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REVIEW ARTICLE

Non-Surgical Treatment Options for Peyronie's Disease

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Abstract

Peyronie's disease, which occurs with the formation of a fibrous plaque in the tunica albuginea; is a disease that causes some physical problems such as bending and shortening of the penis. There are surgical treatment methods of this disease as well as non-surgical treatment methods. Non-surgical treatment methods, which are grouped under six headings: oral treatments, topical treatments, traction and vacuum treatments, shock wave therapy, intraplate injection treatments, and experimental treatments, can be preferred in cases where the symptoms are not very advanced because they provide advantages in terms of ease of application, accessibility, and cost. Although the only non-surgical treatment method approved by the FDA (U.S. Food and Drug Administration) yet is clostridium collagenase histolikum, which is used in intraplaque injection, studies have shown that other methods also reduce curvature, pain, and plaque volume.

Keywords: Peyronie's Disease, Non-Surgical Treatment, Plaque.

INTRODUCTION

Fibrous plaque formation in the tunica albuginea layer surrounding the corpus cavernosum causes Peyronie's disease, although its pathological mechanism has not been fully elucidated. The disease was first described by Francois Gigot de La Peyronie in 1743. The disease, characterized by penile curvature, pain, erectile dysfunction, penile shortening, and deformity, has two phases, acute and chronic. While there is active inflammation in the acute phase, the lesion stabilizes in the chronic phase. Plaque calcification occurs after the inflammatory response resulting from vascular damage in the tunica albuginea (1). In the tissue under the microscope, increased connective tissue and inflammatory cells are seen. The prevalence of the disease, which varies between 3.2% and 13% in studies, is generally seen in men between the ages of 50-60 (2). It should also be considered that patients may not apply to health institutions due to psychosocial or cultural reasons. While Peyronie's disease is associated with increased

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Dupuytren's contractures, plantar facial contractures (Ledderhose disease), tympanosclerosis, trauma, transurethral procedures, diabetes, gout, Paget's disease, and even beta-blocker use, the exact etiology is unknown. Still, penile trauma, genetic conditions, and genital system diseases thought that three main factors, including the history of the disease, increase the risk of the disease (3). In recent years, it has been stated that the increase in TGF-ß expression is also effective in its pathological mechanism (4). The treatment of this disease, which affects patients psychologically by causing problems such as lack of self-confidence, anxiety, and depression, in addition to physical problems very important for improving the quality.

Although surgical applications may be preferred in patients with advanced symptoms, non-surgical treatment options can be advantageous when conditions such as ease of application, easy accessibility, and cost are taken into account. In the guidelines published by the EAU (European Association of Urology) and AUA (American Urological Association), there are tables with suggestions about which method would be more beneficial to use, and studies are still being carried out on the effectiveness of these methods.

Search strategy and selection criteria

Articles on non-surgical treatment methods in the treatment of Peyronie's disease have been reviewed and compiled, emphasizing being up to date. The therapeutic agents' efficacy was discussed with the summaries given at the end of each non-surgical treatment method.

ORAL TREATMENT METHODS

1. Vitamin E

Mechanism

Acting as a natural antioxidant, vitamin E acts by reducing the number of oxygen-free radicals produced during cellular metabolism. Lipid peroxides are selective and potent inhibitors of prostacyclins. Vitamin E fulfills its antioxidant effect by preventing the peroxidation of lipid peroxides. It is still a popular treatment modality due to its low cost and relatively mild side effects (5, 6).

Evidence

In the first studies on vitamin E, a reduction in plaque size was reported in 91% of patients and decreased curvature in 78%. In the literature published between 1952-1982, there are 0-70% response rates when 200-800 mg of vitamin E is used daily. At the NIH Conference on Peyronie's disease in 1993, Devine and Snow presented a study in which 105 patients taking oral vitamin E reported a 99% reduction in pain and a 13% reduction in penile curvature. No objective change was observed in 70% of the patients. Studies have shown that vitamin E affects reducing penile pain, and it affects penile curvature and plaque size relatively less (6, 7).

2. Colchicine

Mechanism

Colchicine is an alkaloid obtained from colchicum autumnale. It is an anti-inflammatory agent that inhibits collagen synthesis and stimulates collagenase activity. It has important effects in both the inflammatory and fibrotic stages of the disease.

Evidence

An uncontrolled study reported a slight reduction in curvature in 11%, a significant reduction in curvature in 26%, and a reduction in plaque size in 50%. However, there was no improvement in hourglass deformity and hardening. Levine reported that more than half of the more than 30 patients treated with colchicine had gastrointestinal disturbances (7, 8). Colchicine is used 2mg/day for 3-6 months in the treatment of Peyronie's disease. Studies have shown significant improvements in penile pain and curvature, with reduction or disappearance of penile plaques. Apart from gastrointestinal side effects, side effects such as fever, skin rashes, agranulocytosis, aplastic anemia, myopathy, and angioneurotic edema have also been observed (9).

Better results can be obtained when colchicine and vitamin E are used together. It has been reported to show significant improvement in plaque size and curvature, especially in early-stage disease (6, 10).

3. Phosphodiesterase Type 5 Inhibitors (PDE-5I)

Mechanism

Activation of the nitric oxide pathway by phosphodiesterase type 5 inhibitors (PDE5is) plays a role in improving erectile function, suppressing collagen synthesis, and initiating apoptosis of myofibroblasts (11).

Evidence

Long-term administration of PDE5i in animal experiments showed increased collagen and a decrease in fibroblasts

in tunica albuginea cells (12, 13). PDE5i was therefore investigated for its effects on plaque formation and remodeling in Peyronie's disease. In one study, 39 Peyronie's patients were administered daily sildenafil or vitamin E for three months. A similar reduction in plaque size was seen, but a statistically more significant improvement in pain reduction scores and erectile function was documented in the Sildenafil group compared to the vitamin E group (14). In another retrospective controlled study, 65 patients with isolated septal scars (ISS) without evidence of penile deformity were treated for six months without treatment. Follow-up and daily use of 2.5 mg tadalafil were compared. The resolution of septal scars was 10% and 69%, respectively, in the untreated and tadalafil-treated groups (15). Finally, a newer RCT, extracorporeal shock wave therapy, and a combination of tadalafil 5 mg once daily improved the erectile function score but significantly reduced penile curvature and plaque size. It was documented that it did not change significantly.

4. Carnitine

Mechanism

Acetyl-L-carnitine and propionyl-L-carnitine, a derivative of carnitine, are inhibitors of acetyl coenzyme-A that help repair damaged DNA and prevent free radical formation during cell stress (16, 17).

Evidence

It has been shown that propionyl-L-carnitine (PLC) regulates the amount of intracellular calcium and reduces penile fibrosis by controlling collagen production and fibroblast proliferation in endothelial cells (8, 18). In a study conducted by Cavallini and Biagiotti in 2001 involving 48 Peyronie's patients, patients were treated with 20 mg of tamoxifen and were given twice a day for three months. Acetyl-L-carnitine was found to be more effective than tamoxifen in reducing curvature and pain and preventing disease progression. Both drugs were found to be equally effective in reducing the amount of penile plaque size (19). In a study conducted by the same group in 2002, the combination of intralesional Verapamil (10mg per week for ten months) and PLC (2g/day for three months) was combined with tamoxifen reported to give better results compared.

5. Q-10

Mechanism

Q10; It is a lipophilic, organic, vitamin-like, and potent antioxidant found in the body (1, 20, 21). It has a role in protecting cells against ischemia, oxidative stress, and oxidative damage by polyunsaturated fatty acids. People with Peyronie's disease have inflammation and overexpression of the TGF pathway in their fibroblasts. Q10 activates Nrf2, which increases antioxidant proteins that protect against oxidative damage activated by inflammation. Nrf2 suppresses the expression of TGF-21. In addition, the increase in oxidative stress damages the tissue, and it has been said that Nrf2 can indirectly initiate cell division for this injury (21).

Evidence

Overexpression of Nrf2 in experiments with Q10, mouse liver, and embryonic fibroblast cells; Expressions of alpha-smooth muscle actin and TGF-21 were suppressed (21). In a prospective, double-blind, placebo-controlled randomized study, an improvement in curvature was observed in 54.3% of patients and a 40% reduction in plaque size; these rates were lower in the placebo group. The increase in curvature was 14.8% in Q10 and 69.5% in placebo. In erectile function, it was 51.9% versus 8.6% in placebo.2 As a result, in studies conducted; Since there is a decrease in penile curvature and plaque size and improvement in erectile function, it can be said that Q10 has a protective effect on the course of the disease (22).

6. Potassium Para-amino Benzoate (POTABA)

Mechanism

POTABA, first used for Peyronie's disease in 1959, is an anti-inflammatory and antifibrotic drug that inhibits abnormal fibroblast growth and secretion of extracellular fluid components (1, 5, 23). POTABA; It reduces fibrogenesis by increasing the oxygen uptake of the tissue and supporting the activity of monoamine oxidase, which enables the breakdown of serotonin (24).

Evidence

In a double-blind, placebo-controlled study, POTABA showed a 74.3% reduction in plaque size compared to placebo, but no difference was found in curvature and pain (22, 24). Researchers said that POTABA prevented and stabilized the degree of curvature (22, 25). It is not commonly used because it has itching, anxiety, chills, cold sweats, confusion, difficulty in concentration, and severe gastrointestinal side effects and is expensive (24, 26). It has also been reported in a study that it may cause hepatitis (27). It is taken in 4 doses of 3 grams per day, and Its use is also limited due to the high daily dose (22). For these reasons, data on the efficacy of POTABA are scarce (28).

7. Oral Treatment Methods Summary

Studies have shown that colchicine and POTABA have some severe side effects. Evidence on the effectiveness of oral treatments is insufficient, and there are few RCT studies (23, 29). In the guideline published by the EAU in 2019, it is recommended that vitamin E should not be used in patients who want to significantly reduce the curvature. According to the International Consultation on Sexual Medicine 2016 guideline (ICSM), oral treatments have been reported to be minimally beneficial or not beneficial in reducing the clinical features of Peyronie's disease; therefore, their use is not recommended (30, 31).

TOPICAL THERAPY METHODS

1. Verapamil

Mechanism

Verapamil is used as a calcium channel blocker in the treatment of Peyronie's disease. In this way, it is aimed to increase collagenase activity and to prevent the secretion of extracellular fluid proteins (32).

Evidence

Studies are continuing on the use of Verapamil, which is also used intralesional, as a topical treatment method. There are data in some studies that Verapamil does not reach the tunica albuginea (33), but dexamethasone and Verapamil applied by ionotophoresis have been shown to reduce the curvature, especially in patients with a curvature degree of less than (30, 34).

At the same time, a guideline published by the EAU in 2019 stated that topical Verapamil reduces penile curvature and plaque size (35).

2. H-100 Gel

Mechanism

H-100, topically applied for the non-surgical treatment of Peyronie's disease, it is a gel with the chemical content of Nicardipine, superoxide dismutase, and emu oil. Emu oil, rich in fatty acids, has been used as a transdermal carrier agent (36). Superoxide dismutase provides clearance of free oxygen radicals that play a role in inflammation (37). Nicardipine is a calcium channel blocker. It may also be effective in reducing glycosaminoglycan synthesis and blocking collagen production (38).

Evidence

In a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of H-100, 22 patients with acute-phase Peyronie's disease were examined. During the first three months, half of the patients received H-100, and the other half received a placebo. For the next three months, all patients received H-100. An increase in penile length (22.6%), a decrease in curvature (40.8%), and a decrease in pain level (85.7%) were observed in patients who received H-100 for six months. An increase in penile length (6.8%) was observed in patients who received a placebo for the first three months, but no improvement was observed in other parameters. Patients who started taking H-100 after taking a placebo had an increase in penile length (17.5%), a decrease in curvature (37.1%), and a decrease in pain level (40%). The treatment had side effects in only three patients, which was self-limiting skin rash. Although this study yielded positive results, due to the small size of the study, more data on H-100 are needed before routine use (39).

3. Liposomal Recombinant Human Superoxide Dismutase (Liposomal RHSD)

Mechanism

In the treatment of liposomal RHSD, a topical gel containing superoxide dismutase is applied to the patient. Theoretically, the aim is to stop the inflammatory steps as a result of superoxide dismutase breaking down free oxygen radicals and throwing them out of the body, and thus slowing down and limiting the progression of the disease.

Evidence

In placebo, controlled randomized clinical trials, 39 patients suffering from bothersome pain from Peyronie's disease were treated with liposomal RHSD and placebo, and when observed for 4-week periods, significant pain reduction was observed after 28 days compared to placebo. At the end of 56 days, 89% of the patients who were treated with liposomal RHSD had a significant reduction in their pain. Recovery in other symptoms of the disease occurred on the 84th day. Plaque consistency decreased in 38% of patients, plaque size decreased by 47%, and improved penile curvature by 5-30 degrees in 23% of patients. Liposomal RHSD treatment also reduced the rate of disease progression, which rose to 40%, to less than 10%. In conclusion, while liposomal RHSD treatment in Peyronie's disease reduced pain, it also showed improvements in other symptoms (40).

4. Transdermal Electromotive Drug Administration (EMDA)

In this method, also known as iontophoresis, the aim is to deliver the drug to be applied to the tunica albuginea tissue in the targeted area. Transdermal transfer of the therapeutic agent is achieved by electrokinetic transport of charged molecules (41). There are also studies indicating that this method is more effective in reducing erectile pain than intralesional applied dexamethasone and Verapamil (42).

5. Topical Treatment Methods Summary

Research continues on the adequacy of topical treatment methods. Although there are studies showing that it can be effective in reducing curvature and pain, there is no topical treatment method approved by the FDA yet. Although there are studies showing that topical Verapamil and EMDA may work, as stated in the EAU guidelines, there is no data to provide a definitive solution.

TRACTION AND VACUUM TREATMENTS

1. Penile Traction Therapy

Mechanism

This treatment is performed using the penile traction device (PTD). The PTT works by holding the penis in the cradle and subjecting it to gentle and gradual traction forces that can be achieved by adding dynamic rods and small metal extensions to the cradle frame every few weeks (43).

Evidence

In in vitro studies, it has been determined that the secretion of matrix metalloproteinase-8 (MMP-8), which has an effect on collagen degradation, increases significantly while it is under the effect of traction in penile plaque tunica albuginea cells. PTT plays a role in the rearrangement of these collagen fibrils and in reducing the activity of myofibroblast cells.

In men with early-stage Peyronie's disease, when the traction device was used for at least 4 hours a day for a total of 3-6 months, an increase in mean penile length and a 14° decrease in mean erect penile curvature were observed (44). When PTT was applied to Peyronie's patients in a stable period for an average of five hours per day for six months, approximately 17 degrees (33%) improvement in penile curvature was observed. An increase in erect penis circumference and flaccid penile length has been observed (45). In men with at least 12 months of Peyronie's disease and pre-existing curvature below 50°, penile curvature decreased from 31° to 27° on average as a result of using the traction device for 5-9 hours a day has fallen. As a result, no significant improvement in penile curvature was observed (46). In acute phase Peyronie's patients, a decrease of approximately 20 degrees in penile curvature, a significant increase in erectile function, and a significant improvement in penile pain were observed when PTT was applied between 6-9 hours daily for a minimum of 6 months. In 40% of the patients, the need for surgery disappeared (47).

In a randomized controlled study using a new device called "Penimaster PRO" in men with stable Peyronie's disease and a minimum of 45 degrees penile curvature, after 3-8 hours of PTT per day for 12 weeks, an improvement of approximately 31 degrees was observed in penile curvature and the daily application time was increased (48).

In men with stable Peyronie's disease and a minimum of 30 degrees penile curvature, "RestoreX" a new traction device, was applied daily for 30-90 minutes for three months, and a decrease of approximately 12 degrees in penile curvature and an average increase of 1.5 cm in penile length were observed (49).

2. Vacuum Erection Device (VED)

Mechanism

VED treatment is performed with devices that create negative pressure to induce events such as retrograde venous blood flow, enlargement of the cavernous sinuses, and increased arterial blood flow.

Evidence

As a result of the use of VED 2 times a day (10 minutes), reduction in penile pain, approximately 0.5 cm elongation in erect penis length, and 5-25 degree decrease in curvature were observed (50).

An average of 16 degrees improvement in penile curvature was seen in men who used VEDs for 10-minute periods twice a day for 11 months. In addition, it was understood that the improvement was not related to the patient's age and that the treatment gave better results in patients with a high degree of curvature (51).

3. Traction and Vacuum Therapies Summary:

In recent years, VED and PTT have received great attention as a new non-surgical treatment option for Peyronie's disease. These seemingly safe and well-tolerated non-surgical treatments require a great deal of patient compliance and commitment. Current literature suggests that selected cases may benefit from a conservative approach with PTT and VED, resulting in a reduction in penile deformity.

Evidence for PTT is limited. However, while some studies did not show significant improvement, several studies have shown a potential benefit of PTT when used as monotherapy or in combination with oral medications, intralesional injections, or surgery, with significant improvement in curvature reduction, erectile function, and penile pain. In addition, PTT was found to be more effective in acute phase Peyronie's patients, and some patients did not require surgery. Future studies will identify key points, including issues of patient compliance and duration of use. Although there are not many studies on VED treatment, a significant improvement was observed in Peyronie's patients, and some patients did not require surgical intervention. More studies on this treatment are needed.

SHOCK WAVE THERAPY

1. Extracorporeal Shock Therapy (ESWT)

Mechanism

Although the mechanism of action of ESWT has not yet been clearly revealed, it is a form of treatment that aims at the effect of acoustic pressure waves sent from the outside to the body, defines the energy size per mm^2, and its density is measured in mJ/mm^2.

Evidence

ESWT was first described in 1989 by Bellorofonte C et al. Although it was applied to patients with cavernous fibrosis due to Peyronie's disease, it was applied by Butz and Teichert in 1996 considering that it would be a well-tolerated method. In the study, 52 patients were used and followed up for nine months. 83% reduction in pain, 40% improvement in curvatures, and 48% improvement in sexual functions were observed. If we look at the recent studies that measured the effectiveness of ESWT in Peyronie's disease; We consider one as randomized without placebo/sham group, three as RCT, and the rest as observational studies. In the studies, treatment methods were applied once a week for 4-6 weeks with an energy density of 0.25-0.29 mJ/mm^2 and the number of pulses varying between 2000-3000. Attention was paid to the fact that the patients included in the study were stable for more than six months without any previous treatment, and at least three months old who received oral treatment before and failed. Hatzichristodoulou et al. (52), while statistically similar percentages were found between the change of curvature and plaque size in the active treatment group and the sham group in the RCT, it was observed that the ESWT treatment group showed greater improvement in the mean pain over VAS than the placebo/sham group. In addition, in this study, 85% reduction in pain was observed in the ESWT group, while the pain reduction was 48% in the placebo/sham group. In 2009 Palmieri et al. (53) study, 100 patients with Peyronie's disease under 12 months were divided into control group and ESWT. The age range was 18-75 years, and the patients were followed for 12-24 weeks in terms of painful erection, plaque size, erectile function, penile curvature, and quality of life. There was an insignificant reduction in curvature and plaque size in the ESWT group, while a small increase was found in the placebo/sham group. In this study, the mean pain over VAS was also looked at, and it was observed that ESWT from the two groups provided more improvement than the placebo/sham group. In 2004, Hauck et al. in the meta-analysis of; It has been stated that the success in ESWT is in very wide ranges such as 0-74% for penile curvature, 0-58% for plaque size, 12-75% for sexual function and 56-100% for penile pain. In the meta-analysis; It was stated that ESWT treatment did not statistically change the degree of curvature, plaque size, and erection score; only after treatment it reduced pain from 37% to 9%, and ESWT application statistically reduced penile pain (54).

2. Shock Wave Therapy Summary

ESWT is a treatment based on sending shock waves from outside to the body. ESWT experiments showed that the degree of curvature, plaque size, and pain decreased, while the erection score increased when first performed. However, in the experiments conducted in the following years, the degree of curvature does not significantly change plaque size, erection score but significantly reduces pain.

PLAQUE INJECTION TREATMENTS

1. Interferon-Alfa-2B

Mechanism

Interferons are low molecular weight proteins and glycoproteins responsible for immunoregulation that can

be synthesized endogenously in the human body. In vitro studies have shown that interferon-alpha 2b (INF-α-2b) suppresses fibroblast proliferation with its antifibrotic effect, decreases collagen and extracellular matrix production in fibroblast cells, and increases collagenase production (51)

Evidence

In the first study, plaque softening, 50% reduction in curvature, and total pain relief were reported. A 1x10-unit dose of INF-α-2b was injected subcutaneously into the plates in a later study. Post-injection pain relief has been reported, with a reduction in 28% of non-calcified or minimally calcified plaques size. Following this treatment, the amount of the drug was increased ($3x10^6$ unit dose IFN-α-2b), and the same treatment was applied, resulting in no reduction in plaque and 82% of side effects were observed. In another study, pain relief, reduction in penile curvature, plaque softening, and reduction in plaque size were reported in patients who received intralesional saline as control and 1.5×10^6 units of IFN-α-2b injection as a treatment (55).

In the most scientifically finalized study of the efficacy of intralesional INF-α-2b in Peyronie's disease, 5×10^6 INF-α-2b was administered to patients. Penile curvature, plaque characteristics (size, density), penile pain, erectile function, and penile hemodynamic parameters were evaluated in the study. At the end of this study, mean penile curvature decreased from 49.9 degrees to 36.4 degrees, mean plaque size reduced by 4.8 cm to 2.2, mean plaque density decreased from 2.07 to 1.84, pain resolution was 67.7% of patients a decrease in of them, and an increase in penile blood flow was observed. However, no difference in mean erectile function was observed. These results provide the best evidence of efficacy to support the use of intralesional interferon in patients.

Taking an overdose of IFN-α-2b has side effects such as flu-like syndrome, anorexia, rashes, hypotension, and cardiac arrhythmia. The use of analgesic drugs before intralesional injection of INF-α-2b reduces these side effects (9).

2. Clostridium Collagenase Histolicum (CCh)

Mechanism

CCh, which is a mixture of AUX-I and AUX-II enzymes produced by Clostridium histolyticum bacteria, both reduces the abnormal expression of type 1 and 3 collagens by enzymatically disrupting the triple helix structure in pathological collagen plaques in Peyronie's disease and destroys these plaques that cause PD curvature.

This enzyme does not act on arteries, nerves, and surrounding connective tissues containing collagen type 4. 54 The efficacy of collagenase treatment on plaque tissue was discovered in 2013 with the phase 3 IMPRESS trial and in vitro studies (56). As a result, CCh, which has demonstrated efficacy and safety in clinical trials for the conservative treatment of Peyronie's disease, has become the only FDA-approved treatment (57).

Evidence

A double-blind, randomized, placebo-controlled study involving 418 patients was completed in 4 treatment cycles of 2 injections 24-72 hours apart. Curvature, erectile function improved, pain, and plaque size decreased (58). In a retrospective cohort study of 918 patients treated between April 2014 and March 2018 and collected from 5 different institutions, penile curvature decreased from an average of 48.2 degrees before treatment to 32.9 degrees after treatment, and it was determined that there was an improvement of 30.1% compared to the baseline. 68.7% of patients had 20% or more improvement in penile curvature. In 502 patients who completed four or more cycles of treatment, penile curvature decreased from an average of 49.7 degrees to 32.7 degrees and showed a 33% improvement from baseline. Of these patients, 74.4% experienced 20% or greater improvement in curvature. Treatment complications developed in 9% of the patients. The number of CCh cycles received was a predictor of curvature improvement. This multi-institutional meta-analysis confirms the safety and efficacy of CCh therapy in men with Peyronie's disease (59). Improvements in penile curvature and Peyronie's Disease Questionnaire score continued without additional CCh therapy up to 5 years after intralesional CCh therapy, and no problems were identified (60)

Most adverse events associated with intralesional CCh therapy (hematoma, bruising, pain, and swelling in the penis) were mild or moderate and resolved without intervention. In addition, the use of CCH was not associated with penile shortening (61). In the sexual function questionnaire, in which a total of 24 couples participated, the satisfaction of the patient and the female sexual partner with the treatment was 67% and 71%, respectively. As a result, CCH treatment provides a significant benefit to a couple's sexual health. Treatment is associated with increased partner satisfaction and increased ability to have sexual intercourse (62, 63).

3. Verapamil

Mechanism

Verapamil, a calcium channel blocker, was first described in 1994 by Levine et al. it has been shown that it can be used in Peyronie's treatment because it changes the metabolism of fibroblasts, inhibits calcium-dependent extracellular collagen transport, and increases collagenase activity (64).

Evidence

In a meta-analysis of seven different studies, intralesional injection of Verapamil significantly improved sexual function ($p < 0.0005$) and penile curvature ($p < 0.005$) in patients. There is an imprecise but significant reduction in pain after the treatment, but less effect on plaque size ($p > .05$) (65). In a prospective, single-blind, randomized study, the use of Verapamil in Peyronie's disease showed improvement in penile curvature and reduction in plaque size (66).

Verapamil injection is clinically safe for patients with Peyronie's disease and appears to cause a rapid and beneficial effect in patients for reducing plaque size. Intralesional injection of Verapamil for Peyronie's disease can reduce pain, reduce penile curvature, and improve sexual function (32).

