocations.

Methods: 21 patients are retrospectively evaluated in the present study whom diagnosed as type III-V ACJ dislocations and treated by two different surgical methods. The hook plate group comprised 9 patients to whom acromioclavicular fixation. The suture-button group comprised 12 patients to whom coracoclavicular fixation. All patients were evaluated by Constant Murley Score (CMS) and visual analogue score (VAS). Loss of reduction and radiological results were evaluated with the coracoclavicular distance (CCD).

Results: The average follow-up was 31 months (range, 15–56 months). There was no significant difference between hook-plate and suture-button groups in terms of CMS. However, VAS in hook plate group better than suture-button group (p = 0.038). Suture-button fixation adjusted the CCD more than hook plate fixation compared to the opposite shoulder (p = 0.482).

Conclusions: There was no statistically significant difference between the hook plate and suture-button group in terms of the clinical outcomes. However, CCD in the suture-button group was better adjusted to the hook plate group. Suture-button fixation is a good option for the treatment of ACJ dislocations, as implant removal may be required in most cases in which the hook plate is applied.

Key words: Acromioclavicular Dislocation, Suture-Button, Hook Plate.
INTRODUCTION

Acromioclavicular joint (ACJ) dislocation is one of the common shoulder injuries(1, 2). ACJ dislocations associated with acromioclavicular (AC) and coracoclavicular (CC) ligament injuries are radiologically classified as type I-VI according to the Rockwood classification system(3, 4). There is no consensus on which of the several treatment methods reported in the literature should be applied for which type of dislocation(5-8). Therefore, the patient’s functional expectation and the orthopedic surgeon’s preference guide the choice of treatment.

Good clinical and radiological results have been reported for hook-plate fixation and suture-button fixation, which are widely used nowadays(2, 9). Hook plates keep constant the ACJ for the natural healing of the AC and CC ligaments in ACJ dislocations (10). With suture-button fixation, AC and CC bonds are somewhat imitated and the main advantages of this method are that the implant does not need to be removed (11).

There are a lot of reports comparing the outcomes and complications associated with the surgical treatment of ACJ dislocations. However, it was thought that different studies with different patient groups would contribute to the literature on this subject. Aim of the present study was to compare short-mid-term clinical and radiological results of suture-button and hook plate fixation methods in patients with ACJ dislocation.

MATERIALS AND METHODS

After approval was obtained from Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval number: 100/07, date: 14.12.2020),

This retrospective cohort study was initiated. A retrospective review was made of all cases of ACJ dislocation surgically treated using either hook plate or suture-button fixation in our clinic between January 1st, 2016 and July 30th, 2020. The electronic documentation system review revealed 24 cases of ACJ dislocation. Patients were excluded from study if they have chronic (more than two weeks after trauma) ACJ dislocation, type I, II, VI ACJ dislocation, surgical fixation other than either hook plate fixation or suture-button fixation, concomitant injuries to ipsilateral upper limb, and less than 1-year follow-up. Three patients were excluded including chronicity of ACJ dislocation (n:1), different surgical technique (n:1), and concomitant proximal humeral fracture (n:1). Of the 24 patients, 3 patients excluded from the study, so the study was conducted with evaluation of 21 patients.

Surgical Technique for Hook-Plate Application

All the patients were operated on under general anesthesia in the beach-chair position by the several different orthopedic surgeons. The skin over the distal clavicle towards the acromion was incised. After anatomical reduction in the ACJ, an anatomical hook plate (Zimed®, Gaziantep, Turkey) was inserted in the subacromial space (Figure 1). After that, the hook plate was fixed to the distal clavicle with cortical and/or locking screws. The position of the hook plate and reduction of ACJ were controlled under fluoroscopy. The operated shoulders were immobilized with an arm sling for 4-6 weeks.

Figure 1. (A) Preoperative radiograph of patient with acute right ACJ dislocation (B) The post-operative radiograph of patient after hook plate fixation after 3 months of surgery (C) The hook plate was removed after 1 year of surgery
Surgical Technique for Suture-Button Application

An approximately 5-cm skin incision was made extending from the distal clavicle towards the coracoid process. The ACJ was then manually reduced and a smooth K-wire was drilled from 2 cm medial of the ACJ to the coracoid. The bony tunnels were done using subsequent over-drilling of the K-wire with a 4.0 mm cannulated drill in the clavicle and coracoid. Using a passing wire, the suture-button device (Aleda, Ankara, Turkey) was passed with the oblique metal button first through the clavicle and then through the coracoid (Figure 2). After the coracoid passage of the button was flipped to the horizontally by pulling one of two traction sutures. The proximal round button was advanced until touch with the superior surface of the distal clavicle. The position of the buttons and reduction of ACJ were controlled under fluoroscopy. The suture button device was tensioned and tied with a locking knot. The operated shoulders were immobilized with an arm sling for 3-4 weeks.

Figure 2. (A) Preoperative radiograph of patient with acute right ACJ dislocation (B) The post-operative radiograph of patient after suture-button fixation after 3 months of surgery (C) The loss of reduction of ACJ after 1 years of surgery

Postoperative Management

Pendulum exercises were started in the immediate postoperatively for both hook-plate and suture-button groups. The exercises progressed gradually, according to the patient's pain tolerance, to achieve passive and passive assisted abduction. Active range of motion was allowed after 6th weeks. In the postoperative period, the patients were advised to avoid movements such as heavy lifting that would cause a significant downward traction in the upper limb until the fourth month. The rehabilitation protocols were explained to the patients, the necessary training was given and they were made to do it on their own at home. All patients were followed up clinically and radiologically for a period of 12 months. The clinical and radiological evaluations were performed immediately postoperatively, then at 2 and 6 weeks, 3, 6 and 12 months. The hook plates of 2 patients were removed in the postoperative 1st year.