4. Nicardipine

Mechanism

Following the success of Verapamil used in the treatment of Peyronie's disease, universities began to conduct randomized placebo-controlled studies on the potency of Nicardipin-a dihydropyridine based on this treatment (calcium channel blocker). Compared with Verapamil, the possibility of its high efficacy in reducing extracellular substance synthesis between the acute and chronic phases of Peyronie's disease was considered.

Evidence

The study included 74 randomly selected men. Patients are given Nicardipine (10 mg in 10 ml of distilled water) or 10 ml of normal saline every two weeks for ten weeks (6 doses in total). The clinical outcomes evaluated were pain during erection, plaque size, erectile function (according to the international index of erectile function 5 [IIEF-5]), and penile curvature.

While the pain was more pronounced in the nicardipine group, it decreased in both groups (p: 0.019). At 48 weeks, significant improvements in mean IIEF-5 score and plaque size were noted in the nicardipine group only ($p<0.0001$ and p: 0.0004, respectively). Penile slope improved significantly and to a similar extent in both groups at the end of the study, consistent with previous Verapamil studies (67, 68).

5. Intraplaque Injection Therapy Summary

As a result of studies with intralesional IFN- α -2b, it is suitable for use in treatment, as the use of the right amount shows a significant improvement in patients. Intralesional CCh and intralesional verapamil treatment can be used clinically in Peyronie's disease as it improves curvature, erectile function and reduces pain and plaque size. As a result of the study, the authors concluded that Nicardipine is an alternative and effective option for patients with transitional phase Peyronie's disease. Nevertheless, it is thought that the search for a non-surgical treatment for Peyronie's disease should continue.

EXPERIMENTAL TREATMENTS

1. Stem Cell Therapy

Mechanism

Adipose tissue-derived regenerative cell (ADSC or SVF) treatment is based on enzymatic reactions of approximately 50 cc of fat taken from the sides of the penis. This fluid, which decreases as a result of enzymatic reactions, is injected into the body from the right and left sides of the penis. In Peyronie's disease, we inject it into the plaque in the penis. However, injecting this liquid alone is not enough. At least six sessions of shock wave therapy should also follow this process because shock wave therapy stimulates stem cells and activates them.

Of course, this treatment is not only used in Peyronie's patients. It is also generally used in patients with erectile dysfunction.

Evidence

In animal experiments, TGF-ß1 was given to rats treated with ADSC. After this situation, it was noticed that the development of Peyronie's disease was prevented. In addition, it was determined that elastic tissue and type 3 collagen tissue decreased.68 In an article published in 2016, a table was given as a result of the application of ADSC and shock wave together. According to this table, the penile hardness of 7 of 11 participants increased. One of the remaining four people already had a normal erection.

The other 3 had an erection that would allow them to have sexual intercourse, although it was not normal. In total, the degree of hardening score increased from 2.7 to 3.5 on average (69).

2. Experimental Treatments Summary

Stem cell therapy is known as a complicated and new treatment method that is applied with the support of liquid injection and then shock wave therapy. In experiments, it was noted that it prevented the development of Peyronie's disease and reduced the production of type 3 collagen. It has been found to increase the degree of hardening.

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ORIGINAL ARTICLE

Roles of the Ratio of C-Reactive Protein to Serum and Pericardial Fluid Albumin Levels in Predicting in-Hospital Mortality in Patients Undergoing Pericardiocentesis

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Abstract

Background: Pericardial effusions occur due to excessive fluid accumulation in the pericardial space. In effusions not responding to medical treatment, pericardiocentesis is an important method of treatment affecting prognosis. CRP/albumin ratios have been found to be associated with prognosis in conditions such as cardiac failure, sepsis, malignancy, and the routinely available parameters used for the prognosis prediction of the patients who underwent pericardiocentesis are limited. This study aimed to examine the usability of CRP/albumin and CRP/pericardial fluid albumin (CRP/pf-albumin) ratios as predictors for in-hospital mortality of patients who underwent surgery pericardiocentesis.

Methods: This study included 54 patients (25 females and 29 males). All patients underwent pericardiocentesis.

Results: The average age was 67±14 years. When the groups were compared with each other, CRP, CRP/albumin ratio and CRP/pf-Albumin ratio were higher in the in-hospital mortality group compared to the group discharged with recovery [19 (14-25), 6.3 (1-30), p<0.001; 4.27 (3.87-12.02), 1.9 (0.24-10.38), p<0.001; 7 (6.25-13.59), 2.5 (0.28-12.22), p<0.001, respectively]. In the univariate logistic regression analysis, CRP (odds ratio [OR]: 0.821, P: 0.004, 95.0% confidence interval [CI]: 0.918-1.049), CRP/albumin ratio (OR: 0.600, P: 0.011, 95.0% CI: 0.406-0.888) and CRP/pf-Albumin ratio (OR: 0.608, P: 0.004, 95.0% CI: 0.431-0.856) was found to be associated with in-hospital mortality in patients who underwent pericardiocentesis.

Conclusion: For the first time in the literature, we demonstrated that CRP/albumin and CRP/pf-Albumin ratios are associated with in-hospital mortalities in patients who underwent pericardiocentesis, irrespective of the etiology.

Keywords: C-Reactive Protein/Albumin Ratio, Pericardial Fluid Albumin, Mortality, Hospitalized Patients.

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INTRODUCTION

Pericardial fluid is the serous fluid released from the pericardium surrounding the heart to the pericardial space. It helps the heart function more efficiently by holding it in place within the chest cavity and preventing it from rubbing against other tissues. The pericardial sac contains approximately 10-50 mL fluid, and the increased secretion or impaired reabsorption of the fluid results in moderate to severe effusions. While the mild fluid accumulations respond to medical treatment, severe fluid accumulations lead to cardiac dysfunction, and pericardiocentesis is the most beneficial therapeutic procedure unless clinically contraindicated.[1,2]

Pericardial effusions cause clinical signs in patients based on their onset type and size. While they may be asymptomatic, fatal clinical presentations may also be observed. Viral, bacterial, neoplastic, autoimmune, and iatrogenic causes are the most common reasons in the clinical practice; the underlying etiology and the size of the fluid accumulation is associated with the prognosis, and there are no clear biochemical parameters recommended by the guidelines, which can be used for in-hospital mortality.[3]

Being functional in many clinical conditions, albumin and C-reactive protein (CRP) can provide information on inflammatory processes. Several studies have shown that increased CRP levels provide information on prognosis in conditions such as malignancy, stroke, coronary artery disease (CAD), and heart failure (HF).[4-6] Similarly, albumin levels have been documented to provide information on inflammatory conditions.[7] In another study, the CRP-to-albumin ratio was shown to be an independent risk factor for mortality in patients with traumatic brain injury (TBI).[8]

On the contrary, it is not clear whether albumin ratios in the pericardial fluid can be used to predict the patients who underwent pericardiocentesis. Using a combination of parameters rather than individual parameters may provide more information.

Our study aimed to examine the usability of CRP-to-albumin and CRP-to-pericardial fluid albumin ratios in predicting in-hospital mortality in patients who underwent pericardiocentesis.

MATERIALS AND METHOD

Study Population and Data Collection

Our retrospective study enrolled 54 patients who consecutively underwent pericardiocentesis from January 2013 to December 2020 in our university hospital. Patients included in the study were those who did not respond to medical treatment with moderate-large pericardial effusion. The study consisted of patients who underwent pericardiocentesis for the first time. Patients who had to undergo surgical treatment due to pericardiocentesis failure, any contraindication of pericardiocentesis, constrictive pericarditis, and patients under 18 years of age were excluded from the study.

For biochemical parameters, blood samples taken from the upper extremity peripheral venous route and pericardial fluid samples collected during pericardiocentesis were studied within the same timeframe, and data for the variables were obtained. Hemogram, CRP, complete blood count (CBC), pericardial fluid albumin, and lactate dehydrogenase (LDH) tests were studied for all patients. Demographic information, clinical results, biochemical and echocardiographic data of the patients were obtained from the hospital records, and all data were compared between the groups.

Patients who were discharged with recovery were placed in Group 1, and patients who died during hospitalization were placed in Group 2.

This study was approved by the Çanakkale Onsekiz Mart University ethics committee of the hospital in which it took place in line with the recommendations of the Declaration of Helsinki (Date: 09.12.2020 Decision no: 2020-14).

Pericardiocentesis procedure and definitions

Any pericardial effusion smaller than 10 mm is defined as minimal effusions between 10 and 20 mm are defined as moderate, and effusions greater than 20 mm are defined as large effusion. In all patients, it was performed by Seldinger technique using 6F sheath at an angle of 30^0 towards the left shoulder under fluoroscopy in a coronary angiography laboratory setting.[9] 500 ml fluid was discharged from all patients in the laboratory. After successful pericardiocentesis, the pigtail catheter was left in the pericardial cavity for drainage. The catheter was removed when the control echocardiography showed effusion smaller than 10 mm.

Echocardiographic assessment

Pre- and post-procedural echocardiographic assessments were performed using a 2.5-Mhz probe in the Vivid 7 Pro device (GE, Norway). LVEF values were calculated using modified Simpson's rule. TTE examinations were performed in line with the imaging guidelines recommended by the US and EU associations.[10]

Statistical analysis

SPSS 20.0 (SPSS Inc, Chicago, IL, USA) software was used for the statistical analysis. The distribution normality of the parameters was analyzed using the Kolmogorov-Smirnov test with continuous variables being expressed as mean ± standard deviation and categorical variables being expressed as percentage and number. Independent samples t-test and Mann-Whitney U test were used for the comparison of normally and non-normally distributed parameters, respectively. A chi-squared test was used for the comparison of odds ratios for categorical variables.

Univariate logistic regression analysis was used to assess the association of biochemical and demographic parameters with in-hospital mortality in patients who underwent pericardiocentesis.

Standardized beta coefficients were calculated with 95% confidence intervals. Receiver operating characteristic (ROC) analysis was performed to determine the ability of CRP/albumin and CRP/pf-Albumin ratios to predict in-hospital mortality. P values under 0.05 were considered to be statistically significant.

RESULTS

Our study consisted of 54 patients and two groups. No life-threatening complication was observed during the pericardiocentesis procedure. The mean age of the patients was 67.87±14.91. Table 1 shows the intergroup comparisons. No statistical difference was detected between the groups in terms of LDH, pericardial fluid lactate dehydrogenase (pf-LDH), albumin, and pf-Albumin values (p>0.05 for all) (Table 1 and 2).

Table 1. Demographic, clinical and laboratory features of the patients

Variables	All patients (n=54)	Discharged patients (n=49)	In hospital death (n=5)	P
Age (years)	67.87±14.91	67.51±14.12	71.40±23.19	0.583
Female n (%)	25(46)	24(49)	1(20)	0.223
HT n (%)	15(28)	14(29)	1(20)	0.690
DM n (%)	13(20)	12(25)	1(20)	0.827
LVEF (%)	51.17±8.17	51.47±7.96	48.20±10.54	0.399
Systolic blood pressure (mmHg)	131.11±9.37	131.47±9.20	127.60±11.43	0.384
Diastolic blood pressure (mmHg)	75.43±9.68	75.51±10.03	74.60±5.68	0.844
Heart rate (beats/min)	90.8±85.4	90.86±89.56	80.4±15.3	0.788
Laboratory values				
Glucose (mg/dl)	118.46±35.78	117.72±36.16	125.68±34.68	0.640
Creatinine (mg/dL)	1.22±0.73	1.19±0.67	1.44±1.27	0.487
Sodium (mEq/L)	140.81±6.97	141.06±7.14	138.40±4.82	0.421
Potassium (mEq/L)	4.25±0.70	4.22±0.66	4.57±1.09	0.301
TSH (mU/L)	2.31±1.59	2.30±1.62	2.32±1.46	0.980
Alanine aminotransferase (U/L)	38.48±55.51	39.68±58.11	26.76±10.70	0.625
Aspartate aminotransferase (U/L)	33.24±31.15	34.08±32.44	25.00±11.57	0.540
Calcium (mg/dl)	9.07±0.52	9.10±0.51	8.74±0.57	0.140
LDH (U/L)	321.63±189.70	317.69±187.04	360.20±234.44	0.638
LDH of Fluid (U/L)	575.48±880.576	599.57±929.832	339.40±210.165	0.534
WBC count, ($x10^3$ μL)	9.93±5.28	10.12±5.47	8.04±2.55	0.407
Hemoglobin g/dL	13.66±13.88	13.58±14.32	14.41±9.58	0.901
Trombosit count ($x10^3$ μL)	276.55±140.03	282.357±142.79	219.700±103.26	0.345
Neutrophil count, ($\times 10^3$ /L)	7.76±4.78	7.79±4.89	7.50±3.94	0.898
Lymphocyte count ($\times 10^3$ /L)	1.38±0.93	1.39±0.93	1.21±1.05	0.683

DM: Diabetes mellitus, HT: Hypertension, LVEF: Left ventricle ejection fraction, TSH: Thyroid Stimulating Hormone, LDH: Lactate dehydrogenase, CRP: C-Reactive protein

Table 2. C-reactive protein and albumin levels of cardiac tamponade patients

Variables	All patients (n=54)	Discharged patients (n=49)	In hospital death (n=5)	P
Albumin (g/dl)	3.58±0.52	3.60±0.49	3.48±0.87	0.631
Albumin of Fluid (g/dl)	2.80±0.57	2.85±0.57	2.34±0.37	0.062
CRP (mg/L)	7.49(1-30)	6.3(1-30)	19(14-25)	<0.001
CRP/albumin ratio	2.17(0.24-12.02)	1.9(0.24-10.38)	4.27(3.87-12.02)	<0.001
CRP/Albumin of Fluid ratio	2.68(0.28-13.59)	2.5(0.28-12.22)	7(6.25-13.59)	<0.001

CRP: C-Reactive Protein

CRP value was found to be more statistically significant in group 2 patients (p<0.001) (Table 2). Similarly, CRP/albumin ratio and CRP/pf-Albumin ratio were found to be numerically and statistically more significant in group 2 patients (p< 0.001 for both) (Table 2). Five patients had a lung cancer diagnosis, one had breast cancer, one had malignant neoplasm, one had larynx cancer, and five had chronic renal failure (Table 3).

Table 3. Etiology of pericardial effusion

Cause	Discharged patients (n=49)	In hospital death (n=5)	Total (n=54)
Breast CA	1	0	1
Lung CA	4	1	5
Larync CA	1	0	1
Malignant neoplasm	1	0	1
Chronic renal failure	4	1	5
Idiopathic	38	3	41

CA: Cancer

Table 4 shows the association between the in-hospital mortality and CRP (odds ratio [OR]: 0.821, P: 0.004, 95.0% confidence interval [CI]: 0.918-1.049), CRP/albumin ratio (OR: 0.600, P: 0.011, 95.0% CI: 0.406-0.888) and CRP/pf-Albumin ratio (OR: 0.608, P: 0.004, 95.0% CI: 0.431-0.856) in patients who underwent pericardiocentesis.

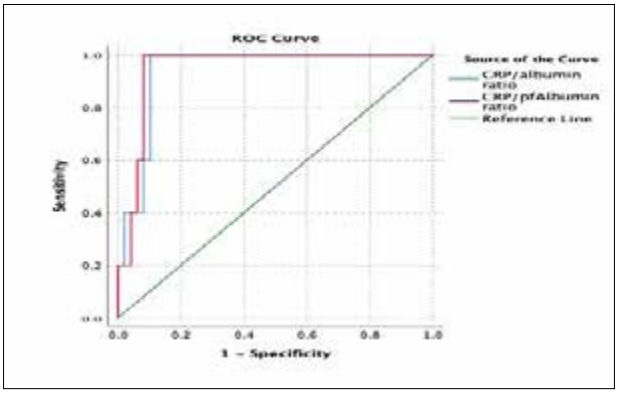
Table 4. Univariate regression analysis to determine in-hospital mortality

	Univariate		
Variables	P	OR	95% CI
Age (years)	0.577	0.981	0.918-1.049
Cancer	0.733	1.500	0.146-15.461
LDH (U/L)	0.633	0.999	0.995-1.003
LDH of Fluid (U/L)	0.552	1.001	0.998-1.003
Albumin (g/dl)	0.625	1.540	0.273-8.679
Albumin of Fluid (g/dl)	0.078	4.531	0.843-24.353
CRP (mg/L)	0.004	0.821	0.716-0.940
CRP/albumin ratio	0.011	0.600	0.406-0.888
CRP/Albumin of Fluid ratio	0.004	0.608	0.431-0.856

CI: Confidence interval, OR: Odds ratio, Abbreviations in Table 1

Receiver operating characteristic (ROC) curve analysis indicates that a CRP/albumin ratio higher than 3.8 may predict in-hospital mortality. [(p<0.001) (100% sensitivity and 90% specificity, 0.939 area under the curve 95% CI: 0.872-1.005)]. Similarly, it was observed that CRP/pf-Albumin ratio might predict in-hospital mortality when it is higher than the optimal cutoff value 6. [(p<0.001) (100% sensitivity and 92% specificity, 0.947 area under the curve 95% CI: 0.887-1.007)] (Figure 1).

Figure 1. Receiver operator characteristic curve of C-reactive protein/albumin and C-reactive protein/ pericardial fluid Albumin ratio to predict mortality in patients undergoing pericardiocentesis



DISCUSSION

Pericardiocentesis is a valuable treatment procedure for diagnosing and treating effusions causing tamponade or serious effusions regardless of the etiology. Since the first time, it was described increasing experiences and using fluoroscopic and echocardiographic devices more frequently have increased the safety and success of the procedure.[11]

As there is no randomized trial on pericardiocentesis, data on prognosis is limited. As far as is known, the prognosis is excellent in the absence of neoplastic disease and in cases where viral pathogens are implicated in the etiology.[12] In our study, eight patients had malignancy with no association being observed with mortality in the short term. As can be seen, since the clinical parameters are not always sufficient, additional parameters are needed. Determining and using laboratory parameters in addition to clinical parameters for the prognosis of pericardiocentesis patients will be effective in predicting prognosis.

Several studies investigated and proved the usability of increased CRP levels. Being an acute phase reactant, it reaches plasma peak levels within 48 hours after being released from the liver.[13,14] While high CRP levels were shown to be associated with metabolic disorder, and

another study has associated the high CRP levels with poor negative outcomes in coronary artery disease.[15] Additionally, they were found to be associated with mortality in patients with heart failure.[16] Similar to the literature, increased CRP levels were observed to be associated with short-term in-hospital mortality in patients who underwent pericardiocentesis in our study.

Similar to CRP, another useful parameter is albumin, and recent studies have associated low CRP/albumin ratios with poor prognosis in patients with heart failure and cancer.[17,18] In a long-term follow-up study such as 5 years, in which 212 pancreatic cancer patients were examined, it was shown that CRP values could be used for survival. In another meta-analysis, pre-treatment CRP/albumin ratio is a prognostic marker of poor overall survival (OS) and CSS in patients with gastric cancer (GC). In addition, high levels of CRP/albumin ratio are associated with clinicopathological features reflecting tumor progression.[19,20] Regardless of the underlying specific etiology, CRP/albumin ratio was a decisive parameter in predicting the in-hospital mortality in patients who underwent pericardiocentesis in our study. Additionally, in the comparison of ROC curves, CRP/pf-albumin ratio was a more specific parameter than CRP/albumin ratio in predicting in-hospital mortality.

Moreover, studies have shown that serum LDH levels are a strong indicator of mortality in cancer patients.[21] In our study, contrary to the literature, serum, and pericardial fluid LDH and albumin levels were not useful in predicting in-hospital mortality in patients who underwent pericardiocentesis. That differece might have been caused by the small number of patients and mixed study groups in our study.

Our study had some limitations. Firstly, it was a single-center study with a small number of patients. Secondly, as it was a retrospective study, we do not have information on the long-term usability of the results obtained in patients discharged with recovery. Prospective and multicenter studies are needed to use the study results globally.

For the first time in the literature, we demonstrated that CRP/albumin and CRP/pf-Albumin ratios are associated with in-hospital mortalities after pericardiocentesis, a life-saving procedure in severe pericardial effusions. We believe that this laboratory test which is easy to calculate, may be useful in the risk classification of the patients who underwent pericardiocentesis.

Declarations

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

This study was approved by the Çanakkale Onsekiz Mart University ethics committee of the hospital in which it took place in line with the recommendations of the Declaration of Helsinki (Date: 09.12.2020 Decision no: 2020-14).

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ORIGINAL ARTICLE

Low Platelet Level May be a Predictor for Mortality in Adult Patients with Common Variable Immune Deficiency

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Abstract

Background: Common variable immunodeficiency (CVID) is the most common symptomatic immunodeficiency in adults. We, therefore, aimed to reveal mortality rates, causes of mortality in CVID patients, as well as demographic and clinical characteristics and differences of survived and dead CVID patients

Methods: The study group included 50 patients [(Female: 23 (46%), Male: 27 (54%)] with CVID, who were followed up on a regular basis for a period of ten years (115.18 ± 80.74 months).

Results: Diagnostic delay was 84 (0-360) months, and the mean follow-up time was 115.18 ± 80.74 months. The most common clinical presenting complaints were frequent and recurrent infections and pneumonia. At diagnosis, serum IgG levels were 1.72 (0.33 – 6.90) g/L. The overall survival rate of the patients during the follow-up time was 88%. As a result of univariate Cox regression analysis, platelet count was determined to be an independent risk factor for mortality in CVID patients (Hazard ratio, HR: 0.990, 95% confidence interval, CI: 981-0.999, p: 0.025). When the patients were classified according to mean platelet counts (platelets < 207770/mm3 and platelets > 207770/mm3), the mortality rate in the patient group with platelets < 207770/mm3 was determined to be statistically significantly higher compared to the patient group with platelets > 207770/mm3 (log-rank: 0.013).

Conclusions: Clinicians dealing with this patient group should remember that immune dysregulation and low platelet count are independent risk factors for mortality and they should remarkably follow up patients with low platelet count closely.

Keywords: Platelets, Common Variable Immune Deficiency, Mortality.

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INTRODUCTION

Common variable immunodeficiency (CVID) is the most common symptomatic immunodeficiency in adults (1). The expression "variable" included in the name defines the heterogeneity of manifestations. The patients suffer from frequent and recurrent infections and disorders affecting several organs and systems, including chronic pulmonary disease, immune dysregulation, autoimmunity, lymphoproliferation, granulomatous diseases, and tendency to malignancies. Diagnosis of CVID is established by low levels of serum IgG together with low levels of IgM and/or IgA, poor vaccine response, and exclusion of secondary causes that may lead to immunodeficiency (2, 3). Its prevalence is considered to be between 1:25.000 and 1:50.000 (4). Although CVID may develop at any age, its findings peak at childhood and early adulthood (5). Due to insufficient awareness of physicians on this issue and reasons such as consideration of primary immunodeficiencies as childhood diseases, the diagnostic delay is, unfortunately, common (6). CVID patients have increased mortality compared to the normal population because of infectious and non-infectious complications (7). In several studies, CVID-related mortality has been shown to vary between 15% to 29% (5, 7, 8). Owing to the reduction of mortality caused by infections with immunoglobulin replacement therapy (IGRT), chronic complications such as chronic pulmonary diseases and malignancies have become significant causes of mortality (9). In previous studies, lymphoid malignancies and autoimmunity have been independent risk factor for mortality and emphasized that autoimmune cytopenia is associated with increased prevalence of bronchiectasis, morbidity, and mortality (10, 11). Thus, the demonstration of risk factors and causes of mortality in this patient group is crucial for both diagnosis of the patients and the treatment of complications.

Therefore, we aimed to reveal mortality rates, causes of mortality in CVID patients who were being followed-up in our clinic, demographic and clinical characteristics and differences of survived and dead CVID patients, and the effect of platelet counts on mortality in these patients.

MATERIALS AND METHODS

The study group included 50 patients with CVID who were followed up on a regular basis for a period of ten years (115.18 ± 80.74 months). Diagnosis of CVID was made according to updated diagnostic criteria of ESID (European Society for Immunodeficiencies) (3). In that cross-sectional study, patient records of who were being followed up with a diagnosis of CVID between 2010 and 2020 were reviewed. Patients' demographic data (including current age, gender, age at diagnosis, diagnostic delay, consanguinity, smoking status, type of immunoglobulin replacement therapy, the status of prophylactic antibiotic use) and clinical characteristics at diagnosis (presence of severe lymphopenia, presence of bronchiectasis, presence of splenomegaly, spirometry results, complete blood count parameters, serum immunoglobulin levels, and peripheral lymphocyte subsets) were obtained from their files. The lymphocyte count <1000 cells/mm^3 was considered severe lymphopenia.

Complete blood count was measured with Sheath reagent by Abbott Cell Dyn 3700 series (Chicago, USA). Quantitative determination of serum IgG, IgM, IgA, and IgE was made by means of particle-enhanced immunonephelometry using the Siemens BN II/ BN ProSpec system (Erlangen, Germany). Peripheral blood lymphocyte subsets were measured using the BD FACS Canto II 8-color configuration flow cytometer system (New Jersey, USA) with fluorescently labeled antibodies.

Spirometric measurements were obtained using a common protocol with the nSpire ZAN 100 spirometer. Three maneuvers were performed, although additional tests may be needed if one or more of the curves are unacceptable. The forced expiratory volume in one second (FEV1), the ratio of FEV1/FVC (forced vital capacity), peak expiratory flow (PEF), and mean expiratory flow 25%-75% of predicted values for similar age, sex, race, and height were recorded.

The study protocol was approved by the Necmettin Erbakan University Meram Medical Faculty Ethics Committee (Date: 03.04.2020 – No: 2020/2401). This study was performed according to the ethical standards laid down Declaration of Helsinki and its later amendments. The authors carried out no animal or human studies for this article.

Statistical analysis was performed with IBM SPSS Statistics Version 22 software package. Normally distributed parameters were presented as mean ± standard deviation, and data that is not normally distributed were expressed as median (minimum-maximum). While Pearson correlation analysis was used for normally distributed parameters,

Spearman rank correlation analysis was used for non-parametric variables. Descriptive data were presented as frequencies and percentages and compared using the Chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exacts, or Chi-square tests where appropriate. Binomial logistic regression analysis was performed to determine independent predictors for mortality. To determine independent predictors for mortality Cox regression analysis and Kaplan Meiers test were performed.

RESULTS

Fifty CVID patients [(Female: 23 (46%), Male: 27 (54%)] were included in the study. Of the study population, the median age was 37 (23-67) years, and the age at diagnosis was 27.94 ± 13.64 years. The diagnostic delay was 84 (0-360) months, and the mean follow-up time was 115.18 ± 80.74 months. The most common clinical presenting complaints were frequent and recurrent infections and pneumonia.

Of the patients, 30% had severe lymphopenia, 56% splenomegaly, and 60% bronchiectasis. At diagnosis, serum IgG levels were 1.72 (0.33 – 6.90) g/L and switched memory B cell percentages 1.70 (0 – 52.0). The overall survival rate of the patients during the follow-up time was 88%. The Demographic, clinical, and laboratory characteristics of the study population were summarized in Table 1.

Table 1. Baseline demographic, clinical, and immunological parameters of the study population

Demographic properties		Clinical and Immunological parameters	
Gender, Female, n (%)	23 (46)	Neutrophil count, mm^3	3660 (1000-12500)
Current age, year	37 (23-67)	Lymphocyte, mm^3	1445 (400-8900)
Age at diagnosis, year	27.94 ± 13.64	Platelet count, mm^3	207770 ± 96657
Diagnostic delay, month	84 (0-360)	Neutrophil / lymphocyte ratio	2.45 (0.74-7.50)
Follow-up time, month	115.18 ± 80.74	Platelet / lymphocyte ratio	114.82 (9.08 – 607)
Consanguinity, n (%)	22 (44)	IgG, g/L	1.72 (0.33 – 6.90)
Smoking, n (%)	7 (14)	IgM, g/L	0.26 (0.06 – 5.99)
SCIG, n (%)	14 (28)	IgA, g/L	0.24 (0 – 190)
Severe lymphopenia, n (%)	15 (30)	IgE, g/L	17 (5-220)
Bronchiectasis, n (%)	30 (60)	$CD3^+$ T cells, %	76.54 ± 11.47
Low FEV1, n (%)	25 (50)	$CD4^+$ T cells, %	31.66 ± 14.32
Malignancy, n (%)	3 (6)	$CD8^+$ T cells, %	37.50 (19-74)
Prophylaxis, n (%)	38 (76)	$CD19^+$ B cells, %	7.10 ± 5.95
BMI	25.75 (14.80-49.0)	$CD16^+$ - 56^+ NK cells, %	7.50 (0 – 26.0)
FEV1	72.17 ± 17.68	IgM^- $CD27^+$ Switched Memory B cells, %	1.70 (0 – 52.0)
FEV1 / FVC	98.02 ± 10.12	IgM^+ $CD27^-$ Naive B cells, %	84.55 (0-98.60)
PEF	66.50 (3.80 – 100)	Mortality	6 (12)
MEF25-75	59.53 ± 25.15	Splenomegaly, n (%)	28 (56)

CVID: Common variable immune deficiency, Ig: immune globulin, SCIG: subcutaneous immune globulin, CD: The cluster of differentiation, FEV1: The forced expiratory volume in 1 second, FVC: forced vital capacity, PEF: The peak expiratory flow, MEF25-75: the mean expiratory flow between the 25% and 75% of the FVC

When the patients who survived and died during follow-up time were compared, there was no significant difference between the groups in regard to gender, duration of diagnostic delay, serum IgG level at diagnosis, CD19+ B cell and IgM- CD27+ Switched Memory B cell percentages, as well as the presence of severe lymphopenia, splenomegaly, bronchiectasis, and malignancy. There was a statistically significant difference in regard to the current age, age at diagnosis, IgM levels at diagnosis, platelet counts and platelet/lymphocyte ratio (p: 0.039, p: 0.049, p: 0.041, p: 0.011, p: 0.042 and p: 0.019, respectively). A comparison of demographic, laboratory and immunological parameters of survived and dead CVID patients was summarized in Table 2.

Table 2. Comparison of demographic, clinical and laboratory parameters of CVID patients who died and survived

	Dead (N=6)	Alive (N: 44)	p
Gender, F, n (%)	1 (16.7)	22 (50)	0.124
Current age, years	61 (59-63)	36.5 (23-67)	**0.039**
Age at diagnosis	38.17 ± 17.31	26.55 ± 12.67	**0.049**
Diagnostic delay, month	48 (0-120)	84 (0-360)	0.211
Follow up time, month	127.17 ± 83.08	105.09 ± 94.33	0.702
Consanguinity, n (%)	2 (33.3)	20 (45.5)	0.746
Smoking, n (%)	0	7 (16.3)	0.329
SCIG, n (%)	0	14 (31.8)	0.103
Severe lymphopenia, n (%)	2 (33.3)	13 (29.5)	0.849
Splenomegaly, n (%)	4 (66.7)	24 (54.5)	0.575
Bronchiectasis, n (%)	5 (83.3)	25 (56.8)	0.214
Malignancy, n (%)	0	3 (6.8)	0.509
Prophylaxis, n (%)	4 (66.7)	34 (77.3)	0.568
BMI	28.6 (28.19-29)	24.68 (14.80-49)	0.151
Neutrophil count, mm^3	1450 (1000-1900)	3825 (1058- 12500)	0.388
Lymphocyte count, mm^3	1100 (1000-1200)	1520 (400-8900)	0.404
Platelet count, mm^3	115333 ± 103511	220375 ± 89697	**0.011**
Neutrophil / Lymphocyte ratio	1290 (1.0-1.58)	2590 (0.74- 7.50)	0.439
Platelet / lymphocyte ratio	51.92 (50.83- 53.0)	119.15 (9.08-607)	**0.042**
FEV1, %	61.33 ± 15.28	73.04 ± 17.75	0.275
FEV1/FVC	97.67 ± 13.61	98.05 ± 10.03	0.951
PEF	42.4 (3.80-81.0)	66.5 (5.39 – 100.0)	0.401
MEF 25/75	67.33 ± 28.50	59.01 ± 25.19	0.588
IgG at diagnosis, g/L	1.96 (1.17-2.75)	1.72 (0.33- 6.90)	0.886
IgM at diagnosis, g/L	0.26 (0.09-0.44)	0.26 (0.06 – 5.99)	**0.041**
IgA at diagnosis, g/L	0.09 (0.07- 0.11)	0.25 (0-1.90)	0.116
IgE at diagnosis, IU/mL	5 (5-5)	17.25 (5-220)	0.568
$CD3^+$ T cells, %	78.60 ± 7.34	76.31 ± 11.89	0.677
$CD4^+$ T cells, %	28.00 ± 24.63	32.08 ± 13.07	0.552
$CD8^+$ T cells, %	31 (19-43)	37.5 (19-74)	0.357
$CD19^+$ B cells, %	7.60 ± 7.63	7.05 ± 5.84	0.846
$CD16^+$- 56^+ NK cells, %	11 (7-15)	7.50 (0-26)	0.449
IgM^- $CD27^+$ Switched Memory B cells, %	0.05 (0-0.10)	2.20 (0-52.0)	0.472
IgM^+ $CD27^-$ Naive B cells, %	93.20 (90-96.40)	83.50 (0-98.60)	0.256

CVID: Common variable immune deficiency, Ig: immune globulin, SCIG: subcutaneous immune globulin, BMI: Body mass index, CD: The cluster of differentiation, FEV1: The forced expiratory volume in 1. second, FVC: forced vital capacity, PEF: The peak expiratory flow, MEF25-75: the mean expiratory flow between the 25% and 75% of the FVC, CD: The cluster of differentiation

As a result of univariate Cox regression analysis, platelet count was determined to be an independent risk factor for mortality in CVID patients (Hazard ratio, HR: 0.990, 95% confidence interval, CI: 981-0.999, p: 0.025) (Table 3 and Table 4). As a result of multivariate Cox regression analysis; current age, BMI, and neutrophil/lymphocyte ratio were not found to be independent predictors for mortality, whereas platelet count was determined to be an independent predictor for mortality (HR: 0.990, CI: 0.981-0.999, p: 0.025) (Table 5). When the patients were classified according to mean platelet counts (platelets < 207770/mm^3 and platelets > 207770/mm^3), the mortality rate in the patient group with platelets < 207770/mm^3 was determined to be statistically significantly higher compared to the patient group with platelets > 207770/mm^3 (log-rank: 0.013) (Figure 1). The most common causes of mortality of the patients were pneumonia and pneumonia-induced sepsis (Figure 2).

Table 3. Univariate Cox regression analyses demonstrating the relationship between demographic characteristics and mortality in CVID patients

Variables	Univariate Analysis	
	HR (95% CI)	P value
Gender	3.527 (0.410 -30.323)	0.251
Age	1.043 (0.983 -1.106)	0.165
Diagnostic delay	0.992 (0.977-1.007)	0.308
Consanguinity	1.418 (0.446-4.321)	0.539
Smoking	0.039 (0 -2817.666)	0.571
BMI	0.902 (0.773-1.054)	0.194
Severe lymphopenia	1.672 (0.302-9.261)	0.556
Splenomegaly	0.900 (0.378-2.147)	0.813
Bronchiectasis	2.307 (0.266-20.021)	0.448
Malignancy	4.87 (0.009-2761.254)	0.624
Prophylaxis	2.827 (0.519-15.407)	0.230

CVID: Common variable immune deficiency, BMI: Body Mass Index

Table 4. Univariate Cox regression analyses demonstrating the relationship between laboratory and immunological parameters and mortality in CVID patients

Variables	Univariate Analysis	
	HR (95% CI)	P value
Neutrophil count	1.000 (1.000-1.000)	0.451
Lymphocyte count	1.000 (0.999-1.000)	0.379
Platelet count (× 10^3)	0.990 (0.981-0.999)	**0.02**5
Neutrophil/ lymphocyte ratio	1.059 (0.988 -1.136)	0.106
Platelet/ lymphocyte ratio	1.002 (0.995-1.008)	0.619
FEV1	0.969 (0.916-1.024)	0.267
FEV1 / FVC	1.007 (0.889-1.140)	0.918
IgG level, at diagnosis	0.926 (0.587 -1.461)	0.741
IgM level, at diagnosis	0.119 (0-70.426)	0.513
IgA level, at diagnosis	0.023 (0- 19.171)	0.272
IgE level, at diagnosis	0.969 (0.859-1.094)	0.615
CD3$^+$ T cells, %	1.015 (0.940-1.096)	0.700
CD4$^+$ T cells, %	0.982 (0.902-1.068)	0.688
CD8$^+$ T cells, %	1.010 (0.949-1.076)	0.749
CD19$^+$ B cells, %	1.020 (0.883-1.178)	0.786
CD16$^+$ - 56$^+$ NK cells, %	0.933 (0.816-1.067)	0.313
IgM$^-$ CD27$^+$ Switched Memory B cells, %	0.982 (0.866-1.115)	0.784
IgM$^+$ CD27$^-$ Naive B cells, %	1.127 (0.861-1.475)	0.383

CVID: Common variable immune deficiency, BMI: Body Mass Index, Ig: immune globulin, SCIG: subcutaneous immune globulin, CD: The cluster of differentiation, FEV1: The forced expiratory volume in 1 second, FVC: forced vital capacity, PEF: The peak expiratory flow, MEF25-75: the mean expiratory flow between the 25% and 75% of the FVC

Table 5. Multivariate Cox regression analyses demonstrating the relationship between baseline characteristics and mortality in CVID patients

Variables	Multivariate Analysis	
	HR (95% CI)	P value
Age	1.013 (0.948-1.083)	0.706
BMI	0.898 (0.714-1.130)	0.360
Platelet count (× 10^3)	0.990 (0.981-0.999)	**0.025**
Neutrophil/ lymphocyte ratio	0.973 (0.880-1.076	0.594

CVID: Common variable immune deficiency, BMI: Body Mass Index

Figure 1. The mortality rate in the patient groups with platelets < 207770/mm3 and platelets > 207770/mm3

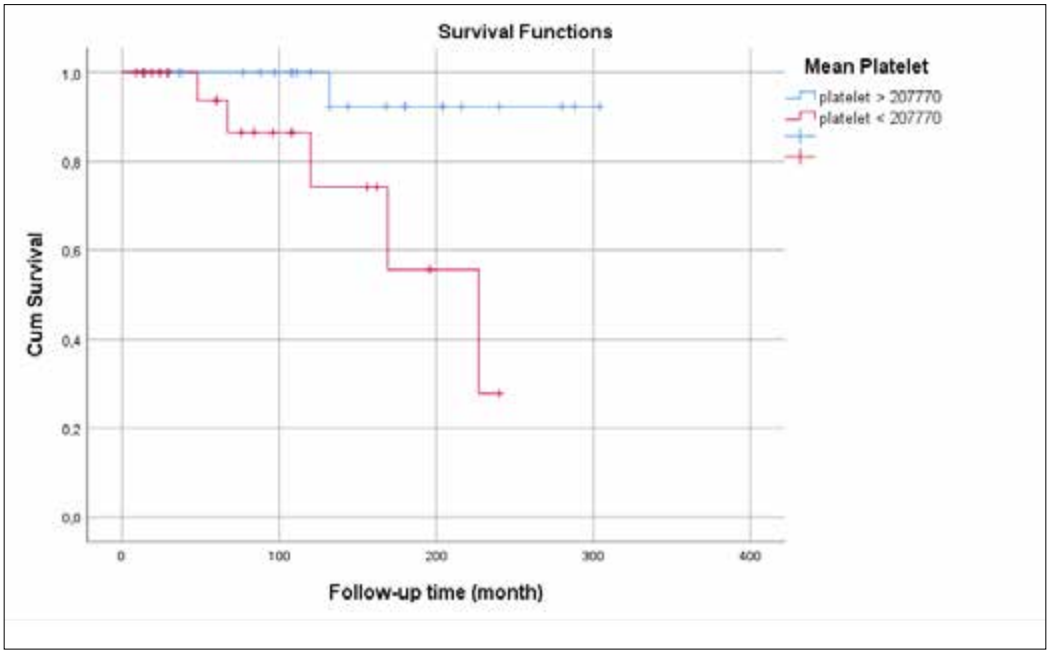
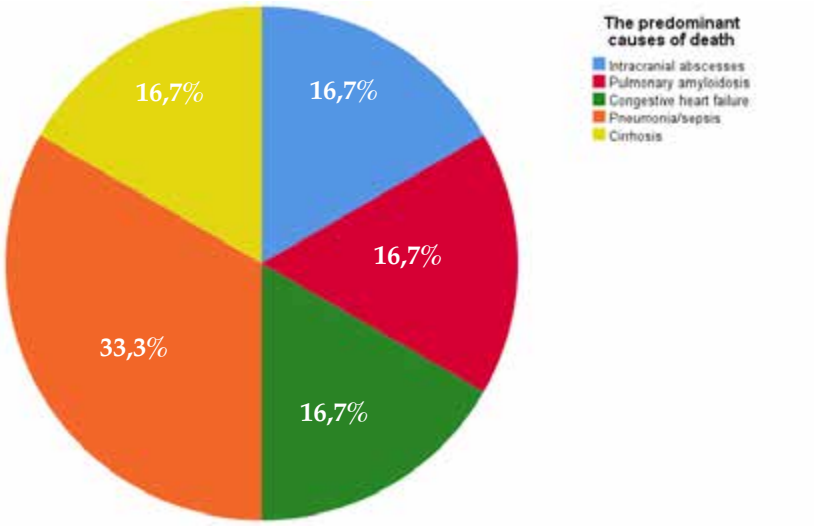


Figure 2. The predominant causes of death



DISCUSSION

Common variable immunodeficiency is the most common symptomatic primary immunodeficiency in adults (1). In addition to frequent and recurrent respiratory tract infections, patients may present with disorders with immune dysregulation. While infection-related mortality rates have been decreasing owing to immunoglobulin replacement therapy in this patient group, complications of other systems and malignancies have become a significant cause of mortality. In our study, the overall survival rate of the patients was found to be 88%. Furthermore, a lower platelet count was determined to be an independent risk factor for mortality.

B cell defects characterize CVID, and poor vaccine response makes the patients vulnerable to respiratory tract infections with encapsulated bacteria. A study of 224 CVID patients by Quinti et al. (12) reported respiratory tract infections as the most prominent clinical problem both at diagnosis and during the follow-up time. In a 2007 study by Aghamohammadi et al. (5), they reported that the most common cause of mortality in CVID patients was respiratory insufficiency and that the 20-year mortality rate of the patients was 27%. In a study by Gathmann et al. (10), the most common clinical presentation in CVID patients was reported to be pneumonia at a rate of 32%. The fact that our patients' most common clinical presentation was pneumonia and upper respiratory tract infections is consistent with the literature.

Mortality in the CVID patient group is higher compared to the normal population. Although infection-related mortality rates have been reduced with immunoglobulin replacement therapy, mortality due to malignancies and organ complications are still problematic. In a study by Cunningham-Rundles et al. (7), the 20-year mortality rate was reported as 36% in male CVID patients and 33% in female CVID patients. In a study by Resnick et al. (9) the mortality rate during a 40-year follow-up time was found to be 19.6%. The median age of death was reported as 44 years in females and 42 years in males. In another study, Quinti et al. (13) reported mortality during a 40-year follow-up time as 19.5% and the median age of death as 54 years, and the primary cause of mortality was reported to be chronic pulmonary diseases (30%). In our current study, the 10-year mortality rate was determined to be 12% (with an overall survival rate of 88%). The most common cause of mortality, however, was pneumonia and pneumonia-related sepsis. Although our mortality rate was supposed to be lower due to both smaller population and relatively shorter follow-up time of our study compared to aforementioned studies, the fact that our study was recently conducted, therefore, reduction of difficulties in availability of the patients to immunoglobulin replacement therapy and appropriate antibiotics, and advancements in diagnosis and treatment may have lowered the mortality rates.

Immune dysregulation is an important complication in CVID patients. Autoimmunity is a sign of immune dysregulation, and autoimmune complications may be the presenting symptom in 25% of the patients (14). The coexistence of immunodeficiency with autoimmunity may be considered paradoxical. Because there are poor responses to pathogens and vaccines in CVID and immunoglobulin levels are low; however, autoantibody reproduction may be increased simultaneously. Self-tolerance is impaired due to the presence of autoreactive B and T cells. Disorders of innate and adaptive immunities may lead to abnormal B cell clones and the secretion of abnormal cytokines. All these associations may lead to the coexistence of immunodeficiency with autoimmune conditions (15). The most common autoimmune complications in CVID are cytopenias, particularly immune thrombocytopenia (16). In the USIDNET (The United States Immunodeficiency Network) registry system, patients with autoimmune cytopenias have been determined to be associated with non-infectious complications, including lymphoproliferation and granulomatous disorders enteropathy, lymphoma, and interstitial pulmonary diseases (16). In another study, reduced platelet count and switched memory B cell ratio was reported to be a risk factor for bronchiectasis (17). Fisher et al. (18) reported that autoimmune conditions negatively affect the overall survival rate. In a study of 334 CVID patients, Gathmann et al. (10) reported lymphoid malignancies and autoimmunity as independent risk factors for mortality. In a study by Cunningham-Rundles et al. (11), autoimmune cytopenias were associated with increased morbidity and mortality. Also, in our study, reduced platelet count was determined to be an independent risk factor for mortality. These findings suggest that the reduction in platelet count may be an indirect indicator of increased immune dysregulation. As reduced platelet count due to increased immune dysregulation may be associated with other factors causing mortality, primarily lymphoproliferation,

granulomatous disorders, and chronic pulmonary diseases, reduced platelet count may be associated with mortality.

In conclusion, infections and infection-related sepsis remain to be a significant cause of mortality in CVID patients. Although survival rates in CVID patients are better than before, mortality rates are still higher than in the normal population. Clinicians dealing with this patient group should remember that immune dysregulation and low platelet count are independent risk factors for mortality, and they should particularly follow up patients with low platelet count closely.

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 Necmettin Erbakan University Meram Medical Faculty Ethics Committee (Date: 03.04.2020 – No: 2020/2401). This study was performed according to the ethical standards laid down Declaration of Helsinki and its later amendments. The authors carried out no animal or human studies for this article.

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ORIGINAL ARTICLE

Depression, Occupational Anxiety, and Related Factors in Medical Students

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Abstract

Background: Depression occupies an important place in medical students' psychiatric disorders, with a prevalence of approximately 20-40%. We aim to examine factors that might affect depression in medical students and investigate the relationship between occupational anxiety and depression severity.

Methods: Eighty-eight medical students who were diagnosed with major depressive disorder were included in the study. A Sociodemographic Data Form, the Occupational Anxiety Questionnaire for Medical Students, Beck Depression Inventory, and Beck Anxiety Inventory were used.

Results: A statistically significant relationship was found between academic success, living with family, Occupational Anxiety Questionnaire for Medical Students, and Beck Depression Inventory scores. The mean value of the occupational anxiety of the students was 35.87±9.82. The most anxious options for students in the Occupational Anxiety Questionnaire for Medical Students were the inability to prepare for and pass the Central Medical Specialty Exam.

Conclusions: It is necessary to focus on factors that may affect the severity of depression, which affect both the social and professional lives of medical students who are physician candidates. The issues about occupational anxiety should be considered when planning medical school education and postgraduate working conditions.

Keywords: Depression, Anxiety, Medical Students.

INTRODUCTION

University life is a period in which students receive education related to their profession, prepare for adulthood and working life (1). It is known that medical education, which is one of the fields of education at university, is a challenging and lengthy process. Unfortunately, many studies show that medical students have higher rates of depression than students of other faculties and the general population (2).

The lifetime prevalence of the major depressive disorder is between 17% and 21%, and according to the World Health Organization (WHO) data, it is the mental illness that ranks first among the causes of disability(3). Studies conducted with university students stated that depression is the most important mental disorder seen in university students(4).

Medical schools have long been considered stressful environments for students entering tertiary education.

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Among the factors that negatively affect the mental state of medical students, many factors such as academic pressure created by the high expectations of society and families, the difficulty of medical education, frequency of examinations, the intense workload that occurs with the transition to clinical classes, sleep deprivation, little time for hobbies, social isolation are reported (5,6). These factors negatively affect students' academic performance, physical health, and psychological status, making them more susceptible to depression.

Depression is a problem that should be addressed for medical students because of the prevalence of suicidal ideas in medical students, causing alcohol or substance abuse, depressive symptoms tend to become chronic, its treatment is complex, and it can affect their future professional life (7,8). In this context, we aimed to examine factors that might affect depression in medical students and investigate the relationship between occupational anxiety and depression severity.

MATERIALS AND METHODS

One hundred twenty-two medical students who were admitted to University Health Care Center Psychiatry outpatient clinic between October 2018 and February 2020 were evaluated. Among these, patients with depressive symptoms such as sadness, tearfulness, emptiness, loss of interest or pleasure in most activities, sleep and appetite problems, concentrating problems were included in the study. The study population consisted of eighty-eight patients diagnosed as major depressive disorder. The participants were informed about the study, and their informed consent was obtained. Permission was obtained from the Gazi University Ethics Committee for the research (Decision No.: 91610558-604.01.02, Decision Date: 04.02.2020).

In this study, a Sociodemographic Data Form, the Occupational Anxiety Questionnaire for Medical Students (OAQ), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were used.

Sociodemographic Data Form

A Sociodemographic Data Form was prepared by the researchers in line with the literature. It consisted of questions including age; sex; marital status; whether they were a foreign national; academic year; history of having to repeat academic years and how many years if any; whether they studied medicine in English or Turkish; whether they lived with their family; whether they had a history of alcohol or substance use, depression attack, and a family history of depression.

Occupational Anxiety Questionnaire for Medical Students (OAQ)

In the study conducted by Ergin et al., the OAQ was used to evaluate occupational anxiety levels of medical students (9). The OAQ, which consists of 17 parameters, includes factors that can cause anxiety about work environment and conditions, occupational competence, and occupational satisfaction. The minimum available score is 17, and the maximum is 68 points from the questionnaire, and as the score increases, the students' occupational anxiety also increases; 17-33 points are considered as low, 34-50 points as a medium, and 51-68 points as high occupational anxiety.

Beck Depression Inventory (BDI)

The BDI was developed by Beck (10) and adapted to Turkish (11). It is a self-report scale with 21 items measuring emotional, cognitive, somatic, and motivational symptoms. The items of the scale are scored between 0 and 3 points. Total scores of 0–12 indicated minimal, 13–18 mild, 19–28 moderate, and 29–63 severe depression.