Evaluations

A total of 21 patients were included in study. Functional results were evaluated using the Constant Murley Score (CMS)(12) and the visual analogue scale (VAS) for pain by two independent orthopedic surgeons post-operatively. CMS is divided into four subscales, including pain (15 points maximum), activities of daily living (20 points maximum), range of motion (40 points maximum), and strength (25 points maximum). A higher score corresponds to a higher quality of function (minimum 0, maximum 100). Radiological results were evaluated with the coracoclavicular distance (CCD).

Statistical Analysis

The sample size was calculated with an open source online application (http://www.openepi.com/) based on a 20% difference in functional scores between the 2
treatment groups with an alpha level of 5% and a power of 80%. Consequently, inclusion of five patients for each group suggested (13). However, all patients who were appropriate for inclusion and exclusion criteria was added to analysis. Statistical analysis was performed using SPSS for Windows, version 19 (SPSS Inc, Chicago, Illinois). Chi-square test was used for the comparison of categorical variables. The data does not conform to the normal distribution due to the limited number of sample size, thus the non-parametric analysis was performed. Mann Whitney U was used to compare suture-button and hook-plate fixation. The means were compared between the groups, with 95% confidence intervals and a p value of less than 0.05 was considered statistically significant.

RESULTS

The mean follow-up period was 31 ± 11.2 months (range: 15–56 months). The general characteristics of patients was given in Table 1. Postoperatively, the mean modified CMS value was 83.8 ± 14.7 (range: 51–98), the mean VAS was 2.0 ± 1.9 (range: 0–6). There were no statistically significant differences in the preoperative injury-related variables including the time between trauma and surgery, age, Rockwood classification of ACJ injury or CCD between the two groups. At the last final follow-up visit, there were no significant difference between hook-plate and suture-button groups in terms of CMS. However, VAS in hook plate group better than suture-button group (p:0.038) (Table 2). Suture-button fixation compared to the opposite shoulder was normalized the CCD more than hook plate fixation (p:0.482).

Table 2. The clinical and radiological results of patients (mean ± standard deviation) (CMS: Constant Murley Score; VAS: Visual Analogue Score; CCD: Coracoclavicular distance)

<table>
<thead>
<tr>
<th></th>
<th>Hook plate</th>
<th>Suture-button</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS</td>
<td>90.5 ± 3.5</td>
<td>78.7 ± 17.8</td>
<td>0.064</td>
</tr>
<tr>
<td>VAS</td>
<td>1 ± 1</td>
<td>2.7 ± 2.2</td>
<td>0.038</td>
</tr>
<tr>
<td>CCD Pre-operative</td>
<td>19.1 ± 3.6</td>
<td>17.5 ± 4.1</td>
<td>0.361</td>
</tr>
<tr>
<td>CCD Post-operative</td>
<td>7.7 ± 3.2</td>
<td>8.3 ± 2.5</td>
<td>0.645</td>
</tr>
</tbody>
</table>

At the final follow-up visit, all patients were observed to have full shoulder joint range of motion. There were no complications including vascular or nerve damage in any patient intra-operatively. In follow-up, there were 6 patients with complications including 3 ACJ arthritis in hook plate group, and 3 reduction loss in suture-button group. In the present study, the hook plate was removed due to pain in a patient with ACJ arthritis.

DISCUSSION

In the present study, we compared the clinical and radiological outcomes of patients who underwent hook plating and suture-button fixation for type III-V ACJ dislocation. There was no statistically significant difference between both groups in respect of clinical and radiological findings.

Typically, ACJ injuries result from direct trauma from a fall or in contact sports when the arm is in an adducted position. There are acromioclavicular fixation, coracoclavicular fixation, and dynamic muscle transfer methods for management of ACJ dislocations. Of course, conservative approach may be preferred for type III ACJ dislocations according to some authors (14, 15). On the other hand, the superiority of surgical treatment for ACJ dislocations has also been reported (2, 8). The debate about the choice of conservative and surgical treatment for ACJ dislocations and which surgical treatment to choose still continues.

Some complications are encountered in both conservative and surgical treatment including implant failure, superficial wound infection, ACJ arthrosis and persistent pain (2, 5, 10, 16). In the present study, the patients who have Type III-V ACJ dislocations, hook plate group had
3 arthritis and suture-button group had reduction loss. Among the patients in the study, the worst clinical results in terms of VAS and CMS evaluations were seen in these patients.

It has been reported that early surgical treatment is associated with low complication rate and high patient satisfaction in ACJ dislocations (17, 18). In the present study, on the other hand, we did not have the opportunity to compare the early and late surgical interventions, as there were no patients who underwent late surgical treatment.

It is known that there is an inverse relationship between ACJ reduction and arthritis (19, 20). Although degenerative changes of ACJ are generally seen radiologically, poor reduction of ACJ does not affect the clinical outcomes (21). The fact that the reduction loss observed in 3 patients in the suture-button group in the present study did not significantly affect the clinical results confirms this finding.

The hook-plate is a useful and easy applicable device for the treatment of ACJ dislocations. Although the main concerns in the application of hook plates are subacromial impingement, acromial osteolysis or needing implant removal, there were no significant differences in complications between the two techniques (22, 23). Because of such complications, implant removal is recommended. Implant removal was performed in only one of the patients in the present study. Other patients did not want a second surgical intervention, but this did not negatively affect the clinical results.