Beck Anxiety Inventory (BAI)

The BAI is an inventory designed to assess physical, emotional, and cognitive aspects of anxiety and fear of losing control. It was developed by Beck et al. (12) and adapted to Turkish by Ulusoy et al. (13). The scale, consisting of 21 questions, is scored between 0-3, and the severity of anxiety symptoms is determined based on the total score. The total score ranges from 0-63 points.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) Ver. 15 software package. Categorical data are presented as percentages and numbers, and as mean and standard deviation values for continuous data. Whether the variables showed normal distribution was evaluated using the Kolmogorov-Smirnov test. Pearson/ Spearman correlation analyses were used to determine the relationship between variables. $P<0.05$ was accepted for the significance level.

RESULTS

Eighty-eight medical students were diagnosed as having major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria were evaluated.

The sociodemographic information and clinical characteristics of the students were presented in Table 1.

Table 1. Sociodemographic information and clinical characteristics of the students

		n	(%)
Age	mean min max	21.75 18 31	
Gender	female male	42 46	47.7 52.3
Marital status	single married	86 2	97.7 2.3
International students		5	5.7
Grade	grade 1 grade 2 grade 3 grade 4 grade 5 grade 6	17 15 12 18 15 11	19.3 17.0 13.6 20.5 17.0 12.5
Existance of grade repetition	yes no	22 66	25 75
The number of grade repetitions	1 year 2 years 3 years	14 4 4	15.9 4.5 4.5
Received medical education in English		4	4.5
Students living with their families		33	37.5
Family history of psychiatric treatment	yes no	18 70	20.5 79.5
History of depression attack	yes no	45 43	51.1 48.9
Alcohol abuse	yes no	2 86	2.3 97.7
Substance abuse	yes no	1 87	1.1 98.9

min: minimal, max: maximal, n: number of patients

Students' BDI, BAI, OAQ score averages, and OAQ levels were shown in Table 2. The mean value of the professional anxiety level of the students was 35.87±9.82.

Table 2. Students' BDI, BAI, OAQ score averages, and OAQ levels

	mean ± SD
BDI	22.84 ± 9.24
BAI	19.78 ± 10.93
OAQ	35.87 ± 9.8
OAQ levels	n(%)
Mild Moderate Severe	36 (40.9%) 44 (50.0%) 8 (9.1%)

BDI: Beck Depression Inventory
BAI: Beck Anxiety Inventory
OAQ: Occupational Anxiety Questionnaire for Medical Students
SD: standart deviation
n: number of patients

The distribution of the reasons for the occupational anxiety of the students was presented in Table 3. The most anxious options for students in the OAQ were the inability to prepare for and pass the TUS *(Central Medical Specialty Exam)*.

Table 3. The reasons for the occupational anxiety of the students

	n (%)
Not being able to prepare for TUS	45 (51.1)
Not being able to pass TUS	45 (51.1)
Dealing with the emergency patient in professional life	42 (47.7)
Not being a specialist doctor	35 (39.8)
Be assigned to undesirable place	28 (31.9)
Working in primary care health services	28 (31.8)
Lower income in professional life	28 (31.8)
Harm someone inadvertently during professional life	24 (27.3)
Lack of clinical skills during professinal life	19 (21.6)
Being insufficient in prescribing during professional life	22 (25)
Being uncertain about the place of work	21 (23.8)
Misdiagnosing patients in professional life	23 (26.2)
Communicating with the personnel of the health care facility	20 (22.7)
Working as an assistant doctor	19 (21.6)
Become unemployed	19 (21.6)
Working away from university	16 (18.2)
Coping with the patient alone in professional life	14 (15.9)

TUS: Central Medical Specialty Exam, n: number of patients

Table 4 shows the relationship of some sociodemographic variables with the BDI scores. A statistically significant relationship was found between the existence of year repetition, the number of year repetitions, the status of living with their family, and total BDI scores (p: 0.003, p: 0.002, p<0.001).

Table 4. The relationship of some sociodemographic variables with the BDI score

BDI	r/rho	p
Age	0.073	0.572
Grade	-0.139	0.098
Existance of grade repetition	0.316**	0.003
The number of grade repetitions	0.328**	0.002
Students living with their families	-0.372**	0.000

BDI: Beck Depression Inventory
r: Pearson's correlation coefficient
rho: Spearman's correlation coefficient
**: p<0.01
*: p<0.05

A statistically significant correlation was found between total OAQ scores and BDI and BAI total scores (p<0.001, p<0.001).

DISCUSSION

In many parts of the world, medical students are at risk for psychiatric diseases, especially depression (6). In this study, we aimed to examine the factors that may affect the depression in medical students and investigate the relationship between occupational anxiety and depression severity.

Our study observed that gender, one of the sociodemographic factors, did not affect the total BDI scores. When studies investigating depression in medical students were examined, some reported that depression was more frequent and severe in women, whereas others declared that gender did not affect depression (14,15). The total BDI scores of two students who were married were higher than those who were single. However, this was not statistically significant because very few students were married among the sample. The total BDI scores of five international students were higher than those of Turkish students. Although these data were not statistically significant given the small number of international students, it is known that international students have

difficulties in many issues such as decreased academic success due to issues such as language problems, accommodation problems, and economic problems. Two students whose marital status was married were among the international students.

Although there was no statistically significant relationship between the years and the BDI total scores, it is seen in Table 1 that most applicants were from the fourth and first-year students, respectively. This condition may be due to the intense workload that occurs with the transition to clinical classes in the fourth year and the adaptation to the new school and accommodation environment in the first year. There are studies in the literature showing that depression increases with advancing school years (16,17). In the study of Eyüboğlu et al., in which first and sixth-year medical students were compared, they stated that the severity and frequency of depression were higher in sixth-year students (15). The total BDI scores of students with a history of repeating academic years were higher than students without a history of year repetition. Also, total BDI scores were higher in students who had a history of repeating academic years of more than one year compared with students with one year of year repetition. Similar results were found in studies evaluating depression in medical students. It was shown that students who stated that their course success was poor had more depression (14,18). As reported by Tunç and Yapıcı in their studies evaluating 631 medical students, it can be planned to monitor the academic success of medical students during the education process, to evaluate the mental status of students who are considered to be in need, and to support those who have problems (14).

Four of the 88 students included in the study studied medicine in English. Although not statistically significant, the total BDI scores of the students who received medical education in English were higher than those who received medical education in Turkish. Students who received medical education in English verbally stated that they had more academic difficulties than students who received medical education in Turkish, especially in the first years of their theoretical education.

In our study, the total BDI scores of students living with their families were lower than those of students who did not live with their families. This result may be due to having to deal with housework after the intensity of education in the school/hospital during the day, problems with adaptation to the environment if staying in the dormitory, and not getting enough social support due to being away from home. In the study conducted by Roh et al., it was determined that the prevalence of depression in medical students living alone was higher than those living with their family or relatives (18).

Family depression history and previous depression history are important factors affecting the frequency and severity of depression(19,20). In our study, no statistically significant difference was found between the total BDI scores of students with a family history of psychiatric treatment and the total BDI scores of students who did not have a family history of psychiatric treatment. Although the total BDI scores of the students with a history of depression attack were higher, no statistically significant difference was found with the BDI total scores of the students who had no history of psychiatric admission. It can be thought that these results may be related to the small sample size. This item was not evaluated due to the small number of students with an alcohol/substance abuse history.

In our study, it was found that the occupational anxiety levels of the students were at a medium level, and the areas they were most anxious about were not being able to prepare for the TUS exam and not being able to pass TUS. A significant number of physicians who have completed primary medical education in our country choose to continue their medical education after graduation and specialize in a particular field by taking the TUS (18). Although fresh graduates prepare for the TUS due to reasons such as professional ideals, career plans, economic concerns, difficulties of working as a general practitioner, concerns about malpractice, and the effects of workload on private life (21), especially with the effect of increasing medical faculty quotas, it is getting harder and harder to pass the TUS (22).

One of the most anxious items in the OAQ was dealing with emergency patients in professional life. Students preparing for the TUS with the mindset of becoming specialists from the early years of medical faculty spend most of their time in training centers for the TUS, starting from the fourth year (23). Fresh graduate physicians are educated with the knowledge of rare diseases in society in detail and equipped with knowledge that requires an advanced level of expertise (24,25). It is thought that this may cause students to avoid being alone with patients

and coping with emergency patients owing to not being able to master the basic health problems of society and not knowing treatment methods very well (6). Another reason students worry about dealing with emergency patients in their professional lives is the lack of practical training before graduation. In the study conducted by Yalçınoğlu et al. with 346 students, the rate of students who considered themselves sufficient to become a physician after the theoretical and practical training they received was 14.8%. In the same study, it was found that 70.5% of students were anxious about approaching emergency patients due to deficiencies in practical education (26).

A statistically significant correlation was found between total OAQ scores and BDI and BAI total scores in our study. In other words, as the professional anxiety levels of students increase, the symptoms of depression and anxiety increase. Considering that depression and anxiety are common and intertwined clinical diagnoses, it can be thought that students with high professional anxiety are at risk for depression and anxiety disorders.

Although studies have investigated depression in medical students, few have investigated its relationship with occupational anxiety. Another important aspect of our study is that the students were evaluated through face-to-face interviews by a psychiatrist under the conditions of an examination room. Our study's limitations are the small sample size, the fact that it was performed only in one medical faculty, and also collecting data by self-reported tests. Also, the OAQ, BDI, and BAI scores of the students who were obtained during an examination period, which may have affected the situation.

Studies have shown that medical students do not get enough psychiatric support compared with the general population, even though they are close to the hospital, and that students do not prefer psychiatric help because of stigmatization (27,28). To prevent this situation, since October 2018, all medical students who want to receive psychiatric help in our university are examined in the psychiatry department of the Health Care Center located in the central campus instead of University Medical Faculty Hospital. Also, regular meetings with the psychologists of the Universıty Health Care Center are planned for students in need. In this way, students can reach psychiatric support more easily without worrying about being stigmatized, and students with depressive symptoms have interventions earlier.

In conclusion academic failure, living far away from family and professional anxiety scores were associated with high BDI scores in medical students. The most anxious issues in OAQ were related to the TUS and dealing with emergency patients. It is necessary to focus on these factors that may affect the severity of depression in affecting both the social and professional lives of medical students. These issues should be taken into consideration when planning medical faculty education and postgraduate working conditions.

Declarations

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

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ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy After Cytoreductive Surgery; Experience and Short Term Outcomes

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Abstract

Background: Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy is an important treatment option in patients with a primary diagnosis of colorectal cancer, ovarian cancer, appendix cancer, gastric cancer(selected cases), malignant peritoneal mesothelioma, and peritoneal pseudomyxoma in the presence of peritoneal involvement and resectable lesions limited to the abdomen. In this study, it was aimed to discuss cytoreductive surgery(CRS) with hyperthermic intraperitoneal chemotherapy(HIPEC) in the light of literature.

Methods: The data of patients who underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy between June 2017 and September 2020 at our institution were analyzed. The study was designed retrospectively, and all patients who were discussed at the oncology council and decided on CRS + HIPEC were included in the study.

Results: 31 patients were included in the study. Primary diagnoses of the patients were colorectal cancer in 15 (48%), ovarian cancer in 9 (29%), stomach cancer in 3 (10%), mesothelioma in 2 (7%), appendix cancer in 1 (3%), and also peritoneal pseudomyxoma in 1 (3%). Therapeutic HIPEC was performed in 30 patients, and prophylactic HIPEC was performed in 1 patient. Cytoreduction score was 0 in all patients. The median peritoneal cancer index was 15 (7-29). the median number of resected organs was 3(1-6). Stoma formation was performed in 14 patients (45%). During the postoperative 30 days, mortality was observed in 1 patient (3%) and morbidity in 5 patients (16%).

Conclusion: The early postoperative mortality and morbidity results reported in our study are compatible with those in the literature.

Keywords: Peritoneal Carcinomatosis, Cytoreductive Surgery, Hyperthermic Intraperitoneal Chemotherapy.

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INTRODUCTION

Peritoneal carcinomatosis (PC) is a clinical entity detected in advanced stages of gastrointestinal and gynecological cancers and primary ones of the peritoneum, such as peritoneal mesothelioma peritoneal pseudomyxoma, as well as gastrointestinal and gynecological cancer, and adversely affects long-term survival (1). With comprehending the intraperitoneal spread biology of tumors in the last thirty years, PC has been accepted as a local-regional disease. 10-35% of colorectal cancer recurrences and up to 50% of gastric cancer recurrences are limited only in the peritoneal cavity. On the other hand, 15% of colorectal cancer patients and almost 40% of gastric cancer patients have peritoneal carcinomatosis during perioperative exploration (2). Malignant peritoneal mesothelioma (MPM), which constitutes 30% of all mesothelioma tumors, is a fatal disease with an average overall survival of 6 -12 months (3). Epithelial ovarian cancer (EOC), a fatal type of gynecological cancer, is responsible for approximately 50% of the mortality from gynecological cancers. Serous adenocarcinoma is the most common subtype of epithelial ovarian cancer. Approximately 95% of the patients are diagnosed with the disease spreading beyond the ovaries (Stage II-IV) and has a poor prognosis. Many patients with diffuse peritoneal disease in EOC develop intraperitoneal recurrence despite of complete cytoreduction and chemotherapy. Alternative methods for increasing the effectiveness of chemotherapy have been investigated (4).

Cytoreductive surgery (CRS), which was firstly described by Sugarbaker, includes organ resection and peritonectomy procedures that leave no visible lesions within the intraabdominal cavity (5). Hyperthermic intraperitoneal chemotherapy (HIPEC) is performed for the curative treatment of invisible microscopic residual tumor deposits that may remain after CRS (4, 6). CRS + HIPEC is indicated for peritoneal metastases of peritoneal pseudomyxoma, malignant peritoneal mesothelioma, colorectal and ovarian cancers. CRS + HIPEC is in the developmental stage in peritoneal metastases of gastric cancer, and it is not used for pathologies such as sarcoma and GIST (7). Although CRS + HIPEC is a technique that has high morbidity and mortality, appropriate patient selection and development of multi-modal treatment options have improved the outcomes to better levels in the last two decades. As a result of these improved outcomes, it was observed that multidisciplinary oncology councils had increased referral of patients with peritoneal carcinomatosis to surgery who are eligible for CRS + HIPEC (8).

In this study, we aimed to present the demographic, clinicopathological characteristics and early postoperative morbidity, mortality results of the patients who underwent CRS + HIPEC in the light of the literature.

MATERIALS AND METHODS

The data of patients who underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy between June 2017 and September 2020 at our institution were analyzed. The study was designed retrospectively, and all patients who were discussed at the oncology council and decided on CRS + HIPEC were included in the study. The oncology council decided the operation for patients with no signs of extra-abdominal solid organ metastasis in thoracoabdominal CT imaging and sufficient cardiorespiratory and renal function to tolerate aggressive procedures. Patients with Eastern Cooperative Oncology Group (ECOG) performance scores above two were excluded from the study (9). The study was conducted in accordance with the principles of the Declaration of Helsinki. Data of patients regarding age, gender, pathological findings, cytoreduction score (CC), peritoneal cancer index (PCI), perioperative complications, length of hospital stay, recurrence, and follow-up were recorded.

The distribution and extent of tumor deposits in 13 abdominopelvic regions were evaluated and recorded as PCI during abdominal exploration. PCI is scored according to the size of the tumor nodules as follows: lesion size(LS)-0: no tumor; LS-1: tumor nodule <0.5 cm; LS-2: 0.5-5 cm tumor nodule; and LS-3: tumor nodule> 5 cm. The patients were divided into two groups according to their PCI scores as less than 20 and more.

Completeness of cytoreduction (CC) was classified by the surgeon for each patient using Sugarbaker's criteria (10). After cytoreduction, completeness of cytoreduction (CC) was determined as follows; CC-0, no visible evidence of disease; CC-1, tumor deposits are less than 2.5 mm in diameter, without a confluence of disease at any site; CC-2, tumor deposits are between 2.5 mm and 2.5 cm and the absence of a contiguous layer of disease at any anatomic site in the abdomen or pelvis; CC-3, tumor deposits are greater than 2.5 cm in diameter or a confluence of disease layered out at any site within the abdomen or pelvis. The

parietal peritoneum, tumor-involved visceral peritoneum, and tumor-involved gastrointestinal tract should be resected in the CRS procedure. If tumor implants are observed, cholecystectomy, segmental liver resection, splenectomy, hysterectomy, and bilateral salpingo-oophorectomy should be performed if possible.

In our study, HIPEC was performed just after SRC using a hyperthermia pump with a closed technique. The peritoneal perfusate was warmed to 42°C and infused into the abdomen with 1000 cc/min. The perfusate at 42-43 °C containing chemotherapeutic agents was rotated in the intraperitoneal area for 60 minutes. After the HIPEC procedure, all catheters and temperature probes were removed. After the perfusion and rotation, the abdominal cavity was opened again and washed with 5000 cc saline solution. Gastrointestinal anastomoses (whether manually or with a stapler) were performed after the HIPEC procedure. All procedures were performed by the same surgical team that has high experience in regional treatments.

Complications were recorded according to the Clavien-Dindo system (grade 1:mild complications, grade 5:death) (11). Operative mortality was defined and recorded as any death within 30 days of surgery.

During the first two years, a postoperative follow-up which includes a physical examination, thoracoabdominal CT imaging, and plasma tumor marker levels, was evaluated every three months. These evaluations were then repeated every six months for three years. Recurrent disease or progression was confirmed pathologically.

Statistical analysis was performed using the statistical software package SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Binary variables were reported as counts and percentages. The Kaplan–Meier test was used to identify differences between curves. Survival was measured from the time of diagnosis.

This study was approved by the Eskişehir Osmangazi University non-invasive clinical research ethics committee with the date of 12.01.2021 and number of 7. The aforementioned study was conducted according to a recent version of the declaration of Helsinki.

RESULTS

There were 31 patients in the study. The median age of the patients was 55(37-76) years. 20 patients were women and 11 patients were men. Demographic and clinicopathological characteristics are shown in Table 1. Primary diagnoses of the patients were 15 (48%) colorectal cancer, 9 (29%) ovarian cancer, 3 (10%) stomach cancer, 2 (7%) mesothelioma, 1 (3%) appendix cancer and 1 (3%) peritoneal pseudomyxoma (figure-1). 14 patients had abdominal distension, 4 patients had abdominal pain, 2 patients had ileus. Peritoneal carcinomatosis or ascites were demonstrated radiologically in all patients. Pathological verification was not carried out for the diagnosis of peritoneal carcinomatosis or ascites, except for mesothelioma and peritoneal pseudomyxoma. All procedures were performed via laparotomy. 30 patients underwent therapeutic HIPEC and 1 patient underwent prophylactic HIPEC. The patient who underwent prophylactic HIPEC had limited peritoneal involvement and ascites in diagnostic laparotomy. An implant in the peritoneum was excised and sent to the pathology laboratory for frozen examination. Frozen examination was reported as adenocarcinoma metastasis. Therefore, the operation was terminated and the patient was referred to the medical oncology clinic for systemic chemotherapy. The patient's condition after systemic chemotherapy was discussed in the oncology council. Oncology council decided to perform prophylactic HIPEC operation together with gastrectomy. CC score was 0 in all patients. The median PCI was 15 (7-29)(Figure-2). The median number of resected organs was 3 (1-6). Stoma formation was performed in 14 patients (45%). The rate of intraperitoneally applied chemotherapeutics were as follows; Oxaliplatin in 16 patients (51%), cisplatin in 7 patients (22%), mitomycin in 3 patients (10%), mitomycin-cisplatin in 2 patients (7%), doxataxel-oxaliplatin in 2 patients (7%) and 1 patient (3%) cisplatin- doxataxel (Figure-3).

Table 1. Demographic and clinicopathological features

Features	Values, (%)
Age (year) mean	55 (37-76)
50>	8 (25%)
50<	23 (75%)
Gender	
Male	11 (35%)
Female	20 (65%)
Location	
Colorectal	15 (48%)
Over	9 (29%)
Stomach	3 (10%)
Mesothelioma	2 (7%)
Appendix	1 (3%)
Peritoneal pseudomyxoma	1 (3%)
PCI	15 (7-29)
20>	23 (75%)
20<	8 (25%)
CC	
Score 0-1	31 (100%)
Score 2-3	0
Differentiation	
Well	12 (44%)
Moderate	5 (19%)
Poor	10 (37%)
Obstruction	
Present	2 (7%)
Absent	25 (93%)
Resection of organ (number) mean	3 (1-6)
Stoma	
Yes	14 (45%)
No	17 (55%)
Protocol of HIPEC	
Oxaliplatin	16 (51%)
Cisplatin	7 (22%)
Mitomycin	3 (10%)
Doxorubicin+Oxaliplatin	2 (7%)
Mitomycin+Cisplatin	2 (7%)
Cisplatin +Doxorubicin	1 (3%)
Perioperative mortality	1 (3%)
Perioperative morbidity	
Grade 1-2	4 (13%)
Grade 3-4-5	1 (3%)
Complications	
Leakage of Anastomosis	1 (3%)
perforation of intestine	1 (3%)
Evisceration	1 (3%)
Bleeding	1 (3%)
Fealure of kidney	1 (3%)
Lenght of Stay (day) mean	10 (5-24)
7≥	16 (51%)
7<	15 (49%)

Abbreviation: CC = Score of Cytoreduction; PCI = Peritoneal carcinomatosis Index

Figure 1. Diseases

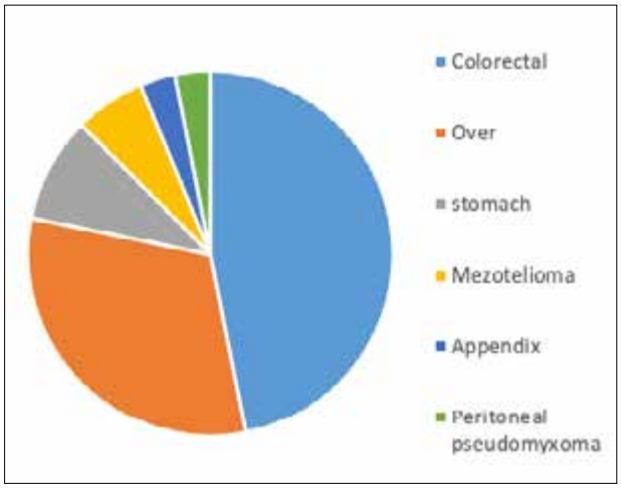


Figure 2. Peritoneal Carcinomatosis Index

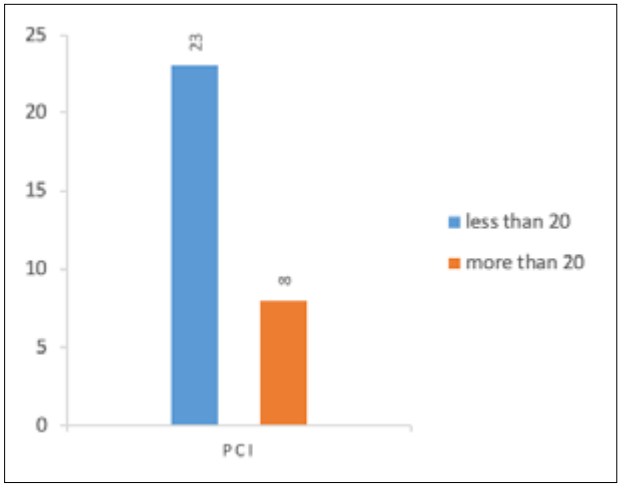
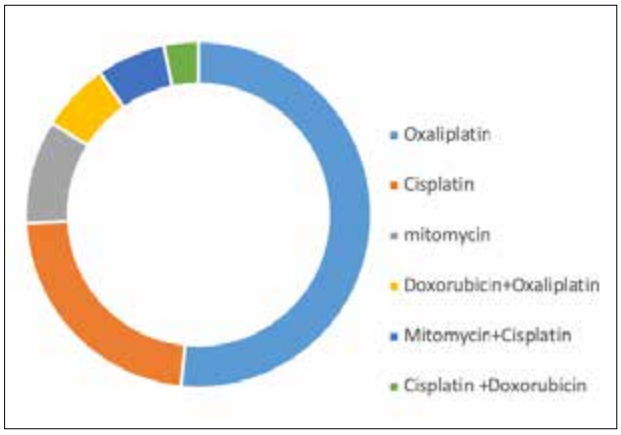


Figure 3. Protocol of HIPEC



Median length of hospitalisation was 10 (5-24) days. ECOG performance status of all patients in the study was 0 or 1. In the postoperative first 30 days, mortality and

morbidity rates were 1(3%) and 5(16%), respectively. In this patient, prophylactic CRS + HIPEC was performed in order to gastric cancer. In the postoperative follow-up, after anastomotic leak, the patient died as a result of septic shock and multiorgan failure. Other complications are presented in Table 1.

The overall mortality rate in our series was 19%. The mean follow-up period was 20 (1-36) months. The mean overall survival time was 22 months. At 12 and 24 months, the survival results were 82% and 78% for overall survival, and 69% and 48% for disease free survival, respectively (Figure-4, Figure-5).

Figure 4. Overall survival of 31 patients with SRC-HIPEC according to the Kaplan-Meier method

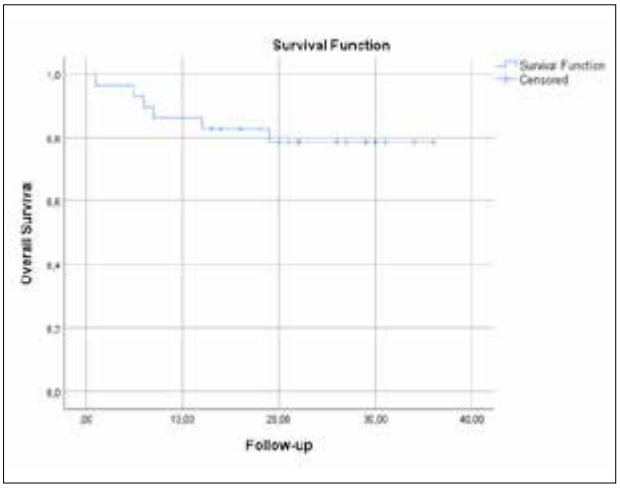
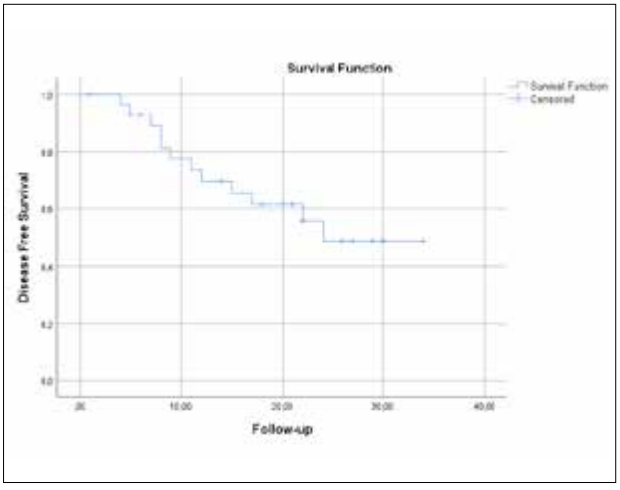


Figure 5. Disease free survival of 31 patients with SRC-HIPEC according to the Kaplan-Meier method



DISCUSSION

Peritoneal carcinomatosis(PC) is a entity with high mortality and low survival. The benefit of systemic chemotherapy is limited. CRS + HIPEC has better results compared to conventional systemic chemotherapy response in diseases such as colorectal cancer, gynecological cancers(especially ovarian cancer), peritoneal carcinomatosis due to appendix cancer, peritoneal mesothelioma and peritoneal pseudomyxoma. CRS + HIPEC procedure is in development stage in stomach cancer, studies regarding its effectiveness are ongoing (12). Delivering chemotherapeutic agents directly to the abdominal cavity via a catheter, provides a high concentration of drug at the peritoneal surface, thus enhances the cytotoxic effect of chemotherapy. However hyperthermia has a direct cytotoxic effect on tumor cells and also increases the effect of chemotherapeutic agent. Philosophy of HIPEC is based on these two basic ideas (4). Tissue penetration depth of chemotherapeutics is up to 1-2 mm. Therefore, it is accepted that patients who do not have macroscopic tumors after cytoreductive surgery are more likely to benefit from HIPEC. This opinion is the main source of the concept for HIPEC after maximal CRS (1). Patient selection was carried out by carefully examining clinical and radiological findings in the multidisciplinary oncology council. For this reason, our rate of complete cytoreduction was high.

In the preoperative period, imaging methods can contribute to the diagnosis of PC and to determine its severity. The sensitivity of computed tomography (CT) is 33% and its specificity is over 90%. The sensitivity of ultrasonography is 9%. İn PC due to stomach cancer, endosonography (EUS) is more sensitive than CT. Magnetic resonance (MRI) provides better soft tissue contrast agent resolution than CT, furthermore there is no risk of contrast agent nephropathy and ionizing radiation. However, a significant superiority to CT in the detection of the PC has not been demonstrated. İn patients with cancer, positron emission tomography (PET/CT) can detect peritoneal carcinomatosis with high specificity. The superiority of PET / CT over CT is clear. PET/CT provides functional information. However, its efficiency in the exclusion of PC is low. It has been reported that the diagnostic accuracy and the negative predictive value increase with the combined usage of MRI and PET/CT. However, both modalities are insufficient in detecting peritoneal lesions below 1 cm (2). In our clinic for patients

with PC, CT is routinely performed and PET/CT is performed in case of necessity.

If patients are carefully selected in terms of operability in multidisciplinary oncology councils, advanced age is not an absolute contraindication to perform cytoreductive surgery + HIPEC. In young patients quality of life after CRS + HIPEC is better. Prospective studies are needed to confirm the results in elderly patients (13, 14).

HIPEC was used in appendix tumors that spread to adjacent peritoneal surface firstly, subsequently it was used in the treatment of intraperitoneally spread colon and stomach tumors. In the following years, it has been used in gynecological cancers such as intraperitoneally spreading endometrial cancer and ovarian cancer. Currently, it has become the standard treatment for peritoneal pseudomyxoma and peritoneal mesothelioma (15).

Multiple organ resections, longer operation and intraperitoneal chemotherapy duration, neoadjuvant chemotherapy, previous abdominal surgeries and low performance scores put PC patients into a high risk group for complications.In the literature, It has been reported that general morbidity and perioperative mortality after CRS + HIPEC were 12-56% and 0-12%, respectively. The morbidity rate is related to the extent of the disease, the time until cytoreductive surgery, the number of removed organs, age, perioperative blood loss and operation time. Morbidity and mortality rates in our study are similar to those in the literature. Although acceptable mortality and morbidity rates have been published from mid-volume centers, another efficacious factor on complication rates has been reported as center experience (1). In a study of 100 patients, Moran et al. reported a mortality rate of 18% in the first 33 cases, 3% in the second 33 cases, and 3% in the last 33 cases. They emphasized that the mortality rate decreases with increasing experience and all relevant teams should gain experience (16). The extent of the disease and ensuring complete cytoreduction are the most important prognostic factors on both perioperative surgical and long-term oncological outcomes (17). Despite the low number of patients in our results, the fact that a newly formed team reaches this number within 36 months gives hope for the future. In addition, surgeons leading the team have advanced experience in CRS + HIPEC from their surgical background.

Approximately 10% of patients with colorectal cancer have metastases in the peritoneal cavity at the time of diagnosis, and 40% of patients with colorectal cancer develop metastasis during follow-up. Overall survival at 5 years of patients with stage IV of colorectal cancer without treatment is anecdotal, with a mean survival of 6 months. Over the past decade, systemic chemotherapy based on 5-FU + leucovorin ± irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) has improved overall survival up to 20 months. Advances in biological treatments (such as bevacizumab, cetuximab, panitumumab, aflibercept) have increased the survival expectancy to around 24 months. However, there are few studies specifically evaluating the true efficacy of systemic chemotherapy in patients with colorectal cancer and isolated peritoneal carcinomatosis. Peritonectomy procedures and multivisceral resections, as well as cytoreductive surgery followed by HIPEC, enable better overall survival outcomes. Currently, in the literature, the median survival of patients with colorectal peritoneal carcinomatosis ranges from 12 to 32 months; 1, 3, and 5-year survival rates range between 65-90%, 18-47% and 17-30% (13, 18).

The risk of peritoneal metastasis in gastric cancer is approximately 40%, with almost 30% of patients presenting with peritoneal metastases at the time of diagnosis (19). CRC + HIPEC can improve survival in selected patients with gastric cancer accompanied by peritoneal carcinomatosis. While the madian survival is 3 months with only basic supportive therapy, it is 15 months in patients with complete cytoreduction + HIPEC. Gastric cancer with PC is typically treated with systemic chemotherapy, but its effectiveness is unclear, according to the literature. In three clinical studies, systemic chemotherapy has been shown to increase median survival in metastatic gastric cancer to 7-10 months. In these studies patient populations were heterogeneous due to inconsistent randomization. On the other hand most patients did not have PC Similarly. Preusser et al. reported that the response rates to systemic chemotherapy decreased in gastric cancer with PC. There are no clinical studies that directly compare systemic chemotherapy with the combination of CRS + HIPEC in gastric cancer with PC patients. Two recent studies reported that the median survival of gastric cancer with PC patients treated with the CRS + HIPEC combination were longer than 15 months. Importantly, both of these studies reported that the CC is an independent prognostic factor for survival (17, 20).

Phase 1-3 studies onto prophylactic CRS + HIPEC in T3/T4 gastric cancer are ongoing in China, America, Germany and France (21). In our study, prophylactic HIPEC was performed to one patient.

The majority of epithelial ovarian cancer (EOC) patients presents with peritoneal metastases and around 75% will relapse in the peritoneal cavity after successful first line treatment. Therefore, EOC appears to be the ideal candidate for IPDD and remains the best studied indication (22). The timing of HIPEC in ovarian cancer is varies. It could be performed at recurrence (first or subsequent recurrences). Accompanied by CRS, during primary staging surgery, for consolidation following primary surgery and adjuvant systemic chemotherapy, during interval surgery after neoadjuvant chemotherapy, and as salvage therapy. However, its most common use is CRS + HIPEC at recurrent disease. Recently, performing HIPEC during interval surgery after neoadjuvant chemotherapy has also become foreminent (4). CRS + HIPEC was carried out as a second or third step treatment in all gynecological cancers included in our study. The first randomized prospective study of HIPEC in gynecological cancers was published in 2015 by Spiliotis et al. In this study, 120 women with advanced ovarian cancer (FIGO IIIc and IV) who experienced recurrence after primary staging surgery and systemic chemotherapy throughout an eight-year period between 2006 and 2013 were randomized. Patient group divided into two subgroups, only CRS followed by systemic chemotherapy was an arm, CRS + HIPEC and systemic chemotherapy was the other arm. When the results were analyzed, mean survival was significantly higher in the group in which HIPEC was performed (26.7 versus 13.4 months, $p < 0.006$). The study also shown that complete cytoreduction is associated with longer survival in parallel with many other studies (23). In the study published by Van Driel et al., 245 patients with advanced stage ovarian cancer were evaluated. HIPEC was performed during interval surgery after neoadjuvant chemotherapy. Following three neoadjuvant chemotherapy cycles, patients were divided into two groups. The first group consisting of 123 patients received CRS and adjuvant chemotherapy, the second group consisting of 122 patients received CRS + HIPEC and adjuvant chemotherapy. According to the results of the study, the mean progression-free survival was 10.7 months in the first group, 14.2 months ($p = 0.003$) in the HIPEC group. Mean overall survival was 33.9 months in the first group, 45.7 months ($p = 0.01$) in the HIPEC group (24).

Peritoneal pseudomyxoma is a clinicopathological syndrome due to the accumulation of abundant mucin (> 90%) in the peritoneum. It may occur in various primary malignancies that produce mucin (90% of appendix tumors, as well as ovarian, colonic, pancreatic and urachus tumors). Histopathological subtypes have a severe prognostic effect. Low-grade peritoneal pseudomyxoma(PP) (common peritoneal adenomucinous) is two times more common than high-grade PP (peritoneal mucinous carcinomatosis). The traditional treatment approach of peritoneal pseudomyxoma is maximal CRS that gives poor results. 5 and 10 years survivals are very low in this approach. The new therapeutic approach is the combination of CRS + HIPEC which gives good results. In a retrospective, multicentric study of 2298 patients which had peritoneal pseudomyxoma, postoperative mortality was 2%, median survival was 196 months (16 years), and 10-year survival was 63%. Recently, an international cohort study was published including 1924 patients with PMP, investigating the outcome after CRS with or without HIPEC . It was found that the addition of HIPEC after CRS was associated with a significantly better overall survival as compared to CRS alone with a 5-year overall survival of 58% versus 46.2% respectively. The addition of HIPEC did not result in more postoperative complications. Therefore, CRS and HIPEC is proposed as the standard of care in patients with low grade appendiceal neoplasms associated with PMP (22, 25). Because of the superiority of these results compared to conventional therapy, the CRS + HIPEC approach has become the gold standard treatment for peritoneal pseudomyxoma. in contrast to peritoneal metastases of colorectal cancers, PCI does not have major effect on prognosis in peritoneal pseudomyxoma (7, 26). In our study, one patient underwent CRS + HIPEC due to peritoneal pseudomyxoma. His follow-up continues with disease-free survival of 26 months.

Malignant peritoneal mesothelioma (MPM) is considered as a fatal entity. Three subtypes of MPM have been defined as epithelioid, mixed / biphasic and sarcomatoid. Systemic chemotherapy and surgery provide limited benefit. CRS + HIPEC achieved remarkable improvement in the results of MPM compared to conventional systemic chemotherapy. In a phase II study in which 49 patients underwent CRS + HIPEC, the median survival was encouraging with 92 months.1, 2, 3, and 5-year survival rates were 86%, 77%, 59%, and 59%, respectively. The morbidity rate was 25%, and none of perioperative mortality was observed. In addition, factors associated with improved overall

survival were previous debulking surgery, absence of deep tissue invasion, minimal residual disease after surgical resection, and being under 60 years of age (27). In another observational study which include 20 patients with peritoneal mesothelioma treated with CRS + HIPEC, the median survival was 29.5 months. 1 and 3 years survival rates were 78.2% and 46.3%, respectively (28). It has been found that survival is affected by the completeness of cytoreduction and histological subtype (28, 29). In our study, two patients were treated due to malignant peritoneal mesothelioma and both patients had PCI scores above 20. One of the patients is followed up in the postoperative 2nd month and the other in the 19th month without recurrence.

Consequently, patients with primary diagnosis of colorectal cancer, ovarian cancer, appendix cancer, gastric cancer (selected cases), malignant peritoneal mesothelioma, peritoneal pseudomyxoma who have peritoneal involvement and/or resectable disease limited to the abdomen should be carefully evaluated in multidisciplinary oncology councils and CRS+HIPEC approach should be considered as the first choice.

Declarations

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This study was approved by the Eskişehir Osmangazi University non-invasive clinical research ethics committee with the date of 12.01.2021 and number of 7. The study was conducted according to a recent version of the declaration of Helsinki.

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ORIGINAL ARTICLE

Comparison of Lateral Pinning and Cross Pinning Results in Pediatric Distal Humerus Supracondylar Gartland Type 3 Fractures

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Abstract

Background: In this study, we aimed to evaluate the functional outcomes and complications of Gartland type 3 patients treated with lateral pinning and cross pinning in children aged between five and ten years.

Methods: Seventy-four fractures participated in the study, and the data were analyzed. Patients in the lateral pinning group (n:41) were treated with the lateral entry pin alone, and patients in the cross pinning group (n:33) were treated with a combination of 2 lateral entry pins and one medial entry pin. Age, gender, fractured side, Vong Baker pain scale score, duration of surgery, postoperative complications, surgical approach, direction of pin application (lateral or cross), and Modified Flynn grading system grade was noted.

Results: No statistically significant difference was found between lateral pinning and crossed pinning groups in terms of the grade of the Modified Flynn grading system and complications (iatrogenic ulnar nerve damage, loss of reduction, and superficial infection) (respectively, p: 0.138 and p: 0.991).

Conclusion: When both techniques were performed carefully, successful clinical results were observed. If the surgeon detects intraoperative instability, s/he should not hesitate to pin the medial K-wire in order to increase stability.

Keywords: Pediatric Fractures, Supracondylar Humerus Fractures, Cross Pinning, Lateral Pinning.

INTRODUCTION

Pediatric distal humerus supracondylar fractures are the most common fractures that account for more than 50% of fractures around the elbow in children (1). Classically, these injuries are divided into extension and flexion types. The extension type is the most common type (2). The most widely accepted classification of pediatric distal humeral supracondylar fractures is the Gartland classification (3). While type I fractures are typically treated non-surgically, some type II and almost all type III fractures usually require surgical intervention (4). Closed reduction and percutaneous pinning is the universally accepted treatment modality for displaced pediatric distal humerus supracondylar fractures. Pin configuration has been the focus of many recent research studies on the treatment of type 3 fractures (5-7).

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There are two common pin fixing techniques: lateral pinning only and cross pinning with at least one medial and at least one lateral (8). Theoretically, cross-entry pins have the advantage of improved mechanical stability of the configuration, however, this technique increases potential injury to the ulnar nerve (9, 10). Although injury to the ulnar nerve can be avoided, only lateral entry pins can reduce the mechanical stability of the structure (11). Biomechanical tests have shown that both medial and lateral cross pinning is more advantageous (12, 13). Nevertheless, the risk of iatrogenic ulnar nerve injury during medial pin placement preoccupies surgeons in medial pin placement (14).

In this study, it was aimed to analyze the functional outcomes and complications of Gartland type 3 patients aged between five and ten years who were treated with lateral pinning and cross pinning.

MATERIALS AND METHODS

This study was approved by the Erzurum Regional Training and Research Hospitals' local ethics committee (Date: 21.06.2021 No: KAEK 2021/12-199), and the study was conducted according to the Declaration of Helsinki 1975. Between May 2017 and May 2020, 99 patients with pediatric distal humerus supracondylar fractures who were hospitalized and planned for surgery were identified. Inclusion criteria were defined as; patients with a Gartland type 3 supracondylar fracture, aged between five and ten years, and at least 12 weeks of follow-up. Patients who had multiple fractures at the time of injury (n:11), whose data could not be accessed (n:8), and whose follow-up was delayed (n:7) were excluded from the study. After applying our criteria, the medical data of 74 patients (31 boys and 43 girls, mean age 7.08±1.42) who underwent surgery for a Gartland type III pediatric distal humerus supracondylar fracture were documented and analyzed retrospectively.

The recorded data were as follows; age, gender, fractured side (right or left), vong Baker pain scale score, operation time, postoperative complications, surgical approach, number of pins, direction of pin application (lateral or cross), and Modified Flynn grading system grade.

Surgical technique

All interventions were performed under general anesthesia by a surgical team working in the same clinic. A closed reduction maneuver was performed to all fractures, and patients who could not achieve closed reduction underwent open surgery with a lateral approach. An anterior open approach was performed to patients with preoperative anterior interosseous nerve (median nerve) injury. After reduction, it was stabilized in the reduction position provided under the scope with two or four percutaneous K-wires (k-wires determined according to the patient's age and bone cortex thickness). Two K-wires were placed laterally as standard procedure. A third K-wire was placed medially in a mini-open not exceeding a total of 3 K-wires, with stability assessed by the intraoperative C-arm fluoroscopy system. After the wires were cut, the ends were bent and left on the skin. After the K-wire dressing, the elbow joint was splinted to be immobilized in neutral rotation and 90° flexion position for three weeks.

Postoperative follow-up was made routinely, radiologically, and clinically at the first, second, third, fourth, sixth, eighth, twelfth, twenty-fourth weeks and at the end of the first year. The splint was terminated in the third week. Active movements were encouraged by teaching the child and family without removing the K-wires. In the fourth week, the K-wires were removed in the orthopedic clinic. Active-passive movements of the elbow were started. Exhausting - demanding activities were restricted for another four weeks.

Pain assessment was performed with the Wong–Baker Faces Pain Rating Scale preoperatively and at the 12th-week clinical examination (15). The children were asked to choose the facial expression that best described their pain.

Evaluation of clinical results was made with the modified Flynn grading system at 12 weeks and at the end of the first year (16,17). Modified Flynn grading system's criteria include two factors: Cosmetic factor (loss of carrying angle degree) and functional factor (motion loss in degrees). Results were grouped into satisfactory [Excellent (0 to 5) - Good (6 to 10)] / Unsatisfactory [Fair (11 to 15) – Poor (>15)]. The final modified Flynn grade result was noted according to whichever cosmetic or functional factor was worse (18). The range of motion of the joint was measured with the goniometer. Measurements were made considering passive movements. Restoration of a full range of motion of the elbow was defined as the range of elbow flexion/extension less than 5° as measured by the uninjured elbow (19).

Statistical Analysis

While making the statistics of the study, numerical data were given as mean and standard deviation, and categorical data were given as numbers and percentages in descriptive statistics. The distribution of numerical data was analyzed with histogram graphics. Student t-test and Mann-Whitney U test were used after checking the suitability of the numerical data to the normal distribution in two separate groups. Chi-square and Fisher's Exact test were used to compare categorical data. P significance value was accepted as 0.05. SPSS 23.0 package program was used in the analysis.

RESULTS

A total of 74 people were included in the study. While 41 of the patients were in the lateral pinning group, 33 of them were in the cross pinning group (Figure 1.). The mean age of all patients was 7.08±1.42. No significant age difference was observed between the groups in the study (p: 0.173). 41.9% (n:31) of the patients were female and 58.1% (n:43) were male. In the study, no significant difference was observed between the groups in terms of gender (p: 0.302). There was no significant difference between the groups in terms of parties (p: 0.898). Some descriptive data of the patients and the differences between the groups are given in Table 1. In the study, no statistically significant difference was found between the groups in terms of Modified Flynn grading system, Common Modified Flynn grading system, and complications (respectively; p: 0.138 and p: 0.991) (Table 1).

Table 1. Analysis of demographic data

Features		Lateral pinning group (n:41)	Cross pinning group (n:33)	p
Age (Mean±SD)		6.88±1.52	7.33±1.26	0.173
Gender	Girl	26	17	0.302
	Boy	15	16	
Side	Right	18	14	0.898
	Left	23	19	
Preoperative neurological examination	No	39	32	0.689
	Anterior interosseous nerve injury	2	1	
Surgical approach	Closed	29	26	0.430
	Open	12	7	
Surgical approach in detail	Closed	29	26	0.397
	Anterior	2	0	
	Lateral	10	7	
Complication	Yes	4	4	0.745
	No	37	29	
Complications in detail	No	37	29	0.991
	Iatrogenic ulnar injury	1	1	
	Reduction loss	1	1	
	Superficial infection	2	2	
Fracture type	Flexion	2	1	0.689
	Extension	39	32	
Modified Flynn grading system results in detail	Excellent	32	19	0.138
	Good	7	8	
	Fair	2	5	
	Poor	0	1	
Modified Flynn grading system results	Satisfactory	39	27	0.067
	Unsatisfactory	2	6	

There was no significant difference between the groups in terms of operation time (min), Preop vong Baker pain scores, and Postop vong Baker pain scores (Table 2).

Table 2. Comparison of operation time and pain score results between groups

	Groups								
	Lateral pinning group (n:41)				**Cross pinning group** (n:33)				
	Min.	Max	Mean	SS	Min.	Max.	Mean	SS	p
Age	5	9	6.88	1.52	5	9	7.33	1.26	0.173
Operation time (min)	20	75	31.68	10.92	19	65	35.85	12.03	0.203
Wong–Baker Scale Score	6	10	7.17	1.26	6	10	7.27	1.48	0.904
Wong–Baker Scale Score	0	2	0.10	0.43	0	2	0.18	0.58	0.476

DISCUSSION

Pediatric distal humerus supracondylar fractures are the most common injuries around the elbow and usually occur in the first decade of life (20). The treatment of displaced pediatric distal humerus supracondylar fractures is surgery. There is no accurate consensus on the appropriateness of the optimal K-wire configuration technique (12, 13, 21). The two most preferred techniques are the cross K-wire or just lateral K-wire techniques (5, 6). In our study, we also did not find a statistical difference between lateral pinning and cross pinning in terms of functional results and complications in Gartland type 3 distal humerus supracondylar fractures in children aged between five and ten years.

Cross pin fixation of a pediatric distal humerus supracondylar fracture was first described in 1948 (22). Although there is a risk of iatrogenic ulnar nerve injury in this technique, the cross K-wire pinning technique continues to be used today with excellent results and low morbidity (5, 6, 11). We consider that the average of 5% ulnar nerve injury reported in the literature can be prevented by clever placement using the medial mini-open technique (23-25). In our study, we observed iatrogenic ulnar nerve damage in 1 patient in each group, and this was below the literature average.

In a study conducted by Kwak-Lee et al. (26), the crossed pinning technique was performed on 47 patients, and it was reported that iatrogenic ulnar pin terrain was not observed in any of the patients. It was suggested that the medial pinning was safe to use when an appropriate technique was followed. It was also argued that although insertion of the medial pins leads to more extended operations, it does not result in a higher incidence of complications.

In another study comparing lateral and cross pinning by Maity et al. (27) 160 supracondylar fractures were evaluated; a statistically significant difference about complications was not found between the two groups. It was stated that if a standard technique is followed, there will be no difference in terms of effectiveness and safety.

In a meta-analysis conducted in 2018; considering the potential risks of lateral pinning with only two K-wires (risk of poor functional outcome) and crossed K-pins (risk of iatrogenic ulnar nerve injury), it was suggested the recommended technique for the treatment of pediatric distal humerus supracondylar fractures as the lateral access technique. Moreover, it was stated that the stability of the fracture fixation with a third k-wire placed laterally could be increased and that extra K-wire may be an option for surgeons who want to avoid the medial pinning. It was also indicated that additional protective measures should be taken for the ulnar nerve by surgeons who want a more stable structure with the cross-entry technique (11).

Our study has several limitations. First, it was a retrospective study, and no randomization was performed. Another limitation was that the number of patients included in the groups was not very high. Randomized and prospective studies involving bigger groups are needed for better results.

Consequently, when performed carefully, both techniques yield successful clinical results. When medial K-wire

placement is desired, ulnar nerve iatrogenic injury can be minimized when the K-wire is placed using a careful mini-open technique. If the surgeon detects intraoperative instability, s/he should not hesitate to pin the medial K-wire in order to increase stability.

Declarations

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This study was approved by the Erzurum Regional Training and Research Hospitals' local ethics committee (Date: 21.06.2021 No: KAEK 2021/12-199), and the study was conducted according to the Declaration of Helsinki 1975.

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ORIGINAL ARTICLE

Abduction Orthosis in Treatment of Primary Acetabular Dysplasia: Results of Three Years Follow-up

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Abstract

Background: Acetabular dysplasia (AD) may appear after six-months-old despite normal previous physical and ultrasonographic examination, and management remains unclear. The purpose of the current study was to evaluate the success of abduction orthosis in the treatment of primary AD patients.