Bin Abd Razak et al. stated that suture-button had a significantly better CMS than hook plate fixation in short-term outcomes (2). Furthermore, they also found a significantly better shoulder abduction of suture-button than hook plate fixation at 6th months. The authors stated that the superiority of suture-button over hook plate fixation might be explained by the necessity of secondary surgical intervention for removal of hook plate. The current literature presented superior clinical results about suture button fixation unlike the present study (2, 10). The suture-button used in the patients in the present study was of UHMWPE structure which had higher failure load (24). Therefore, the better clinical results in the hook plate group compared to suture-button group in this study may be due to a surgical technique rather than the implant used. However, the retrospective nature of the study prevents us from reaching more information on this subject.

Biomechanical complications have been reported for both techniques in the literature. In the hook plate technique, the most common complication was reported as re-dislocation of ACJ after removal of the implant (25). Sun et al. reported that it was developed loss of reduction in 30 (23.1%) of 130 patients in suture-button technique (26). In the present study, there was not enough data in the hook plate group for comparison. In addition, loss of reduction was detected in 3 of 12 patients in the suture-button group. Although not statistically significant, suture-button fixation, except 3 patients with loss of reduction, shortened the CCD more than hook plate fixation compared to the opposite shoulder.

There were several limitations of this present study. There was retrospective design, limited number of patients, and no long-term results. Another limitation was that the patients in the present study was operated by more than one surgeon. Also, due to the retrospective nature of the study, no evaluation has been made on type 3 ACJ subgroups.

In conclusion, there was no statistically significant difference between the hook plate and suture-button group in terms of the clinical outcomes. However, the suture-button technique was normalized CCD more than hook plate, as implant removal may be required in most cases in which the hook plate was applied. Although both techniques have positive and negative aspects, the orthopedic surgeon can determine which technique to use by considering them.

Declarations of interest: None

Ethical Approval: The study protocol was approved by the Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Date: 14.12.2020, No: 100/07). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work.
No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work.

REFERENCES

Clinical and Functional Outcomes of Using Double-Row Transosseous Fixation Material in Advanced Age Treatment of Rotator Cuff Tears

Mehmet Cenk Turgut1  Serdar Toy2  Mehmet Köse3  Muhammed Çağatay Engin3

Abstract

Background: Rotator cuff tears are the most common cause of shoulder pain in the elderly. Various techniques have been used in the treatment of rotator cuff tears. This study discusses the clinical and functional outcomes in patients in whom rotator cuff tears have been repaired using double-row transosseous fixation material.

Methods: The study is carried out on 37 elderly patients who underwent mini-open arthroscopy-supported transosseous repair between February 2017 - March 2019. Age and gender of the patients as well as the tear development mechanism, tear grade, fatty degeneration grade, acromion type, and the University of California - Los Angeles (UCLA) Shoulder Scale and Constant-Murley functional and clinical scores (CMS) before and six months after the surgery were recorded.

Results: Mean patient age was 61.19±6.74 (range: 52-76). 17 (45.9%) were female, and 20 (54.1%) were male. The mean preoperative CMS score was 37.68±8.64, and the mean UCLA score was 14.19±8.64. Mean postoperative CMS and UCLA scores were 76.84±9.57 and 28.14±3.02, respectively. Preoperative and postoperative CMS and UCLA scores were statistically significantly different (p<0.001).

Conclusions: Arthroscopy-aided transosseous method using Sharc-FT instrument both prevents open surgery complications and results in lower infection rates and less muscular power loss. Considering both its functional and clinical outcomes, Sharc-FT is a utilisable instrument.

Key words: Rotator Cuff Rupture, Advanced Age, Mini-Open, Transosseous Fixation, Arthroscopy.
INTRODUCTION

The shoulder joint has the most comprehensive range of motion in the body, and most of its functionality is provided by rotator cuff muscles. Since most daily life activities require a normal shoulder joint range of motion, tears of this muscle group substantially impact shoulder functions and quality of life (1).

Rotator cuff tears are the most common cause of shoulder pain and have a strong relationship with advanced age (2). These ruptures may be traumatic or degenerative. The humeral head cannot be centralized in the glenoid due to rotator cuff tear, and pain with muscular weakness develops, eventually leading to superior migration. The dominant side is usually affected—patients present with nighttime pain, a difficulty raising the arm, and pain. Despite being able to accomplish most of the daily activities, patients frequently cannot perform overhead moves. The objective of the treatment is to reduce pain, increase function, and prevent rotator cuff arthropathy. Surgical treatment within six weeks is recommended for acute traumatic tears. For chronic degenerative ruptures, surgical treatment is recommended for patients who do not benefit from 3 to 6 months of conservative treatment (3, 4).

Rotator cuff tears used to be diagnosed and treated with open techniques using traditional methods. Transosseous open repair, defined by Codman in 1911, had been the gold standard of treatment for many years (5). In time, closed treatment of rotator cuff tears using anchors was introduced to develop minimally invasive methods alongside arthroscopy in shoulder pathologies. Over these years, single-row, double-row, and double-row bridge methods had been performed by an arrangement of anchor configurations. Utilization of double-row suture remained at the forefront in trials except for tears smaller than 1 cm (6, 7). However, re-occurrence of tears and anchor problems in massive tears with low bone quality and high amount of degeneration, especially those accompanied by tuberculum majus cysts, prompted transosseous repair methods again these types of ruptures (8, 9).

This study targeted demonstrating the advantages and use of the double-row transosseous repair technique as a new method.

MATERIALS AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the ethics committee of Atatürk University Medical Faculty (Date: 15.02.2018; Decision Number: 38).

Thirty-seven elderly patients who did not benefit from a previous six months of conservative treatment and underwent arthroscopy-aided mini-open transosseous repair after being admitted to the Department of Orthopedics and Traumatology of Atatürk University Faculty of Medicine Research Hospital for shoulder pain and movement restriction between February 2017 and March 2019 and receiving the diagnosis of rotator cuff tear after a physical examination and radiological studies (direct X-ray and MRI) were included in this study. Patients with partial rupture of the rotator cuff, those under the age of 50 with rotator cuff tear, patients with very advanced fatty degeneration as well as patients treated with biceps tenotomy, operated by a different surgical team, treated with an additional surgical procedure, and those failed to attend final controls were excluded from the study.

Data recorded included age, gender, mechanism of tear development, tear grade, the grade of fatty degeneration, acromion type, superior migration of humeral head, symptoms of glenohumeral arthritis, whether additional acromioplasty is performed or not, and the University of California - Los Angeles (UCLA) Shoulder Scale and Constant-Murley functional and clinical scores (CMS) before and six months after surgery.

UCLA evaluates pain, function, patient satisfaction, flexion muscle strength, and flexion angle on a total of a 35-point scale. Each ache and function is evaluated on a scale of 1 to 10. Each of the active flexion angles, flexion muscular strength, and patient satisfaction are assessed on a scale of 1 to 5. A total point of 34-35 is considered excellent, 29-33 as good, and points under 29 are regarded as poor.
The Constant-Murley rating system is a full scale of 100 points with 15 points for pain, 20 for function, 40 for active range of motion, and 25 for muscle strength. Total Constant score includes four groups as excellent (90-100), good (80-89), moderate (70-79), and poor (<70).

**Surgical Technique**

All patients were operated on at beach chair position under general anesthesia. The upper limbs of the patients were stained three times with batticon and covered with double layers of the green sheet. Shoulder joints were assessed by arthroscopy. Rotator cuff tears were confirmed for each patient by adequate subacromial bursectomy.

Following the arthroscopic assessment of shoulder joints, the margin between cartilage and bone was reached by crossing the tissues through a mini-incision of 3 cm on the portal used to laterally stitch rotator cuff projection of rotator cuff tear was cleaned using a shaver. Thus, the surface where the tendon will be identified was cleaned until reaching the tissue with hemorrhage. The distal edge of Taylor Stitcher was placed on the footprint of the rotator cuff. The targeting needle was placed using a targeting guide, and the needle was removed from the base area by checking that its tip is pointing to the desired exit site. We prepared two tunnels by repeating this procedure twice. Suture edges that come out of the tunnels were passed through the cuff and tied. One out of two strings in each knot was passed through Sharc-FT (NCS Lab Medical Devices Factory, Carpi (MO), Italy) that is placed on the lateral cortex, and a double-row-like fixation was achieved by tying the tips left on the top (Figure 1-2).

**Figure 1.** Sharc-FT (A), Taylor Stitcher (B), Targeting needle are removed from the rotator cuff footprint, and carrying strings are passed. The other carrying string is passed, leaving a gap of at least 1 cm (C). Final view of the rotator cuff tear after being repaired using Sharc-FT instrument (D) (Source: SHARC-FT AND TAYLOR STITCHERNCS Lab Medical Devices Factory)
Figure 2. Rotator cuff repair during surgery. The arthroscopic portals had been marked before the operation began (A). Sutures were made with a mini-open incision (B). Rotator cuff repair has been successfully done with the Sharc-FT (C).

Postoperative Follow-up

The patients were followed up for three weeks under shoulder sling with abduction support. Passive exercises were started at three weeks and active exercises at six weeks. Wound site dresses were changed every three days, and stitches were removed at 15 days if no problem is observed. The stitches were removed on day 21 for overweighted and diabetic patients.

Statistical Analysis

Demographic data and others were reported as frequency and percentages. The arithmetic mean±standard deviation was calculated for the numerical variables. The distribution characteristics of the data were determined by the Shapiro-Wilk test, while Levene’s test calculated the homogeneity of variances. Statistical analysis was performed using SPSS for Windows 23.0 (IBM Corp., Armonk, NY, USA). Categorical data were analyzed by using Fisher exact or chi-squared tests. Parametric data were analyzed by using the Paired-Samples t-Test. P <0.05 was considered statistically significant.
RESULTS

The mean age was 61.19 ± 6.74 for the 37 subjects included in the study (range: 52-76). 17 (45.9%) were female, and 20 (54.1%) were male. The rotator cuff tear was small, moderate, large, and massive in 4 (10.8%), 19 (51.4%), 8 (21.6%), and 6 (16.2%) of the subjects, respectively. The data regarding fatty degeneration, patte classification, acromion types, and the presence of migration and arthritis are presented in the table (Table 1).