Methods: Patients presented with AD between 2010-2017 were retrospectively reviewed. The study included AD patients who had stable hip joints on previous physical examination and Graf type1 on ultrasonography when younger than six months. AD was diagnosed according to the age-related acetabular index (AI) values. Abduction orthoses were applied full-time for five months plus part-time for three months. AI was re-measured at the sixth month, at the end of the first and third year. AI change was compared between dysplastic and nondysplastic hips.

Results: It was evaluated 60 hips of 39 patients with AD treated with abduction orthosis at the median age of 6 months. The mean AI was 31.4 (range: 29-35)°±2.1° in dysplastic hips. AI decreased to 26.5°±2.2°, 24.5°±2°, 21°±2.1° at sixth months, first and third years after treatment; respectively. The mean AI of non-dysplastic hips was 25.3°(range: 22-28)±2.1°; and decreased to 22.6°±2.4°, 21.1°±2°, 17.9°±1.8° at sixth months, first and third years follow-ups, respectively. At the end of the first six months, dysplastic hips had significantly better improvement in AI (4.9±2.1°) compared to non-dysplastic hips (2.7°±0.8°) ($p<0.001$). There was no significant difference in AI improvement after six months.

Conclusion: Primary acetabular dysplasia should not be ignored despite normal previous physical and ultrasonographic examination. Abduction orthosis may be used in the treatment of children with primary AD older than six months.

Keywords: Hip Dysplasia, Abduction Brace, Acetabular Index.

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INTRODUCTION

Developmental dysplasia of the hip (DDH) denotes a wide spectrum of pathologic conditions, ranging from subtle acetabular dysplasia to irreducible hip dislocation. The main factors for the normal development of acetabulum are a stable, concentrically reduced femoral head into the acetabular cavity and adequate femoral head growth. Despite a normal acetabulum-femoral head positioning, in some cases, the development of acetabulum may remain inadequate. This condition is defined as acetabular dysplasia and can be secondary to treatment or primary in case of inadequate development of acetabulum.

Despite the growing number of cases presenting with clinically stable, reduced hips but with an increased age-related acetabular index (AI) on the anteroposterior (AP) pelvic radiographs after the age of six month; in the literature, there is little data about identifying those patients. Furthermore, management is still controversial. Spontaneous resolution of dysplasia without intervention is unlikely in children over the age of 6 months (1). When DDH is recognized in the first 6 months of life, treatment with a Pavlik harness frequently results in an excellent outcome (2-4). In contrast, treatment of older children may be challenging due to the lower efficacy and difficulty of using the Pavlik harness. There is increasing data in the literature about abduction orthosis that can be used in the treatment of DDH patients older than six months of age instead of Pavlik harness (5-8).

The aim of the current study was to evaluate the success of abduction orthosis in treating acetabular dysplasia patients with an increased age-related AI on AP pelvic X-rays with clinically normal hips on both previous physical and ultrasonographic examinations.

MATERIALS AND METHODS

The study protocol was approved by the Dışkapı Yıldırım Beyazıt Training and Research Hospitals' Ethics Committee (Date: 22.11.2016 – No: 32/18), and it was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all subjects.

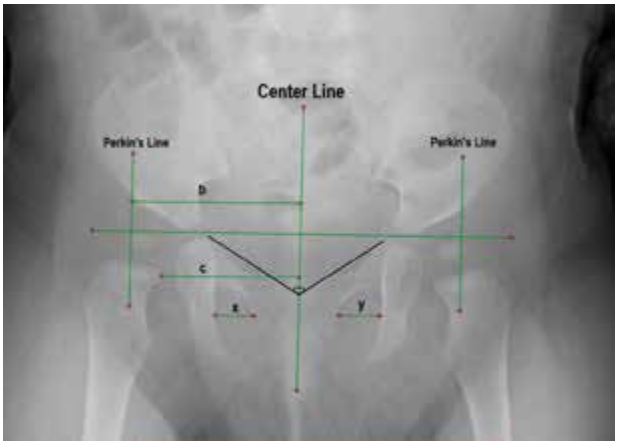
Patients who presented with DDH to our department between January 2010 and January 2017 were retrospectively reviewed. On previous physical examination, acetabular dysplasia patients with increased age-related AI had stable hip joints (Ortolani test and Barlow maneuvers were negative), and Graf type 1 hip on ultrasonography when younger than six months were included study. Patients with teratologic hips, syndromic dysplasia, and those who required closed or open reduction were excluded. Sixty eligible hips of 39 patients treated with abduction orthoses and followed at least three years completed the study. Sex, family history of DDH, and other risk factors for DDH, including firstborn status, multiple gestations, delivery presentation (such as vertex and breech), oligohydramnios, swaddling for each patient, were recorded.

The angle of the acetabular index(AI) measured from the pelvic AP radiograph is an easy and reliable method for diagnosing acetabular dysplasia (9-11). Initial AI was measured, acetabular dysplasia was diagnosed by AI according to the age-related values given by Tönnis (12) (Table 1). Acetabular dysplasia was classified into two categories: mild dysplasia as between 1-2 standard deviations; and severe dysplasia as above two standard deviations at the beginning and end of the three-year follow-up. In order to diagnose primary acetabular dysplasia, it is necessary to rule out hip dislocation. So, the femoral head must be developed adequately and concentrically reduced into the acetabular cavity. For the definition of the concentrically reduced femoral head into the acetabular cavity, we evaluated two conditions: first, the femoral head should be located in the inferomedial quadrant of Perkins; second, eccentration index of Smith (c/b index) (13) should be within normal ranges. In order to minimize errors due to pelvic rotation in both the longitudinal and transverse body axis, measurements were made on radiographs which pelvic rotation(x/y) and the AP pelvic tilt index(symphysis-os ischium angle) is normal range as previously described (12) (Figure 1).

Table 1. Age-related acetabular index according to Tönnis

Ages	Girls				Boys			
	Mild dysplasia above (S)		*Severe dysplasia above (2S)*		*Mild dysplasia above (S)*		*Severe dysplasia above (2S)*	
	right	*left*	*right*	*left*	*right*	*left*	*right*	*left*
5-6 months	27.3	29.3	31.8	34.1	24.2	26.8	29.0	31.6
7-9 months	25.3	26.6	29.4	31.1	24.6	25.4	28.9	29.5
10-12 months	24.7	27.1	28.6	31.4	23.2	25.2	27.0	29.1
13-15 months	24.6	26.9	29.0	31.7	23.1	24.0	27.5	27.7
16-18 months	25.0	26.1	29.3	30.4	23.8	25.8	28.1	30.0
3-5 years	17.9	21.2	21.3	25.8	19.2	19.8	23.5	23.8

Figure 1. Parameters measured on pelvic radiography



Abduction orthoses were applied in patients with acetabular dysplasia for five months (range 4-6 months) full-time (only one hour of brace-free time was allowed for bathing, diaper changes etc.). If improvement was achieved in follow-up visits, families were instructed to use braces part-time (mean 12 hours a day) for three months (range 2-4 months) more. Braces were custom-made for each patient individually. Abduction braces are semi-rigid orthoses that maintain 45° abduction and 30-40° flexion of bilateral hips and reduce femoral head into the acetabulum. It allows partial hip movements while knees are free to move so that patients can sit.

AI was re-measured at the sixth month, at the end of the first year, and third year. (Figure 2-5) Changes in the AI values between the initial and follow-up visits were evaluated. In the current study, all radiographic measurements were made by a single, experienced researcher. An intraclass correlation coefficient (ICC) analysis was also performed. Digital PACS software was used for radiographs, which had been shown good reliability and reproducibility (14).

Figure 2. Acetabular Index at initial X-ray

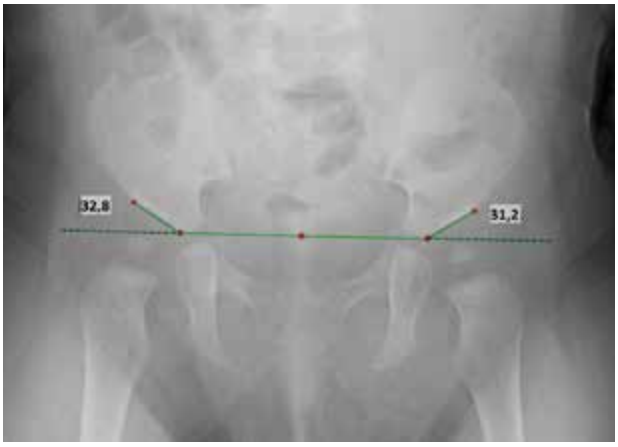


Figure 3. Acetabular Index at sixth-month follow-up

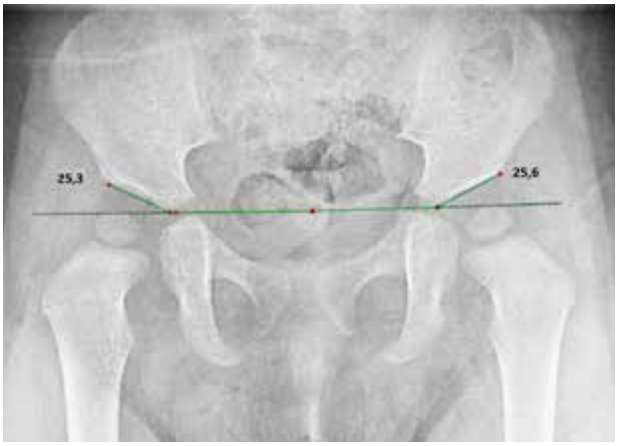


Figure 4. Acetabular Index at first-year follow-up

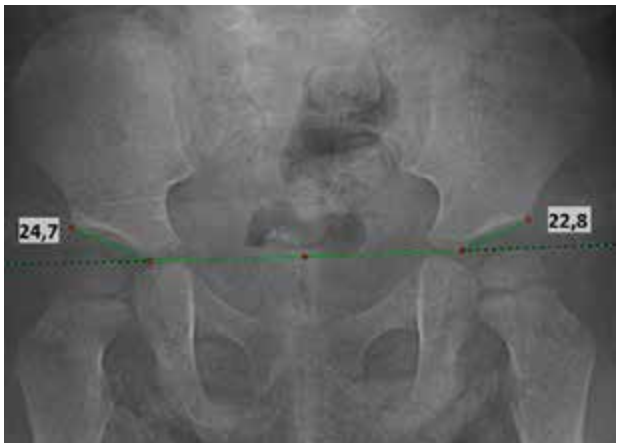
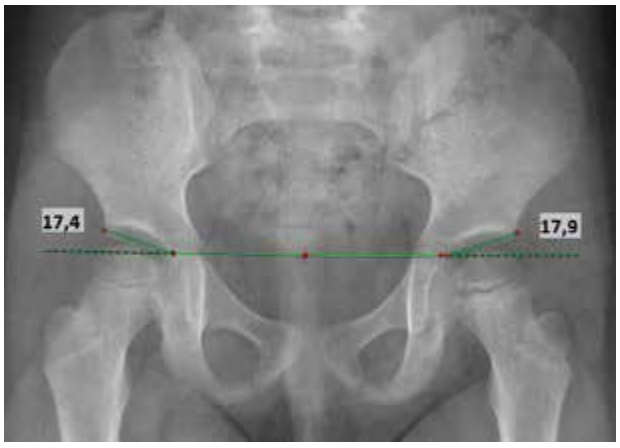


Figure 5. Acetabular Index at third-year follow-up



Since there is no control group in the current study due to ethical considerations regarding left children untreated, we compared the change in AI between the dysplastic hips group and the non-dysplastic hips group.

Statistical analysis was performed using the statistical software SPSS for Windows, version 26. Shapiro-Wilks test was used to evaluate the distribution of continuous variables. Data are presented as mean-SD after testing for normal distribution. If the test for normal distribution failed, the median (minimum-maximum) values were given. Nominal variables are shown as the number of cases and percentage (%). The significance of the differences between the dysplastic and non-dysplastic hips was investigated using Student's t-test and the Mann-Whitney U test. The Chi-square and Fisher's exact Chi-square test were used to test the difference in nominal data between the groups. A multivariate analysis of variance (ANOVA) was used to test time effects combined with group effects on the dependent variables (e.g., AI). The Bonferroni test was used (for all changes) to understand when and how the time was different. A p-value of below 0.05 was considered statistically significant.

RESULTS

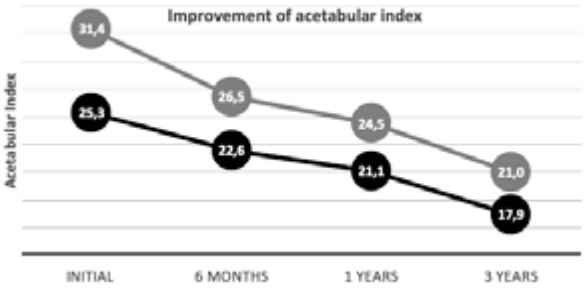
It was identified 96 dysplastic patients who met inclusion criteria from patients admitted to our clinic for DDH. Fifty-seven patients were excluded from the study (due to inappropriate radiographs in 37 patients, inadequate data in 16 patients, inability to use the brace in 2 patients, and closed reduction because of subluxation in 2 patients). We evaluated 60 hips of 39 patients with acetabular dysplasia treated with abduction brace at the median age of 6 months old (range 5- 10 months). 34 (87%) of patients were females, 21 (54%) patients had bilateral acetabular dysplasia. 27 (45%) of 60 hips were right-sided, 33 (55%) hips were left-sided. According to Tönnis classification; 33 (55%) hips (23 left/10 right) had mild dysplasia, and 27 (45 %) hips (10 left/17 right) had severe dysplasia. The demographics and baseline clinical characteristics of the patients who completed the study were summarized in Table 2.

Table 2. Demographic and clinical characteristics of patients

Age at initial examination (months) *[median (min-max)]*	6 (5-10)
Gender, *[n (%)]*	
Male	5 (13)
Female	34 (87)
Risk Factor, *[n (%)]*	18 (46)
Family history of DDH	12 (31)
First Born	9 (23)
Swaddling	1 (3)
Oligohydramnios	2 (5)
Breech presentation	4 (10)
Location *[n (%)]*	
Unilateral	18 (46)
Right	6 (15)
Left	12 (31)
Bilateral	21 (54)
Tönnis *[n (%)]*	n:60
Mild Dysplasia	33 (55)
Right	10 (17)
Left	23 (38)
Severe Dysplasia	27(45)
Right	17(28)
Left	10(17)
DDH: Developmental dysplasia of the hip	

The mean AI was 31.4°±2.1° (range: 29-35°) at the initiation of the brace treatment of 60 dysplastic hips. After abduction orthosis treatment, AI decreased to 26.5°±2.2° at six months follow-up, to 24.5°±2°, and 21°±2.1° at 12 months and 36 months; respectively. The decrease in AI value was statistically significant in all follow-up ($p<0.001$). The mean AI change was 4.9°±2.1 in the first six months, 2°±1.3 in the second six months of period, and 3.5°±1.7 in the subsequent two years. The improvement in AI was significantly better in the first six months compared to the second six months and subsequent two years ($p<0.001$). The mean AI of 18 non-dysplastic hips was 25.3°±2.1° (range: 22-28°) before bracing. AI decreased to 22.6°±2.4°, 21.1°±2°, and 17.9°±1.8° at six months, 12 months, and 36 months follow-up visits after treatment, respectively. The decrease in AI value was statistically significant in all follow-up($p<0.001$) (Figure 6).

Figure 6. Improvement of Acetabular Index



When we compare dysplastic and non-dysplastic hips, AI decreased more in dysplastic hips in all follow-up. At the end of the first six months of follow-up, dysplastic hips had significantly better improvement in the AI of 4.9±2.1° compared with non-dysplastic hips, which had improvement in AI of 2.7°±0.8° ($p<0.001$). There was no significant difference between the two groups in terms of improvement in AI after six months follow-up visit (6-12 months p: 0.175; 6-36 months p: 0.134; 12-36 months p:0.38).

At the end of three years follow up period, dysplastic hips were reclassified according to Tönnis: 14 of mild dysplastic and 6 of severe dysplastic hips were stratified into normal group, and also 18 of severe dysplastic hips were stratified into mild dysplasia group; while the remaining 18 mild and four severe dysplastic hips had shown no improvement. Follow-up was continued without surgical intervention due to the absence of luxation or subluxation in nonresponders to acetabular bracing.

None of the patients had avascular necrosis or complications of using a brace.

DISCUSSION

The current study aims to evaluate primary acetabular dysplasia, excluding residual acetabular dysplasia secondary to management with surgery or conservative method, and this is the most significant difference from the earlier studies in the literature (15). Our findings show that abduction orthosis is an effective method in the treatment of patients with acetabular dysplasia. Regarding dysplastic hips, nearly half (47%) of the average 10.4 degrees improvement in AI during a three-year follow-up period occurred in the first six months of abduction orthosis. 37% of AI improvement in non-dysplastic hips was observed in the same period (Figure 4). AI improvement after the first six months did not differ between dysplastic and non-dysplastic hips groups. Salter reported that acetabular remodeling slows down after 18 months of age (16). It was considered that AD could be treated with abduction orthosis more effectively in this highest remodeling time.

Acetabular dysplasia could be easily underestimated due to late-onset symptoms or even asymptomatic contrary to hip dislocation, but prevalence and importance are more than predicted. In a systematic review of the literature conducted by Shaw and et al. (15), radiographic evidence of late dysplasia was present in 9,49% hips and 4,14% hips requiring additional surgery of 6029 hips treated with the Pavlik method an average of 5.29 years follow-up. Dornacher et al. detected residual dysplasia in 30% of their patients on pelvic X-rays when children started walking even after successful ultrasound-monitored treatment (17). Sarkissian et al. showed that 17% of all infants, who had achieved both normal ultrasonographic and clinical examinations at an average of three months, demonstrated radiographic signs of acetabular dysplasia at the age of average six months (18). Based on the findings, they suggested radiographic follow-up in this population of infants through at least walking age to allow timely diagnosis and early intervention of residual acetabular dysplasia. Management of acetabular dysplasia remains unclear despite high prevalence. Especially treatment between 6 months and 18 months is highly controversial; because the effectiveness of Pavlic harness decreases after the age of 6 months, and the pelvic osteotomy is recommended after 18 months of age. Expecting and

waiting for enough acetabular remodeling to enhance normal development and optimal femoral coverage with aging is not realistic and also leads to late interventions and results with more complicated dysplasia cases. It will be unexpected to resolve spontaneously (1). Pavlik harness is an effective and reliable method in the treatment of DDH, but effectiveness decreases in infants older than six months of age and even older than four months(19). Abduction orthosis is increasingly used in this age group of patients after unsuccessful results of Pavlik harness in these older and more active children. There is little data about using abduction orthoses in the treatment of acetabular dysplasia in the literature. Gans et al. studied infants with stable, treated DDH but residual acetabular dysplasia at six months of age, started bracing when the 6-month radiograph demonstrates an AI>30 degrees, whereas others do not; compared the analysis of treated with abduction bracing or observation, part-time bracing significantly improved the acetabular index between 6 and 12 months of age(6).

Dysplastic hips were reclassified according to Tönnis' gender and age-related classification at the end of the three-year follow-up period. Although significant improvement in AI of 28 severe and 32 mild dysplastic hips with the establishment of abduction orthosis, 4 (7%) hips was still found severe dysplastic, and 36 (60%) hips were mild dysplastic at the end of three years follow up period. Four still severe dysplastic hips were followed up without treatment due to the non-existence of luxation or subluxation. 2 of the hips achieved normal AI at an average of 5 years of age, and the remaining two hips achieved it at about six years of age. It could be expected the vast majority of hips may be achieved normal values of AI if the follow-up period had been longer.

There are some limitations of the current study. First, a small number of primary acetabular dysplasia cases were eligible for our inclusion criteria despite a 6-year study period. The second was the absence of a control group which was followed without treatment. Because the inclusion of a control group including untreated children with AD is unethical, we could emphasize that unilateral dysplastic hips benefited more than their symmetric normal hips with the treatment of abduction orthosis. Therefore, we could not argue the superiority of abduction orthosis to observation without treatment. Similarly we could not argue treatment differentiation of primary acetabular dysplasia from the residual dysplasia cases secondary to conservative or surgical management. A third of the limitation was an accumulation of the cases in a range of age, so we cannot comment about abduction orthosis is effective into which age and how long we should continue bracing the patients. The most important strength of the current study is the long follow-up period with three years, which we believe is long enough to demonstrate the effectiveness and safety of abduction orthosis.

In conclusion, acetabular dysplasia may appear after six months old despite normal previous physical and sonographic examination. Abduction orthosis may be used in the treatment of children with primary acetabular dysplasia older than six months of age. AI improved significantly better in dysplastic hips compared to non-dysplastic hips in the first six months of an orthosis. The current study does not conclude that abduction orthosis is better than the natural course of dysplasia since a control group is absent. However, abduction orthosis is a safe, effective, and conservative method that may reduce the risk for early-onset osteoarthritis and the need for future surgical management. There is a need for future studies to assess which age effectivity lasts and how long orthosis should continue to apply.

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 Dışkapı Yıldırım Beyazıt Training and Research Hospitals' Ethics Committee (Date: 22.11.2016 – No: 32/18), and it was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

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ORIGINAL ARTICLE

Outcomes of Consultations to Burn Units from Emergency Service

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Abstract

Background: In addition to being painful, burns cause aesthetic anxiety, causing patients to apply to the emergencies as soon as it occurs, and their first interventions are made in the emergency. In this study, the compliance with the guidelines in the consultations requested from the burn center and the referral of the patients to the center was evaluated.

Methods: Burn etiology, TBSA, burn depth, and area of adult patients were recorded, applied to our hospital's emergency with burns in 2019 and 2020, and were asked for consultation from the burn center.

Results: Within two years, consultation was requested from the burn center for a total of 288 patients. Of the consulted patients, 73 (25.3%) were admitted to the center. When the evaluation was made between the patients who were hospitalized and not, the burn depth, etiology, and the percentage of TBSA were statistically significant.

Conclusions: Indications for referral and hospitalization to burn centers have been determined with specific clinical guidelines. A significant result that stands out in this study is that 215 out of 288 consultations requested from the burn center didn't have an indication for hospitalization. With this study, the necessity of reconsidering the tendency to ask for a consultation has emerged. Emergency medicine physicians should be well-equipped with minor burn dressings as well as having knowledge about first response, referral decision and management. In this regard, if there is a burn unit/center in university hospitals or education hospitals, rotation of emergency medicine residents to burn treatment units should be discussed.

Keywords: Burns, Consultation, Burn Treatment Center.

INTRODUCTION

As in many countries, burn trauma is quite common in Turkey. In recent years, burn-related death rates have been decreasing thanks to burn treatment centers where new approaches in burn management, early resuscitation, and multidisciplinary treatment strategies can be applied. However, long-term rehabilitation and reconstructive surgery are gaining importance (1). Burn injuries occur in all segments of society. In addition to being painful, it causes aesthetic anxiety and causes patients to apply to the emergency service immediately from the moment it occurs. The first response to burn trauma is very important. For this reason, The Burn Treatment and Referral Guideline published by the American Burn Association (ABA) is used worldwide (2). Countries have made revisions to these guidelines in accordance with their own internal dynamics (1,3,4). In Turkey, Yastı et al. published a guideline in accordance with current burn treatment principles and taking into account the

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conditions of our country, and it has been put into practice (5). In this study, it has been evaluated how well the guidelines are complied with regarding the consultations requested from the burn center for burn patients admitted to the emergency department and the referral of these patients to the center within a training and education hospital.

MATERIALS AND METHODS

In this retrospective study, the records of adult patients who applied to the emergency department of our hospital with burns and were consulted from the burn treatment center in 2019 and 2020 were scanned through the hospital information management system. Burn etiology, total body burn surface area (TBSA), burn depth, burn area were recorded. As a result of the requested consultation, the patients were evaluated according to their hospitalization status in the burn treatment center. Statistical analysis of clinical and demographic data was performed using mean and standard deviation. Chi-square test was used to compare the groups; $p < 0.05$ was considered statistically significant. The study was conducted with the approval of the Ankara City Hospital Ethics Committee dated 09/12/2020 and numbered E1-20-1383. Since the study was retrospective, an informed consent form was not used.