Table 1. Demographic and clinical data of patients

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Percentage (%)</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>45.9%</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>54.1%</td>
</tr>
<tr>
<td>Fatty degeneration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>16</td>
<td>43.2%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>21</td>
<td>56.8%</td>
</tr>
<tr>
<td>Patte Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>20</td>
<td>54.1%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>17</td>
<td>45.9%</td>
</tr>
<tr>
<td>Acromion Types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>6</td>
<td>16.2%</td>
</tr>
<tr>
<td>Type 2</td>
<td>17</td>
<td>45.9%</td>
</tr>
<tr>
<td>Type 3</td>
<td>14</td>
<td>37.8%</td>
</tr>
<tr>
<td>Rupture Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor (&lt;1 cm)</td>
<td>4</td>
<td>10.8%</td>
</tr>
<tr>
<td>Intermediate (1-3 cm)</td>
<td>19</td>
<td>51.4%</td>
</tr>
<tr>
<td>Large (3-5 cm)</td>
<td>8</td>
<td>21.6%</td>
</tr>
<tr>
<td>Massive (&gt;5 cm)</td>
<td>6</td>
<td>16.2%</td>
</tr>
<tr>
<td>Migration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>34</td>
<td>91.9%</td>
</tr>
<tr>
<td>Present</td>
<td>3</td>
<td>8.1%</td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>33</td>
<td>89.2%</td>
</tr>
<tr>
<td>Present</td>
<td>4</td>
<td>10.8%</td>
</tr>
</tbody>
</table>

The assessments revealed that mean Constant and Murley shoulder scores (CMS) were 37.68±8.64 points before the surgery and 76.84±9.57 points after the surgery. The lowest and highest preoperative CMS scores were 23 and 56, respectively. The lowest and highest postoperative CMS scores were found to be 60 and 94, respectively. There was a statistically significant difference between the preoperative and postoperative CMS scores (p<0.001) (Table 2).

Table 2. Preoperative and postoperative functional results of patients

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS</td>
<td>37.68±8.64</td>
<td>76.84±9.57</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>UCLA</td>
<td>14.19±4.04</td>
<td>28.14±3.02</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

CMS: Constant and Murley shoulder scores; UCLA: University of California-Los Angeles Shoulder Scale; SD: standard deviation

The mean preoperative and postoperative UCLA shoulder scores were found to be 14.19±8.64 and 28.14±3.02 points, respectively. The lowest and highest preoperative UCLA shoulder scores were 8 and 26, respectively. The lowest and highest postoperative UCLA shoulder scores were found to be 22 and 34, respectively. There was a statistically significant difference between the preoperative and postoperative UCLA shoulder scores (p<0.001) (Table 2).

No subjects exhibited symptoms of infection or re-rupture during the postoperative period. 6th month MRI control revealed partial recovery in 4 subjects and full-thickness healing in 33 subjects.

DISCUSSION

This study showed that the results of rotator cuff tear repair, which we performed with a new device that we could perform double-row trans-osseous repair, provided structural integrity similar to other successful methods in the literature, and were associated with good clinical results (10-12).

Rotator cuff tears are most frequently seen in individuals between 40 to 70 years of age. Many factors may play a role in the etiology of the rotator cuff tears. The most commonly considered causes include tendon tensile tension and the excessive load on the rotator cuff. Acute trauma develops in almost all subjects over the age of 60 due to overload onto the rotator cuff. Repeated shoulder
movements constitute another cause of the rotator cuff tears. It has been reported that larger rotator cuff tears are seen in individuals with advanced age and that weakening occurs at the point of attachment to the bone, which becomes more frequent by age (4, 13).

Mini-open or arthroscopic methods are used to repair rotator cuff tears surgically. Although these methods are reported to demonstrate good clinical and functional outcomes in both the short and long term, the best technique to repair full-thickness rotator cuff tears is still a matter of debate (14).

Some studies in the literature compare mini-open methods with full arthroscopic techniques and claim that full arthroscopic methods have benefits such as less morbidity during the surgical procedure and faster postoperative recovery of joint motions (15, 16). However, some investigators found no difference between the full arthroscopic and mini-open methods in clinical and functional terms (17).

When the studies on the infection rate were examined, it was observed that the infection rate was between 0.27% and 1.9% in the operations performed with mini-open and fully open methods. On the other hand, this rate varied between 0.04% and 0.23% in operations performed with the arthroscopic technique (18-21). These studies also showed that there was no severe infection rate among all methods. We did not encounter any infection in any of the patients, but this might relate to the short follow-up period.

Zhang et al. achieved a significant increase in muscle strength in subjects undergoing full arthroscopy, while the rate of re-rupture was higher (22). In this study, we observed a lower need for analgesics and a more straightforward postoperative rehabilitation process. We did not prefer a fully open surgery approach due to higher infection rates, deltoid dysfunction, and difficult postoperative rehabilitation. Today, the fixation quality in open surgery can be achieved by mini-open arthroscopy-aided surgery. The success rates are similar in the literature. Considering that complication rates in the arthroscopy-aided mini-open method are not as high as open surgery, we have chosen this method.

Various tendon fixation methods have been reported in the literature for rotator cuff repair. These include suture anchor (single-row, double-row, double-row transosseous and equivalents) and transosseous plans. Today, surgical methods based on the double-row fixation technique over the rotator cuff footprint have been developed to prevent repeated ruptures based on the hypothesis that single-row fixation does not generate a natural tendon attachment, leading to insufficient recovery. Apreleva et al. found in their study assessing the rotator cuff footprint in 3D in the normal rotator cuff. After many different rotator cuff repair methods, single-row fixation restores 67% of the original rotator cuff footprint. The same study demonstrated that transosseous simple suture repair restores approximately 85% of the surface area. The authors indicated that a broader footprint repair might enhance recovery and the mechanical endurance of the repaired tendons, which cannot be achieved using a single-row repair method (13).

Kim et al. demonstrated that double-row repair significantly reduces gap formation and that the addition of medial row anchors increases repair toughness by 46% and final insufficiency strength by 48% (23).