RESULTS

A total of 288 patients, who were admitted to the emergency center, were consulted from the burn treatment center in the two years that patient records were reviewed. As a result of the consultation evaluation, 73 patients (25.3%) were admitted to the burn treatment center. Considering all the consultations were requested, it was seen that 122 (42.4%) patients were burned with hot liquid and 95 (33%) patients with flame. Flame burns were the most common among hospitalized patients (42.5%). While the mean TBSA was 13.22% in hospitalized patients, with a range of 1 to 80%, 68.5% of these patients had specific burn areas. Burn-related demographic data of the patients for whom consultation was requested are presented in Table 1 in detail. When the evaluation was made between the patients who were admitted to the hospital and those who were not, the depth of burn, etiology, and percentage of TBSA were evaluated as statistically significant. ($p<0.001$, $p<0.001$, $p<0.001$, respectively)

Table 1. Characterestics of Patients Consultated Burn Unit

	Outpatient	Inpatient	Total	p-value
# of patients	215 (74.7%)	73 (25.3%)	288	
Burn Etiology				**<0.001**
Scald	103(82.8%)	21(17.2%)	124(43.1%)	
Fire	64(67.4%)	31(32.6%)	95(33%)	
Electric	10(40%)	15(60%)	25(8.7%)	
Chemical	19(86.4%)	3(13.6%)	22(7.6%)	
Radiation	7(87.5%)	1(12.5%)	8(2.8%)	
Frosbite	3(100%)	0	3(1%)	
Others	9(81.8%)	2(18.2%)	11 (3.8%)	
Burn Debth				**<0.001**
First degree	34	0	34(11.8%)	
Second degree	173 (77.2%)	51(22.8%)	224(77.8%)	
Third degree	8 (26.7%)	22 (73.3%)	30(10.4%)	
TVYA%(Avg)	4.48%	13.22%	6.69%	**<0.001**
First degree	8.21%	-	8.21%	
Second degree	3.58%	8.86%	4.79%	
Third degree	8%	23.3%	19.23%	
Late admission				0.807
Present	35(76.1%)	11(23.9%)	46(16%)	
Absent	180(74.4%)	62(25.6%)	242 (84%)	
Area (Face,Hand, Joints, Foot) Present				0.780
Absent	151(75.1%)	50(24.9%)	201(69.8%)	
	64(73.6%)	23(26.4%)	87(30.2%)	

DISCUSSION

Burn injuries are the fourth most common type of trauma in the world (6). Since it is quite painful, it often causes people to apply to the hospital, especially to the Emergency Services, as soon as it occurs. Today, Burn Centers, which provide a more professional approach to burn trauma, provide healthcare in many countries (7). Burn centers provide care in all phases of severe burn patients, from early intervention to rehabilitation and, if necessary, reconstruction. The number of centers and their capacities are determined locally by calculating the patient density in each country. Since these centers are accepted as reference centers all over the world, the indications for referral and hospitalization to the burn center were determined with reference to certain clinical guidelines. Some studies have shown that it is very important that the initial evaluation of the burn patient is carried out in accordance with the published and applied referral and hospitalization guidelines (8). Evaluation of the patient as severe or mild may lead to unnecessary referral of the patient to the burn center or to long-term negative consequences, including death. Therefore, existing guidelines and practices should be reviewed periodically (3). In this study, the rate of admission to the burn center of burn patients who applied to the emergency department of a training and research hospital with a burn treatment center that gives healthcare with specialists and assistants 24 hours a day was found to be 25.3%. In Europe, this rate varies between 4-22% (9). In this study, we attribute the fact that the hospitalization rate is slightly higher than the literature, that our center is an adult patient reference center for all of Turkey and that it accepts patients from many countries, especially from neighboring countries.

In the guideline published by Yastı et al. in 2015, indications for referral and hospitalization were determined (5). According to this

- Any age group with 2nd and 3rd degree burns with TBSA > 20%
- Any age group with 3rd degree burns with TBSA ≥ 5-10%
- Patients younger than 10 years and older than 50 years with TBSA ≥ 10%
- Patients with face, ear, hand, and foot burns
- Patients affected by large joints
- Patients with perineal and genital burns
- Chemical burns
- Electrical burns and lightning strike
- Inhalation damage
- Concomitant trauma
- Having a chronic disease
- Pregnancy
- Suspected child abuse

are hospitalization criteria.

In this study, it was observed that the patients admitted to the burn center followed the aforementioned guideline in terms of TBSA, burn depth and affected area, and were significantly higher than those who were followed up as outpatients.

An important result that stands out in the results of this study is that 215 out of 288 consultations requested from the burn center did not hospitalize, and 207 of patients had first, and second-degree burns with less than 10% TBSA. Eight patients with third-degree burns were small surface area patients who applied after the first 24 hours of trauma and were followed up in outpatient clinics. Patients who were not admitted to the center were followed up in the outpatient clinic.

Considering the patient density and regional factors, burn treatment units in Turkey have been classified as a burn center, burn unit, or burn room according to the medical disciplines, physical conditions, bed capacity, medical technological equipment, and personnel standards by the Ministry of Health. (10). According to this regulation, burn centers accept mild and moderate burn cases that need to be hospitalized.

Our burn center is a center where approximately 2000 patients apply annually, and 300 patients are treated as inpatients, and 10-15 % of those were consulted from the emergency department. This rate is consistent with the literature (9). The hospital we serve within, on the other hand, has approximately 10,000 patient applications per day. Providing burn treatment service in a hospital serving in this capacity requires much effort. In this study, 74.7% of the patients were only dressed, and outpatient control was recommended by arranging analgesic prescriptions by burn center physicians, While critical burn patients in the center were served in this intense pace, responding to consultation for first and second-degree superficial burns with TBSA less than 10% or even 5% causes loss of workforce. On the other hand, the patient has to wait until the consultant physician arrives. Elimination of this undesirable situation, which occurs for both the patient and the burn center/unit physicians, can only be achieved if the emergency medicine physicians know the indications for hospitalization and make the necessary dressing for the patients who do not require hospitalization.

When the predisposition to request consultation detected in this study is evaluated together with clinical experience, it is obvious that the system needs to be revised. The presence of a burn unit and center within university practice and research centers and training and research hospitals is a very important opportunity for family medicine, general surgery, pediatric surgery, and aesthetic and reconstructive surgery residents, especially emergency medicine residents. It is especially important for emergency medicine specialists to learn the first and correct response to burn cases, which they will encounter quite frequently in emergency services in their professional life. On the other hand, according to the Ministry's regulation, it is obligatory to open a burn room and treat at least two patients in hospitals that have a general surgery or a pediatric surgery or an aesthetic, plastic and reconstructive surgery specialists. Again, in hospitals where there is no unit/center, emergency medicine specialists have to make the first intervention of the burned patient. In the light of all these, ignorance of the indication for hospitalization causes a delay in the treatment of the patient who is suitable for outpatient treatment and increases the stress, while it brings with it serious workload and loss of workforce.

Burn cases are emergency cases where first aid is very important. The first to encounter these cases are often emergency medicine physicians. For this reason, they should be well-equipped with minor burn dressings within the framework of general medicine and have knowledge about first response, referral decision, and management. In this regard, if there is a burn unit or center in university hospitals and training and research hospitals, rotation of emergency medicine assistants to burn treatment units should be discussed.

Declarations

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The study was conducted with the approval of the Ankara City Hospital Ethics Committee dated 09/12/2020 and numbered E1-20-1383. Since the study was retrospective, an informed consent form was not used.

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ORIGINAL ARTICLE

Analyzing Electrocardiography Abnormalities in COVID-19 Patients Admitting to Emergency Department

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Abstract

Background: One of the groups affected at the highest level by the outbreak with the highest mortality rate is individuals with known cardiovascular diseases. Proinflammatory mediators play an important role in the pathophysiology of the disease cause cardiac and arrhythmic complications. This article aims to provide practical recommendations by evaluating ECG data in the follow-up and management of the disease to the Emergency Medicine workers to whom patients affected by COVID-19 first apply.

Methods: We randomly collected the ECG data of the patients applying to our Hospital Emergency Medicine Clinic green, yellow and red areas who were positive for viral RNA in throat swabs were carried out.

Results: The ECGs of 502 patients diagnosed with COVID-19 were collected in the 2-week period between June 15, 2020, and July 15, 2020. The study included 287 males (57.17%) and 215 females (42.83%). Normal sinus rhythm was detected in 241 patients (48.01%) at ECG. A total of 3 ECG patterns, which suggested ST elevation, and 11 ECG patterns, which suggested ST depression, were decisive in terms of emergency intervention. The number of patients with atrial fibrillation was 17 (3.39%).

Conclusions: This infection was associated with multiple, direct, and indirect cardiovascular complications, including acute myocardial damage, myocarditis, arrhythmias. Sinus tachycardia was determined to be 30.08%, LVH 5.38%, and VES 4.18% in our study. As a result, we believe that our initial ECG recommendation is that cardiac monitoring will play an important role in treatment planning.

Keywords: COVID-19, Electrocardiogram, Comorbidity, Emergency Department.

INTRODUCTION

After the COVID-19 disease, which is caused by the novel coronavirus (Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2), which emerged in Wuhan, Hubei, China, in December 2019, and rapidly spread to nearly 200 countries around the world, was also detected and declared officially in our country on March 11, 2020, the number of cases has increased rapidly. One of the groups affected at the highest level by the outbreak with the highest mortality rate is individuals with known cardiovascular diseases (1). SARS-CoV-2 infection is associated with several proinflammatory diseases. Proinflammatory mediators play an important role in the pathophysiology of the

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disease cause cardiac and arrhythmic complications (1, 2). Electrocardiography (ECG) changes due to microvascular damage (ST elevation, non-specific ST-T segment changes, and rhythm disorders), rise in cardiac biomarkers (troponin and natriuretic peptide levels), and accompanying myocardium involvement can be detected in patients with respiratory distress and admitted to the emergency department due to COVID-19 (1-5).

This article aims to provide practical recommendations by evaluating ECG data in the follow-up and management of the disease to the Emergency Medicine workers to whom patients affected by COVID-19 first apply.

MATERIALS AND METHODS

Our hospital is a 3200- bed tertiary referral hospital in the central region of Turkey. This prospective study was conducted from June 15 to July 15, 2020, at the Emergency Department (ED) of our hospital. The current study was approved by the Ankara City Hospitals' Ethics committee (Date: 21.05.2020, No: E1-20-599), and permissions were obtained. After ethical approval, we randomly collected the ECG data of the patients applying to our Hospital Emergency Medicine Clinic to the green, yellow, and red areas who were positive for viral RNA in throat swabs were carried out.

Patients who were at and above the age of 18 were included in the study. The study was conducted 24 hours, seven days a week. After patients' admission to the emergency department with COVID-19 symptoms, throat swap was collected for viral RNA. Positive patients' ECG data were collected and loaded to the SPSS database. All the ECG results were evaluated by an emergency medicine specialist who was also an ECG trainer. Continuous data are expressed as mean standard deviation (SD) and categorical data as number (percentage). All statistical analyses were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY).

RESULTS

The ECGs of 502 patients diagnosed with COVID-19 were collected in the 2-week period between June 15, 2020, and July 15, 2020. The study included 287 males (57.17%) and 215 females (42.83%). The mean age was 50.45± 19.14 years (18-98 years).

Normal sinus rhythm was detected in 241 patients (48.01%) at ECG. As a result of ECG examinations of the patient, many rhythm disorders were detected in the remaining 261 (51.99%). A total of 3 ECG patterns, which suggested ST elevation, and 11 ECG patterns, which suggested ST depression, were decisive in terms of emergency intervention. The number of patients with atrial fibrillation was 17 (3.39%). As a result of the follow-ups of 502 patients in the Emergency Department: 1 patient died in the Emergency Department, 142 (28.29%) patients were admitted to the intensive care unit, and 246 (22.5%) patients were admitted to isolated COVID services. The other 263 (44.42%) patients who had COVID-19 positive but without symptoms and complaints were guided to isolated accommodation with medical advice accompanied by paramedics. Three patients were admitted to the Cardiology Coronary Care Unit for invasive intervention and follow-up purposes. The ECG of the patient who died in the Emergency Department was compatible with inferior MI.

Table 1. Emergency Department Admittance of COVID-19 Patients: Electrocardiography Evaluations (n: 502)

Variable	n	(%)
Sinus rhythm	**241**	48.01
Sinus tachycardia	**151**	30.08
Sinus bradycardia	**14**	2.79
ST elevation	**3**	0.60
RHV	**19**	3.78
LVH	**27**	5.38
Atrial fibrillation	**17**	3.39
LBBB	**8**	1.59
RBBB	**12**	2.39
Ventricular early systole	**21**	4.18
Anterior ischemia	**2**	0.40
Inferior ischemia	**11**	2.19
AV Block 1^0	**2**	0.40
QT extension	**0**	0.00

LVH: Left Ventricular Hypertrophy, RVH: Left Ventricular Hypertrophy LBBB: Left bundle branch block, RBBB: Right bundle branch block

The three most common diseases in the comorbidities of the patients were hypertension in 127 patients (25.30%), cardiovascular disease in 112 patients (22.31%), Diabetes Mellitus in 109 patients (21.71%). The top three symptoms were weakness in 51.00% of patients, cough in 50.60%, fever in 42.03%, respectively.

Table 2. Comorbidities in the Cases

Comorbidities	n	(%)
Diabetes Mellitus	109	21.71
Hypertension	127	25.30
Cardiovascular Disease	112	22.31
Chronic Lung Disease	106	21.12
Chronic Kidney Disease	33	6.57
Chronic Liver Disease	47	9.36
Malignancy	74	14.74
Cerebrovascular Disease	68	13.55

Table 3. Frequency of Symptoms

Symptoms	n	%
Chest Pain	116	23.11
Fever	211	42.03
Cough	254	50.60
Palpitation	102	20.32
Shortness of Breath	186	37.05
Weakness	256	51.00
Headache	165	32.87
Anosmia	9	1.79
Ageusia	12	2.39
Diarrhea	24	4.78
Asymptomatic	223	44.42

DISCUSSION

The main characteristics of SARS-CoV-2, the new member of the Coronavirus family, are that it easily binds especially to lung Type 2 alveoli cells, ACE2 receptor in myocardia, kidney proximal tubules esophagus, intestinal epithelial cells, and bladder urothelial cells in humans (7). COVID-19, which has a high infectious characteristic, is spread especially through droplets and direct contact. The average incubation period is 5.5 days; however, it is also known to last up to 14 days (5). The symptoms of the disease usually appear within the first 14 days. In symptomatic cases, the most common symptom is fever, dry cough, weakness, muscle pain, sore throat, less frequent nausea-vomiting, and diarrhea (9). Although it is reported in the literature that the most frequent and higher rate symptom was fever in COVID-19 patients with lung infection at a rate of 31-89% (9,10), the most common complaint was weakness in our study at a rate of 51.00%, and high fever was 42.03% ranking the 3rd frequent symptom. It is also important to question and follow-up on the ageusia and anosmia disorders and diarrhea complaints reported in the literature in COVID 19 patients (11-13). As a matter of fact, 4.78% of the patients who were admitted to our Emergency Department had diarrhea, 1.79% were unable to smell, and 2.39% and 2.39% complained that they could not taste.

Patients with underlying medical problems like the elderly, hypertension, cardiovascular disease, or diabetes are more likely to develop serious diseases. Individuals from all age groups may be infected with COVID-19, but adults of middle age and older are more frequently affected and are more likely to experience the disease more severely. In the literature, the median age of patients diagnosed with COVID-19 in hospitals ranges between 49 and 56 (9-11). In our study, the mean age was 50.45± 19.14 years.

The COVID-19 outbreak presented several difficulties in terms of cardiovascular emergencies. The risk of disease severity and death increased in COVID-19 patients with previous cardiovascular disease. This infection was associated with multiple, direct, and indirect cardiovascular complications, including acute myocardial damage, myocarditis, arrhythmias, and venous thromboembolism. The most important characteristic that makes COVID-19 infection so dreadful is that it causes respiratory failure, especially in high-risk cases; and it can severely disrupt the cardiac hemodynamic with direct myocardial development. ECG changes (ST elevation and non-specific ST-T segment changes) and elevation in cardiac biomarkers (i.e., troponin, etc.) are detected in COVID-19 patients with respiratory distress admitting to Emergency Department. It was reported in a previously published patient series that 40% of patients admitted due to COVID-19 positivity had cardiovascular or cerebrovascular diseases, 17% might develop arrhythmia, and 7% might develop acute cardiac damage. In a case reported, however, it was reported that the initial admission in COVID-19 might be acute-onset heart failure, acute Myocardial Infarction (ME), myocarditis, and sudden cardiac arrest (14,17,18). The cardiovascular disease rate in terms of comorbidity was reported between 14.5% and 40%, hypertension 14.6% and 31.2%, and diabetes 10.1 and 19.5% in some publications (9). In our cases, in line with the literature, the cardiovascular rate was 22.31%, hypertension 25.30%, and diabetes 21.71%.

The clinical impact of COVID-19 infection will be greater with advanced age and comorbidities. In this sense, it was reported that previously cardiovascular patients accounted for 22.7% of all the morbidities (19). Most

patients suspected of COVID-19 and especially patients with severe diseases or those with the probability of QT-extension should undergo ECG after admitting to the Emergency Department (20); ideally, this may be a 12-lead ECG (21). This will allow that the initial QRS-T morphology is documented in case symptoms develop, suggesting myocardial damage or acute coronary syndrome in the patient. In our study, we find no QT extension patients.

There are no adequate publications in the literature about cardiac rhythm disorders in COVID 19 patients. Arrhythmias were reported in 17% of patients and in 44% of patients admitted to the Intensive Care Unit in a study conducted with a total of 138 patients with pneumonia associated with Wuhan-induced COVID-19 (14). It was reported in another study that atrial arrhythmias were more common in patients requiring mechanical ventilation (22), and the frequency of ventricular tachyarrhythmias was also mentioned (23). There were T-wave depression and inversion, ST-segment elevation or depression, and Q waves among the coronary ECG abnormalities reported in patients with COVID-19 (24-27). In case of ST-segment elevation, other diagnostic examinations are necessary to distinguish MI from other causes of myocardial damage (25-27). In a series that included 18 COVID-19 patients with ST-segment elevation, MI developed clinically due to coronary obstruction in 8 patients (coronary angiographies that confirmed obstructive coronary disease were carried out in 6), and the remaining 10 patients were diagnosed with non-coronary myocardial damage (27), 4 of the patients with MI and 9 of those with non-coronary myocardial damage died in hospital. Obstruction was confirmed with Coronary Angiography in two of our three patients with ST-elevation, and one died despite the advanced cardiac life support.

The most common arrhythmia in COVID-19 patients is sinus tachycardia; however, atrial fibrillation, atrial flutter or ventricular tachycardia might also occur (27). Sinus tachycardia was determined to be 30.08%, LVH 5.38%, and VES 4.18% in our study.

An important issue that should not be ignored in this process may be that physicians might focus on symptoms and complaints of this disease because of primary COVID 19 diseases and neglect the presence of cardiac problems, incomplete diagnosis, or delayed diagnosis. A significant problem in MI patients who require medical care may also occur for emergencies where admissions of patients are made separately because of delays in diagnoses and treatments. Since the delay of specific treatments of acute coronary problems can cause cardiovascular emergencies, standardization is also needed for interventional cardiology.

Our study showed that ECG plays an important role in diagnosing, following up, and treating patients admitted with COVID 19 pre-diagnosis. There are several limitations to consider when interpreting the results of our study. Firstly, the study duration was short (1 month), and the study included only one hospital; for this reason, more studies are needed to generalize the results.

It is necessary to determine the treatment process by considering cardiovascular complications and non-COVID emergencies for COVID-19 patients. Continuous ECG monitoring is not required for the patient if the cardiac arrhythmias are documented if there are no suspicious myocardial ischemia or other standard indications. However, as part of the infection control mechanisms for patients with or suspected COVID-19, continuous ECG follow-up by many hospital nurses instead of standard vital parameter follow-ups requires that clinical staff are also careful about the risk of infection.

Emergency Medicine workers must be cautious and consider the intense distribution of ACE2, which is the binding point of SARS-CoV-2, in cardiomyocytes and monitor changes in the ECG in the Emergency Department step and see the problems. As a result, we believe that our initial ECG recommendation and cardiac monitoring will play important roles in treatment planning.

Declarations

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

The current study was approved by the Ankara City Hospitals' Ethics committee (Date: 21.05.2020, No: E1-20-599), and permissions were obtained.

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ORIGINAL ARTICLE

Effect of the Immunoglobulin G-A-M Treatment on Hepatic Functions and Mortality rates in Patients with Septic Shock

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Abstract

Background: In this study, we aimed to explore the effects of conventional sepsis treatment, including classical antibiotherapy and Immunoglubin (Ig) G-A-M combination (Pentaglobin®), on liver function tests and mortality rate in patients with septic shock.

Methods: All patients diagnosed with septic shock and treated with Pentaglobin® in the adult intensive care unit of Suleyman Demirel University Practice and Research Hospital between 2005-2013 were retrospectively examined. Demographic properties, age, gender, intensive care treatment duration, general exitus day, the death rate in the first 28 days, general death-survival period, 28th-day death rate, mortality rate, and diagnosis of cases were recorded.

Results: At the end of the treatment, it was found that 35 of the cases died, and 35 were transferred to various clinical wards. The overall mortality rate was calculated as 50% from the obtained data. It was found that 40 patients survived in the first 28 days while 30 patients died. In this study, it was observed that Pentaglobin® treatment had no statistically significant impact on AST-ALT- Albumin values and mortality rates.

Conclusions: However, early diagnosis of sepsis, early initiation of antibiothearpy, early source control, and timely initiation of appropriate fluid therapy play a key role in the succsess of sepsis treatment. For this purpose, as emphasized in the sepsis 3 guideline, we think that raising awareness by physicians and practitioners in the early diagnosis of sepsis is the most important step in the treatment of this clinical condition.

Keywords: Sepsis, Liver Function Tests, Immunoglobulin G-A-M.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by the host response to dysregulated host response to infection (1). It is still a clinical manifestation with high mortality, despite the pathophysiology of the disease being better defined in recent years, advances in antimicrobial treatment, diagnostic methods, and advances in technology (2). With the development of advanced diagnosis and treatment methods, the early mortality rates of patients hospitalized in intensive care units due to massive bleeding, major trauma, cardiogenic shock, and necrotizing pancreatitis are decreasing (3-6). However, while the follow-up and treatment of these patients continue, the prolongation of the length of stay

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in the intensive care unit may increase the mortality rate of these patients due to sepsis-septic shock-related multi-organ failure (7).

Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain Mean Arterial Pressure (MAP) ≥65mmHg and having a serum lactate level> 2 mmol/L despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40% (1).

Sepsis and septic shock occur at a rate of 10.5-40% in intensive care patients (8, 9), and although there has been a severe decrease of mortality rates in recent years, it is still high, ranging from 18-75% (8-10). In the point prevalence survey conducted by Baykara et al. (11) in our country, the prevalence of sepsis and septic shock in intensive care was 38.8%, and the mortality rate in sepsis and septic shock was 55.7% and 70.4%, respectively.

There have been studies reporting that the addition of intravenous immunoglobulins to treatment in severe sepsis positively affects mortality (12). The effects of intravenous immunoglobulins are activating leukocytes, increasing bactericidal activity in serum, inhibiting cytokine effects, and regulating the complement system (13-15).

The liver, also the target organ, plays a crucial role in sepsis pathology. Two primary mechanisms explain this dual role of the liver. The first is liver blood supply, which takes 25% of the total cardiac output. The portal blood flow providing this blood supply originates from the splenomesenteric area, which is the most affected vascular area by vasoconstriction and bacterial translocation in sepsis. The second is the heterogeneous cellular structure of the liver consisting of Kupfer cells, hepatocytes, and sinusoidal endothelial cells. All of these cells have immune, anti-infectious and metabolic roles. In this study, we aimed to investigate the effect of conventional sepsis treatment, including classical antibiotherapy and Pentaglobin®, on liver function tests in severe sepsis patients.

MATERIALS AND METHODS

The current study was approved by Suleyman Demirel University Medical Faculty Hospital Local Ethics Committee (Date: 31.07.2013, No: 172). This study was performed according to the ethical standards laid down Declaration of Helsinki and its later amendments. All cases diagnosed with severe sepsis and treated with the combination of Pentaglobin® between 2005 and 2013 in the adult intensive care unit of Suleyman Demirel University Research and Training Hospital were screened. The records of the patients in the hospital and intensive care unit were extracted from the electronic database and the archived files and were analyzed retrospectively.

Study design and patients

Demographic characteristics of the cases, age, gender, diagnosis, duration of stay in intensive care, exitus day, rate of death-survival in the first 28 days, rate of death-survival, 28th-day death rate, and mortality rate were recorded. Patients with positive reproduction of pathogenic microorganisms in blood culture, patients aged 18 years and over, patients with APACHE II score of 25 and above, and patients with severe sepsis (Body Temperature (BT) of >38 °C or <36 °C, Heart Rate (HR) of >90/min, Respiratory Rate (RR) of >20/min or $PaCO_2$<32 mmHg, leukocyte count >12000/mm^3 or <4000/mm^3) were included in the study. Patients with a diagnosis of chronic liver failure and those who did not complete the 3-day treatment period were excluded from the study.

Data

In our clinic, the Pentaglobin® is administered with a daily infusion dose of 5 mg/kg in 12 hours for a total of 3 days. Data from 2 different periods were collected and recorded to measure the effectiveness of the treatment. These periods were named "Pre-Treatment Period" (AST 1, ALT 1, Albumin 1) and "Post-Treatment Period" (AST 2, ALT 2, Albumin 2). The pre-treatment period was considered the period in which the diagnosis was made, and treatment was initiated. The post-treatment period was considered as 24 hours after the termination of the Pentaglobin® infusion, in other words, 96 hours after the initiation of the Pentaglobin® therapy.

Statistical Analysis

"SPSS for windows 15.0" Statistical Package Program was used for statistical analysis of the collected data. Wilcoxon Signed Ranks test was used to compare demographic data and AST-ALT-Albumin values before and after Pentaglobin®. Results were submitted as Mean±Standard Deviation (SD), median (minimum-maximum). The p-value of <0.05 was considered significant.

RESULTS

A total of 82 patients received Pentaglobin® therapy. Since 2 cases were diagnosed with chronic liver failure, and 10 cases could not complete the 3-day Pentaglobin® infusion treatment period, 12 patients were excluded. A total of 70 patients who met the study criteria were included in the study. The mean age of the patients was 59.10±20.29 years. 19 of the cases were female (27.2%), 51 were male (72.8%).