The success of the rotator cuff repair depends on high fixation strength, small gap formation, preservation of mechanical stability, and the maintenance of biological recovery at the tendon-bone interface. Many surgical techniques have been developed due to these factors. One of the said techniques is the transosseous method. Studies have demonstrated that transosseous repair results in small gap formation and the highest resistance. The literature suggests that the transosseous process provides stronger fixation than double-row repair (24, 25). Combining the transosseous method with double-row repair ensures a much steadier fixation in elderly patients with more inadequate muscle and bone quality. None of our subjects experienced re-rupture.

The limitations of our study were that it was a retrospective study, it was not comparative with other methods, the number of our patients was not very large, and the relatively short duration of 6 months. The low complication rate might be related to the short duration of the study. There were also no comparative group of patients repaired with a different technique, such as the traditional trans-osseous technique.

In conclusion, our method allowed for avoiding the complications of fully open surgery. Moreover, a fully arthroscopic method provided benefits like lower infection rates and less muscular strength loss, resulting in a steadier and safer fixation. This study showed that it is appropriate to implement the arthroscopy-aided transosseous method considering the functional and clinical outcomes.
Declarations

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The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the ethics committee of Atatürk University Medical Faculty (Date: 15.02.2018; Decision Number: 38)

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Renal Epithelioid Angiomyolipoma with Aggressive Progression: A Case Report and Literature Review

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Abstract

Epithelioid cellular morphology can be seen in clinically benign usual (or classic) angiomyolipoma (AML). Perivascular Epithelioid Cell Tumors (PEComa) are rarely seen as a variant of AML and usually benign in nature; however, they may have unpredictable pathological behavior. Here, we present a case of renal PEComa with malignant clinical progression and compare it with the current literature. A 56-year-old patient with a history of recurrent side pain present for about four months applied to our clinic. A hypodense mass was detected on the upper pole of the left kidney by ultrasonography. Computerized tomography showed an 8x4 cm mass originating from the upper pole of the left kidney and the adrenal gland, and was thought to invade the psoas muscle. The patient underwent a left transperitoneal radical nephrectomy. During the operation, vena cava inferior repair was required due to invasion and performed. Histopathologic examination revealed a PEComa. During the third month follow-up visit, a recurrent mass and lymph node enlargement were detected at the operation site. The mass was excised, and histopathology revealed a PEComa again. Considered as a rare variant of AML, PEComa is a tumor with the potential to exhibit malignant behavior. Although only a limited number of cases of renal PEComa have been reported; diagnosis, treatment, and follow-up are important due to their high potential for malignancy.

Key words: Renal Epithelioid Angiomyolipoma, PEComa, Angiomyolipoma.
INTRODUCTION

Angiomyolipoma (AML) constitute 3% of solid renal masses (1). Although AMLs are mostly composed of smooth muscle, blood vessels, and fat cells, Epithelioid AML (Perivascular Epithelioid Cell Tumor-PEComa), a type of AML that may show malignant potential, is caused by perivascular epithelial cells (2). 2016 WHO Renal Neoplasia Classification defined Renal Epithelioid AML as a potentially malignant mesenchymal neoplasm (3) PEComa is in the “Tumors of uncertain differentiation” group in the 2020 WHO classification of soft tissue tumors. (4) Like classic AML, PEComa can be seen as sporadic or with tuberous sclerosis syndrome (1). PEComa group consists of renal and hepatic AMLs, clear cell-sugar-tumor of the lung, lymphangioleiomyomatosis, myelomelanocytic clear cell tumor of ligamentum teres. Therefore, PEComa can be observed in many tissues such as retroperitoneum, abdominopelvic region, gastrointestinal tract, kidney and the liver (5). In this case report, an aggressive case of renal PEComa showing invasion to adjacent tissues is presented.

CASE REPORT

A 56-year-old male patient was admitted due to left flank pain that had been ongoing for a few months. The patient had no history of hematuria, another disease, or a previous surgical operation. Following the physical examination, ultrasonography (USG) was performed because of a suspected mass in the left lumbar region. A hypoechoic mass approximately eight cm long was detected in the middle-upper pole of the left kidney. Later, computed tomography (CT) revealed a heterogeneous hypodense mass of 84 mm by 52 mm that extended exophitically in the upper-middle part of the left kidney (Figure 1). The mass was invading the left diaphragmatic crus and partially holding in the adrenal gland. It also was invading the psoas muscle and part of the renal vein. No abnormality was shown by the patient’s routine laboratory tests. The patient underwent an open transperitoneal radical nephrectomy. Vena cava inferior was opened due to the possible invasion and repaired afterwards. On the 10th postoperative day, the patient was discharged without any complications.

Figure 1. Computerized Tomography (CT) images of the heterogenous hypodense mass, 84x52 mm

The pathology result was reported to be an epithelioid AML or PEComa with dimensions of 8 x 6 x 4.5 cm. Tumor cells were immuno-diffused positive with immunohistochemical staining for vimentin. Focal staining was observed with HMB-45, Cd31, and SMA. (Figure 2) Staining with CD34, S100, desmin, and melanin A was not observed. The Ki-67 index was high. Local necrosis areas were observed. The tumor invaded the kidney parenchyma. There was no sign of invasion of the renal artery and vein.

Figure 2. Microscopic images of tumor cells:
   A: Tumoral structure consisting of nesting of epitoid cells around the vessels (HEX200)
   B: Widespread vimentin positivity in tumor cells (X200)
   C: HBM45 positivity in tumor cells (X200).
At the third month follow up visit, a control CT revealed a mass 10 mm in diameter which was reported to be possibly a lymphadenopathy (LAP) in the left kidney lobe. No surgery was planned at this stage and a decision was made to check the progression of the mass 3 months later with another follow-up CT. 3 months later, the patient’s positron emission tomography using fluorodeoxyglucose (FDG) revealed a mass of 27 mm by 18 mm (SUV max: 16.68) adjacent to the psoas anterior muscle in the left kidney lobe. In addition, another mass with a size of of 20 mm by 26 mm (SUV max: 22.27) with FDG involvement was observed in the left paraaortic region. The patient was presented and discussed at the oncology council, and the decision was made that the recurrent mass be removed surgically. The recurrent mass and LAP were excised 3 months after the first operation. Epithelioid AML that was compatible with the first pathology, was determined again from the histopathologic examination. Lymph node involvement was present. (Diffuse staining was performed with vimentin, EMA, and SMA S-100; focal immunosuppressive with HBM-45, desmin, and Melan-A.)

DISCUSSION

Martignoni first described PEComa as a potentially mesenchymal neoplasm that is a variant of AML (6). In 2016, tumors consisting of 80% or more epithelioid cells were defined by World Health Organization (WHO) as a PEComa (3). Histologically, classic AMLs consist of mature adipose tissue, dysmorphic blood vessels, and spindle-shaped smooth muscle cells. An AML consists of polygonal, atypical, and dense cytoplasm, vesicular nucleus, and prominent nucleoli (6).

Renal PEComas usually present with nonspecific symptoms such as flank pain and hematuria. Laboratory tests are often normal. CT observes the PEComas as a solid mass with heterogeneous changes. Unlike classic AMLs, they contain very little or no adipose tissue. In radiological evaluations, PEComa can be confused with renal cell carcinoma (1). In our case, the kidney mass observed by CT was reported by radiology as renal cell carcinoma.

Immunohistochemically, PEComas are observed to be mostly diffused or focally stained with melanocyte markers such as HMB45, Melan A, and A103. PEComas can also be stained with smooth muscle markers such as SMA and negatively stained with the S100 marker (7). In our case, focal staining with HMB45 and diffuse staining with vimentin was observed, and negative staining was observed with S100. Some studies have suggested that Ki-67, a proliferation marker, can also be used as a marker in PEComas. (8). Tumor cells were stained with Ki-67 in the case of a renal PEComa with ileum and lung metastasis reported by Shi et al. (9). In another study, it was reported that the Ki-67 index was above 10% and that overexpression of p53 could increase the potential for malignant behavior of PEComas (10). The PEComa in our case was high Ki-67 index and therefore exhibited malignant behavior.

In a study by Brimo et al. (11), they examined 40 epithelioid-AML cases. In order to predict malignant behavior, they have determined four features: (1) >70% atypical epithelioid cells, (2) >2 mitotic figures per 10 hpf, (3) atypical mitotic figures, and (4) necrosis; the presence of 3 or all of the features was highly predictive of malignant behavior. In another study, Nese et al. (12), which included 41 renal PEComa cases, metastasis was detected in half of the cases, and three of these patients died during the follow-ups. In the same study (12), the relationship with tuberous sclerosis, necrotic areas larger than 7 cm, extrarenal spread, renalvein invasion, and a pattern of cancer-like growth have been reported as criteria of malignancy.

In our case, the size of the tumor was 8 x 6 x 4.5 cm. Invasion of the surrounding tissues (especially the vena cava’s inferior wall) in CT, necrosis, and strong staining with Ki-67 in the pathological evaluation showed a high potential for malignancy. There was no relationship with tuberous sclerosis in the case. The patient who was diagnosed with metastatic lymph nodes after nephrectomy; consulted with the oncology department and was evaluated for chemotherapy. Currently, there is no conventional and routine chemotherapy protocol for PEComas. A 50% reduction in PEComa recurrence was detected after two cycles of doxorubicin in a study with doxorubicin (13).

Regarded as a rare variant of AML, PEComa is a tumor with the potential to exhibit malignant behavior. When imaging methods of detection are used, PEComas can often be confused with renal cell carcinomas. Although only a limited number of cases of renal PEComa have been reported, its diagnosis, treatment, and follow-up are important due to its high potential for malignancy. High-risk patients may receive adjuvant treatment; however, there are not well-established treatment guidelines.
Declarations
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Unexpected Arrhythmia in a Young Patient: Hookah Smoking Triggered Atrial Fibrillation

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Abstract

In the current literature, although it has been known that hookah smoking increases the heart rate and predisposes to arrhythmia, no case report has been published regarding hookah smoking and the development of arrhythmia, including atrial fibrillation (AF). In this case report, we presented an adult patient without known cardiovascular disease who experienced AF after a heavy hookah smoking session. Following IV amiodarone infusion, normal sinus rhythm was achieved. The patient was advised to stop hookah smoking and discharged with a beta-blocker therapy and an oral anticoagulant treatment for 3 weeks. The patient’s rhythm was normal at one-month outpatient visit. This case emphasizes that hookah smoking could not be considered as a less harmful alternative to cigarette smoking because of its' apparent side effects to the cardiovascular system.

Key words: Atrial Fibrillation, Hookah, Smoking.

INTRODUCTION

Smoking is one of the major causes of mortality and morbidity, especially in patients with cardiovascular disease. In recent years, hookah (water pipe) smoking, which is considered to be less harmful than cigarette smoking, is becoming increasingly popular among young population. However, experimental studies have shown that the chemicals and toxic substances in the hookah have the potential to cause cardiovascular events as much as cigarette smoking (1-3). Following the inhalation of smoke through hookah leads to increase of blood pressure, heart rate, and peripheral vascular resistance in the body. In addition, people who smoke hookah have a higher risk of acute myocardial infarction due to abnormal platelet activation (4). In the current literature, although it has been known that hookah smoking increases the heart rate and predisposes to arrhythmia, no case report...
has been published regarding hookah smoking and the
development of arrhythmia, including atrial fibrillation
(AF) (5). In this case report, we presented an adult patient
without known cardiovascular disease who experienced
AF after a heavy hookah smoking session.

CASE REPORT

A 28-year-old male patient without a history of alcohol or
illegal drug use presented to our emergency department
with complaints of palpitation, which developed
approximately 30 minutes before admission. The
patient expressed that he smoked hookah for 1 hour and
suddenly felt irregular heartbeats. The patient did
not experience a chest pain or dyspnea during this
period. The past medical history was not contributory
and he did not smoke hookah before. On emergency
admission, patient’s heart rate was 180 beats per minute
and his blood pressure was 138/73 mmHg. Physical
examination did not reveal any abnormal findings other
than increased heart rate. Electrocardiography (ECG)
obtained in the emergency room showed an irregular
heart rhythm with the absence of P waves (Figure
1-A). The patient’s oxygen saturation was 94% in
ambient air and blood gas analysis revealed that his
carboxyhemoglobin level was 6%. The patient was
diagnosed with an AF, and intravenous (IV) diltiazem
(25 mg) was administered to control his heart rate
by an emergency physician. The laboratory analysis
demonstrated no abnormal findings. Echocardiography
was performed providing a normal left ventricular
ejection fraction and mild mitral insufficiency.
Despite the administration of IV diltiazem (25 mg) and IV
metoprolol (5 mg) at the emergency room, a control over
the heart rate was not achieved. Therefore, the patient
was consulted to our department and a single dose of
600 mg propafenone was given to achieve normal sinus
rhythm. In addition, the patient was anticoagulated with
a low-molecular-weight heparin (enoxaparin, 8000 anti-
Xa IU/0.8 ml, SC). It was observed that the patient’s
abnormal rhythm did not convert to sinus rhythm after
3 hours of propafenone treatment. Hence, it was decided
to administer IV amiodarone to convert the patient’s
abnormal rhythm into sinus rhythm. A loading dose
of IV 150 mg amiodarone was given over 30 minutes,
followed by a 1 mg/min infusion for 6 hours. After that,
a normal sinus rhythm was achieved following 4 hours
of IV amiodarone infusion (Figure 1-B). After medical
cardioversion, a bed-side echocardiography performed
and revealed no abnormal findings. A posterior-anterior
chest scan was also performed, revealing normal
findings (Figure 2). The patient was advised to stop a
hookah smoking, and he was discharged with a betablocker therapy and an oral anticoagulant treatment for
3 weeks. The patient’s rhythm was normal at the two-
week and one-month control appointments after the first
admission.

Figure 1. (A) Electrocardiography showed an irregular
heart rhythm with the absence of P wave (B) Following
IV amiodarone infusion, normal sinus rhythm was
achieved
DISCUSSION

Currently, the negative effects of cigarette smoking on the cardiovascular system are well-known. So far, there have been fewer studies on hookah smoking than cigarette smoking despite the fact that hookah has been available for many years, especially in the Middle East region. The primary chemical and toxic substances present in hookah are nicotine, carcinogenic polycyclic aromatic hydrocarbons, aromatic amines, aldehydes, phenolic compounds, tar, heavy metals, and ammonia (1-5). Hookah smokers are exposed to these toxic compounds for much longer periods than those who smoke cigarette. Moreover, plasma carboxyhemoglobin levels are usually higher in hookah smokers than cigarette smokers due to the prolonged exposure to carbon monoxide (CO) (2). Since CO’s affinity for hemoglobin is 200 times greater than oxygen, the oxygen curve shifts to the left, resulting in a cellular hypoxia and deterioration in cellular respiration. This cellular hypoxia and prolonged exposure to toxic substances may lead to cardiac arrhythmia as shown in our case.

Hookah smoking also might have some negative effects on the cardiovascular system. Heavy hookah smoking can lead to the hyperactivation of the sympathetic nervous system, thereby resulting in an increase in the peripheral vascular resistance and heart rate (6-9). Moreover, abnormal fluctuation in systolic and diastolic blood pressures can occur due to the deterioration in the baroreflex mechanism (10). The prolonged exposure to hookah smoking also increases susceptibility to acute ischemia because of endothelial dysfunction and hypercoagulability. Moreover, the levels of nicotine during hookah smoking are considerably higher than cigarette smoking. Consequently, cardiac arrhythmia, including AF, can occur due to increased sympathetic activation and plasma catecholamine levels. Previously, occurrence of ischemic heart disease, atherosclerosis, and heart failure after long periods of hookah smoking have been reported (8-9). Even though abnormal elevation in heart rate and predisposition to arrhythmia after hookah smoking is demonstrated in experimental studies, no specific hookah-related arrhythmia has been reported in the current literature. According to our literature research and to our knowledge, this is the first case of acute AF due to heavy hookah smoking. Besides, this case emphasizes that hookah smoking should not be considered as a less harmful alternative to cigarette smoking because of its apparent side effects to the cardiovascular system. In this case, for the first time in the literature, we presented an adult patient who presented with AF following heavy exposure to hookah smoke.

Declarations

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