At the end of the treatment, it was found that 35 of the cases died, and 35 were transferred to various clinical wards. The overall mortality rate was calculated as 50% from the obtained data. It was found that 40 patients survived in the first 28 days while 30 patients died. The mortality rate in the first 28 days was calculated as 42.85%. The overall mortality rate of male patients was 47% (n: 24), and the first 28-day mortality rate was 37% (n: 19). While the overall mortality rate of female patients was 57% (n: 11), all of the female patients died within the first 28 days. The duration of the adult intensive care unit stay was 44.21±49.82 days. The mean day of death was 16.14±18.80 days, while the shortest period was six days, and the longest was 363 days.

Of the 70 cases included in the study, 37 patients were in sepsis due to pneumonia, 18 were due to after elective post-operative surgery, eight were due to posttrauma, three were due to emergency post-operative surgery, two were due to syndromes such as Guillain Barre, HELLP, and two were due to acute poisoning.

Before Pentaglobin® treatment, the minimum AST value of the patients was 2 IU/L, while the maximum value was 1296 IU/L, the median value was 36 IU/L, the mean value was 98.32±229.40 IU/L. After treatment, the minimum AST value was 2 IU/L; the maximum value was 873 IU/L, the median value was 34 IU/L, the mean value was 91.80±151.29 IU/L. Changes in AST values before and after treatment were statistically insignificant (p: 0.842). Before Pentaglobin® treatment, the minimum ALT value of the patients was 2 IU/L; the maximum value was 1037 IU/L, the median value was 30 IU/L, the mean value was 72.94±154.42 IU/L, while the minimum value after treatment was 4 IU/L, the maximum value was 958 IU/L, the median value was 26 IU/L, the mean value was 74.91±140.46 IU/L. Changes in ALT values before and after treatment were statistically insignificant (p: 0.649). Before Pentaglobin® treatment, the minimum albumin value of the patients was 1,51 gr/dL; the maximum value was 4.1 gr/dL, the median value was 2.75 gr/dL, the mean value was 2.75±0.55 gr/dL, while the minimum value after treatment was 1.52gr/dL, the maximum value was 4.26 gr/dL, the median value was 2.62 gr/dL, the mean value was 2.70±0.56 gr/dL. Changes in Albumin values before and after treatment were statistically insignificant (p: 0.346).

DISCUSSION

Sepsis is a life-threatening condition that occurs with the impaired response of the body to the invasion after the passage of microorganisms or toxins into normally sterile tissues and blood, in other words, after the development of infection (16). The process initiated by microorganisms or their toxins can lead to multi-organ damage and multi-organ failure caused by dysregulated host response. Hemostatic imbalance, which develops in the clinical course of sepsis, plays an important role in increasing endothelial dysfunction, organ and tissue damage, and aggravating the clinical manifestation, and is characterized by impaired intracellular homeostasis. Cell hypoxia and apoptosis, in other words, programmed cell death, are responsible for organ dysfunctions and death in sepsis (17).

The liver, on the one hand, provides the clearance and detoxification of the bacteria that cause sepsis, endotoxins, and vasoactive substances formed during sepsis; on the other hand, it regulates the activities of the cells involved in the host defense. The liver is both a source of inflammatory mediators and the target organ affected by these mediators. One of the main reasons for this dual role is that the liver uses approximately 25% of the total blood flow. Most of the blood supply of the liver is provided by the portal vein system. This splenomesenteric region is the most vascular area affected by vasoconstriction - vasodilation and bacterial translocation in sepsis. The second reason is that the liver consists of very heterogeneous cell groups. Almost all of these cells have immune, anti-infectious and metabolic roles.

The properties of intravenous immunoglobulins, such as increasing the bactericidal serum activity, stimulating leukocytes, neutralizing bacterial endotoxins and exotoxins, and regulating complement activity, suggest that these agents in sepsis may be used in sepsis be beneficial. In the study conducted by McCuskey et al. (18) on sepsis-modeled rats, it was reported that the microvascular changes in sepsis were minimized, leukocyte adhesion

was decreased, and the number of perfused sinusoids increased with intravenous IgG administration. They also reported that the increase in plasma endotoxin level and decrease in endotoxin neutralization capacity observed in septic rats changed the least in rats that were administered intravenous immunoglobulin. Again, in the study conducted by Shmygalev et al. (19), it was found that phagocytic activity was increased in polymorphonuclear leukocytes in rabbits with endotoxemia with Ig M administration, and liver energy stores were higher than in control groups.

In our study, although there was an arithmetic decrease in AST value in the post-treatment period compared to pre-treatment, this decrease was not considered statistically significant (p: 0.842). Although there was an arithmetic increase in ALT value in the post-treatment period compared to pre-treatment, this increase was not statistically significant (p: 0.649). There was an arithmetic decrease in albumin value in the post-treatment period compared to pre-treatment, which was not statistically significant (p: 0.346).

Alejandria et al. (20) reported that the mortality rate was significantly lower in patients given polyclonal immunoglobulin than patients given placebo or monoclonal immunoglobulin. The meta-analysis conducted by Kreymann et al. (21) in 2202 patients reported a significant reduction in mortality rates with Pentaglobin®.

Pilz et al. (22) reported that the APACHE II score decreased in the group treated with intravenous immunoglobulin and that intravenous immunoglobulin treatment improved disease prognosis.

Reith et al. (23) in their study, patients who developed an intra-abdominal infection after surgery, were divided into two groups, and they applied Pentaglobin® and albumin treatment, respectively. In the group given Pentaglobin®; observed that procalcitonin level decreased, clinical symptoms improved, shortened hospital stay, decreased APACHE II score, decreased endotoxin, TNF-α, IL-8, IL-10 levels.

In a controlled study by Özcan et al. (24) sepsis model was created in 48 rats via cecal ligation, and behavioral deficiencies and functions were examined. It was observed that these dysfunctions started to improve in the early period in rats using intravenous immunoglobulin.

In a research article published by Abroun et al. (25), they stated that the early use of Ig solutions enriched with immunoglobulin M at high doses for at least five days in critical patients with severe infections improved the results in these patients.

The microcirculatory disorder that develops during the clinical course of sepsis causes organ dysfunction by disrupting tissue oxygenation (26). A single-center, double-blind, randomized study conducted by Domizi et al. (27) revealed that sublingual microvascular perfusion was higher in patients using Pentaglobin®.

Although the positive effects of intravenous immunoglobulin are mentioned in the studies conducted, it was stated in the sepsis survival guideline that the use of intravenous immunoglobulin did not provide any benefit in adult patients, especially in the light of recent studies (16).

In a meta-analysis by Cui et al. (28) examining published studies with a total of 1530 patients reported that mortality decreased in patients using Pentaglobin®, but this low mortality was due to the low quality of the studies and insufficient evidence

In a study conducted by Tagami et al. (29), 4919 patients who developed sepsis after emergency laparotomy in a total of 845 hospitals were examined according to intravenous immunoglobulin treatment presence. They stated that the use of intravenous immunoglobulin did not make a significant difference in terms of mortality.

Again, in a multi-center controlled study conducted by Tagami et al. (30), 1014 hospitals and 8264 pneumo-sepsis patients were examined, and no difference was observed regarding mortality between patients who received immunoglobulin treatment compared to patients for whom it was not used. Similarly, Kadri et al. (31) examined 121 centers and 4127 patients with necrotizing fasciitis and did not observe any difference in mortality in patients receiving intravenous immunoglobulin.

Although the standard deviation was high and the sample size was small in our study, in line with our results, we think that the Pentaglobin® treatment used in sepsis patients has no positive effect on liver function tests.

In literature, there are many studies reporting the positive or negative effects of the use of immunoglobulin therapy in sepsis patients. We also did not see any positive effect

of this treatment in our study. Although the antimicrobial, anti-infective, and immune-modulatory effects of this treatment are stated, we believe that this does not significantly benefit patient mortality.

While discussions continue about the effectiveness of advanced anti-infective treatment modalities, it is evident that sepsis mortality will decrease by early diagnosis of sepsis specified in the sepsis 3 guideline, triage, rapid transfer to the relevant unit, and initiation of treatment without delay (1, 32). In our study, the point we want to highlight is that this clinical situation, which still has such high mortality, should be noticed by the clinicians in the early period, and the treatment should be initiated immediately.

Declarations

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

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ORIGINAL ARTICLE

Emergency Major Surgery in Thoracic Trauma: Timing and Decision Process

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Abstract

Background: Surgery is required in 10-15% of patients with thoracic injuries. Surgery performed within the first few hours of the injury is considered as an emergency surgery. The aim of study is to share our experiences with emergency surgical approaches in thoracic trauma.

Methods: Our study was carried out between June 2012-June 2020, by retrospective analysis of cases who were evaluated for thoracic trauma in the emergency department and who underwent emergency surgery.

Results: There were 5784 patients who requested for thoracic surgery consultation due to thoracic trauma. Of these cases, 1317 (22.8%) were patients who were evaluated in the emergency service due to isolated thoracic trauma. There were 18 patients (1.3%) who underwent emergency surgery for isolated thoracic trauma.

Glasgow score was higher in the group that was discharged after recovery among all groups; and this was statistically significant (p= 0.045). It was statistically significant that intubation and low modified trauma scores were a poor prognostic factor (respectively p= 0.035, p=0,025).

Conclusions: Tube thoracostomy is sufficient for most of the thoracic traumas. After emergency evaluation, fast and correct decision in the appropriate surgical indication significantly reduces mortality.

Keywords: Thoracic Trauma, Emergency Surgery, Prognostic Factors.

INTRODUCTION

Thoracic trauma constitutes 25-50% of all traumatic injuries, and it is one of the main causes of death in all age groups in the world (1). Majority of the fatal thoracic injuries can be treated with emergency invasive interventions such as the provision of rapid ventilation through intubation, tube thoracostomy, thoracentesis and pericardiocentesis. Thoracic trauma can be classified as blunt and penetrating thoracic trauma. Blunt thoracic trauma constitutes 70%, and penetrating thoracic trauma constitutes 30% of all cases of thoracic trauma (2, 3). Blunt thoracic trauma is a common in the emergency departments. The most common pathologies accompanying the thoracic trauma are the fractures of the rib, sternum and clavicle, rib,

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the costal, sternum and clavicle fractures, hemothorax, pneumothorax, ruptures of the diaphragm, cardiac injury, pneumomediastinum and parenchymal injuries of the lung. The most common finding is the rib fracture (3). Emergency thoracotomy is generally performed in patients, who are evaluated in the emergency department with massive bleeding, who have hypotension, who develop cardiopulmonary arrest, and whose tube drainage continues after the tube thoracostomy. The indications of delayed surgical operation are continuous or recurrent bleeding, mediastinal widening, hemoptysis and recurrent hemothorax (1). Some patients may require exploratory thoracotomy, and surgical removal of the foreign body via thoracotomy during the course of the trauma.. Thoracic trauma of the large vessels and the heart, and thoracic traumas with massive bleeding are generally caused by the gunshot wounds. Patients, who have to be intubated due to respiratory distress after flail chest, are the patients who are performed emergency thoracotomy (4). If flail chest causes severe paradoxical breathing, it necessitates intubation and surgery. In cases of thoracic injury, 10-15% of patients require thoracotomy (5). Emergency thoracotomy refers to the thoracotomy performed within the first few hours of the injury (6).

The aim of the study is to share our experience about emergency surgical approaches in chest traumas evaluated in the emergency department and undergoing emergency surgery.

MATERIALS AND METHODS

Our study was conducted based on the retrospective examination of the cases, who were evaluated in the emergency department due to thoracic injury, and who were performed emergency surgery, between June 2012 and June 2020 in the clinics where we provide healthcare services. The information regarding age, gender, type of trauma, radiological findings, interventions in the emergency department and vital signs, Glasgow coma scores, the first thoracic surgery interventional procedure administered in the emergency department, administration of intubation in the emergency department, localization of the trauma, indication of emergency surgery, the surgical operation performed, the length of hospitalization and the results of the treatment were recorded in the database using the files of the cases included in the study. These data were analyzed in detail, and mortality analysis was performed using Revised Trauma Score (7). The Revised Trauma Score is one of the more common scores aimed at measuring the functional consequences of an injury. It uses three specific physiologic parameters: the Glasgow Coma Scale, systemic blood pressure and the respiratory rate. Scoring in the revised trauma score ranges from 0 to 4.

As the score increases, the risk of mortality and morbidity decreases. The Revised Trauma Score, which was modified in the study by Champion et al. (7), there are three specific clinical parameters (GCS, respiratory rate and systolic blood pressure). Accordingly, each parameter is scored between 0 and 4, and a score between 0 and 12 is obtained for each patient with trauma. It has been reported that the patients with trauma scores below 11 are associated with very high mortality rates.

Ethical statement

Ankara City Hospital Ethics Committee of the Ministry of Health Provincial Health Directorate on 25/06/2020 (No: E1-20-825)

Statistical analysis

The data obtained were evaluated using SPSS for Windows Version 23.0 software. Variables, means, standard deviations and percentages were recorded. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were performed to test the normal distribution. In the analysis of variables without normal distribution, the means of the pairs were compared using the non-parametric Mann-Whitney U test. In order to find the direction and magnitude of the relationship between the categorical (nominal) variables, the nonparametric Spearman's rho correlation coefficient was calculated. Kendall's tau-b and Spearman's rho correlation coefficients were calculated in order to find the direction and size of the relationship between the continuous variable and the categorical variable.

Multidimensional Scaling (MDS), which is a multivariate statistical analysis, is used for analyzing behavioral data such as personal preferences, attitudes, tendencies and expectations. The representation of the objects of interest in single or multi-dimensional space is obtained through MDS analysis based on the distance values, consisting of observed similarities or differences between objects or units. This chart demonstrates how the variables change according to each other.

RESULTS

There were 5784 patients that were referred for emergency thoracic surgery consultation due to thoracic trauma, and 18 of these patients (0.31%) underwent emergency surgery after evaluation. All of these patients were male. The mean age was 26.8 (15-57). When the types of trauma were examined, there were 5 (27.8%) sharp object injuries, 7 gunshot wounds (38.9%), 3 assaults (16.7%), 1 traumatic asphyxia (5.6%), 1 non-traffic accident (5.6%), 1 in-vehicle traffic accident (5.6%).

Of the patients, who were evaluated in the emergency department, 7 (38.9%) patients underwent emergency surgery without radiological imaging, and 11 (61.1%) patients underwent emergency surgery after radiological imaging. When the localizations of the trauma in the patients were evaluated, 13 (72.2%) had trauma localized in the left hemithorax and 5 (27.8%) had trauma localized in the right hemithorax. The mean score was found as 11.5 (4-15) in the evaluation performed in the emergency department using the Glasgow coma scale. While 11 of the patients underwent tube thoracostomy as the first intervention in the emergency department before surgery, 7 patients were performed surgery without tube thoracostomy. Of the 7 patients that did not undergo tube thoracostomy, 6 were not performed thorax CT due to their emergency. In the 1 patient with traumatic asphyxia, to whom Thorax CT was performed, there was an anamnesis due to squeezing in a construction truck dumper. Looking at the vital signs of the patients, arterial blood pressure (ABP) examinations revealed normal BP values in 13 patients (72.2%), and hypotension in 5 (21.8) patients. According to the laboratory data, it was observed that hemoglobin values were between 4.8 and 13.4 (mean; 9.9 g / dl). There were 9 patients with hemoglobin values below 10. In patients with the lowest hemoglobin values of 4.8 g/dl and 6.8 g/dl, the lowest Glasgow coma values were found as 5 and 4, respectively.

While 6 patients were intubated in the emergency department, 12 of them were not intubated. Thorax-CT was not performed to 4 of the patients, who were intubated. In these patients, the HGB values were between 4.8 and 12.4 g/dl, and the mean HGB value was found to be 8.2 g/dl. All of these cases had hypotension. Tube thoracostomy was performed in only 1 patient, whose HGB value was 12.4 g/dl, and Glasgow coma score was 10.

When the indications of emergency surgery were examined, massive drainage was observed in 10 (55.6%) patients (800-1600cc (mean 1200 cc)), hypovolemic shock was observed in 5 (27.8%) patients, open thoracic injury was observed in 2 (11.1%) patients, and cardiac arrest was observed in 1 (5.6%) patient.

Among 9 patients (50%), who were diagnosed with vascular injury due to trauma, 1 (5.6%) patient had internal thoracic artery injury, 7 (38.9%) patients had injury to the intercostal artery, and 1 patient (5.6%) had superior pulmonary vein injury. In addition, 2 (11.1%) patients were diagnosed with cardiac injury.

The findings of the Thorax-CT were analyzed in detail. The type and localization of the trauma, surgical indication and the surgical operation are presented in the Table 1.

Table 1. Classification according to type of trauma, CT findings, surgical indication and surgical operation performed

Patient	Trauma	CT Findings	Indication for surgery	Type of Surgery
1	Gunshot injury	no	Cardiac arrest	LAT + ligation of intercostal artery
2	Gunshot injury	no	Hypotensive shock	S +repair of left anterior cardiac and superior vena cava injuries
3	Asphyxia	Total left lung parenchymal bleeding	Hypotensive shock	LAT + pneumonectomy
4	Stab and impalement wounds	Massive right hemothorax	continuing drainage	RT+ repair of parenchyma + ligation of thoracic internal artery
5	Stab and impalement wounds	no	Hypotensive shock	RT + repair of cardiac injury
6	Gunshot injury	Left hemothorax and defect of anterior chest wall	continuing drainage	S + repair of parenchyma and chest wall deformity
7	Gunshot injury	no	Hypotensive shock	S + LAT + repair of cardiac injury
8	Gunshot injury	no	Hypotensive shock	S + repair of parenchyma
9	Stab and impalement wounds	Massive left hemothorax	continuing drainage	LT + repair of parenchyma
10	Gunshot injury	Left hemothorax	continuing drainage	S + repair of parenchyma
11	Stab and impalement wounds	Left hemopneumothorax	continuing drainage	LT + repair of parenchyma + ligation of intercostal artery
12	Acts of violence	Left lower lobal contusion and pnemothorax	continuing drainage	LVATS + ligation of intercostal artery
13	Acts of violence	Right hemopneumothorax and multiple costal fractures	continuing drainage	RVATS + ligation of intercostal artery
14	in-vehicle traffic accident	Left hemopneumothorax and multiple costal fractures with tissue loss	Open wound at chest wall	RT + repair of parenchyma + fixation of ribs +chest wall reonstruction
15	Stab and impalement wounds	no	continuing drainage	LVATS + ligation of intercostal artery
16	Gunshot injury	Left hemothorax	continuing drainage	S + repair of parenchyma
17	Acts of violence	Left hemopneumothorax	continuing drainage	LVATS + ligation of intercostal artery
18	Out-vehicle traffic accident	no	Open wound at chest wall	LAT + ligation of intercostal artery + repair of parenchyma + chest wall reonstruction

LAT Left anterior thoracotomy, S Sternotomy, LT Left thoracotomy, RT Right thoracotomy, LVATS Left videothoracoscopic surgery, RVATS Right videothoracoscopic surgery

The length of stay in the hospital was analyzed as the length of stay in the intensive care unit, and the total length of stay in the hospital. The length of stay in the intensive care unit ranged between 0 and 15 days (mean 4.4 days), and the total length of stay in the hospital was observed to be between 0 and 27 days (mean 12.3). The patient, who underwent pneumonectomy and left anterior thoracotomy due to traumatic asphyxia, was observed to be hospitalized in the intensive care unit during the entire stay, for a period of 15 days. All patients had low hemoglobin and low Glasgow coma scores; and all were performed surgery without performing tube thoracostomy. In our study, pneumonectomy was performed in 1 patient, while non-resection surgical procedures were performed in the other patients. This patient was administered a dialysis program 2 days a week due to chronic kidney disease. The frequency of dialysis was increased to 3 days a week after trauma. The patient died in the intensive care unit due to sepsis and multiple organ dysfunction. The patients who died had traumatic asphyxia, cardiac injury and superior vein injury. Active bleeding and hemopneumothorax were the predominant intraoperative findings in others.

While 16 of the patients, who underwent early surgery due to trauma, were discharged with full recovery, 2 of them died. The patients who died had traumatic asphyxia, cardiac injury and superior vein injury.

A total of 9 patients had cardiovascular injuries. In patients with cardiovascular injury, the mortality rate was found as 11.11%. When the results of the treatment and the Glasgow coma scores were compared, it was observed that the mean Glasgow score was 12.2 in 16 patients, who were discharged with full recovery; and the mean Glasgow score was 6.2 in 2 patients who died. According to the evaluations, the Glasgow score was higher in the group of patients, who were discharged with full recovery compared to the other groups; and the difference was statistically significant (p= 0.045). Cases; age, glasgow score and length of hospital stay were classified in table 2.

Table 2. Classification in age, glasgow score, and length of hospital stay.

Patient Number	Age	Age Percent (%)	Galsgow Score	Total hospitalization days	Intensive care hospitalization days
1	15	5,6	14	7	2
2	16	5,6	9	11	4
3	17	11,1	14	14	2
4	19	5,6	4	10	5
5	20	5,6	15	13	2
6	21	5,6	15	8	2
7	23	5,6	12	27	12
8	24	11,1	14	12	7
9	27	11,1	12	14	5
10	29	5,6	7	15	15
11	31	11,1	15	10	2
12	36	5,6	15	11	2
13	49	5,6	8	9	2
14	57	5,6	10	13	3
15	15	5,6	5	0	0
16	16	5,6	9	17	4
17	17	11,1	15	12	5
18	19	5,6	14	19	5
Average	**26,8**		**11,5**	**12,3**	**4,4**

The comparison between intubation and the results of the treatment revealed that 2 patients that were intubated died; and the patients, who were not intubated, survived. It was statistically significant that intubation was a poor prognostic factor (p= 0.035). Indications of emergency surgery and the results of the treatment were evaluated. It was found that hypovolemic shock was the surgical indication of the two cases who died. No statistically significant relationship was found between the results of the treatment and indications of emergency surgery (p= 0.287).

Since parenchymal damage was observed in 3 patients who underwent emergency thoracotomy for bleeding, wedge resection was performed in 2 patients and pneumonectomy was performed in 1 patient.

When the correlation between the hemoglobin value and the length of stay in the intensive care unit was evaluated, a negative correlation was found between the two variables. This correlation was not found to be statistically significant (Kendall's tau-b, p= 0.456, Spearman's rho, p= 0.481). Based on the results of the optimal scaling, it was determined that the results of the treatment were good in the patients with high Glasgow coma scores, who were performed emergency intervention in the emergency department, and who were not intubated.

Mortality analysis was performed using the Revised Trauma Score. The scoring was made according to the Glasgow Coma Score, arterial blood pressure and the respiratory rates. Among the patients with trauma scores between 3 and 12 (mean 8.5), the scores of the two patients who died were found as 4.

DISCUSSION

Adebonojo et al. (8) mentioned that 10% of the patients with thoracic trauma evaluated by the emergency and ambulance medical teams died at the time of the event, 5% died within the first hour after presenting to the hospital. In addition, they stated that 80% of the victims responded only to resuscitative treatment and tube thoracostomy, while the remaining 5% required thoracotomy at the emergency department due to various reasons. Similarly, Wall et al. (9) reported that most patients with thoracic trauma can be treated by tube thoracostomy or by follow-up without surgery. They further mentioned that sufficient treatment results were obtained in 90% of the patients with careful monitoring of vital signs, appropriate fluid therapy and analgesia; however, emergency thoracotomy was still required in 10-15% of the patients with trauma (9). In our study, only 18 (0.31%) of the 5784 cases, who were transferred to the emergency department and evaluated by the department of thoracic surgery, were performed emergency surgery. It was determined that the rate of emergency surgery was not as high as mentioned in the literature.

According to the previous studies, the risk of thoracic injuries and death due to trauma was higher in the males compared to the females; nonetheless, gender was not reported as an important variable in terms of mortality (10). In our study, all patients, who underwent emergency surgery, were male; therefore, no comparison was made on the gender.

In patients with thoracic trauma, the initial objective is to identify the injury as soon as possible; however, the first intervention is usually the tube thoracostomy (11-13). While 11 of the cases underwent tube thoracostomy as the first intervention in the emergency department before the surgery, 7 cases were performed surgery without tube thoracostomy. Thorax-CT could not be performed in 6 of these 7 cases due to their emergency. Although most penetrating thoracic injuries could be treated with simple surgical procedures, 10-15% of patients presenting with thoracic trauma require surgical repair (14, 15). In our study, it was observed that the majority of the patients, who were performed surgery, included the cases of hypovolemic shock, massive drainage and vascular injury. If the patient has cardiovascular injury, hypotension, clinical picture of shock, a hemorrhagic drainage of 1500 cc during tube thoracostomy or approximately 200 cc of drainage in every 1 hour, the patient should be operated immediately (16). There was massive drainage (800-1600 cc (mean 1200 cc)) in 10 (55.6%) of our patients, 5 (27.8%) of them had hypovolemic shock, 2 (11.1%) of them had open thoracic injury, and 1 (5.6%) of them had cardiac arrest. While 13 patients (72.2%) had hypotension, 5 (21.8) patients were normotensive. Hemoglobin value was below 10 in 9 patients. While the lowest hemoglobin value was 4.8 g/dl, the mean HGB value was 9.9 g/dl. It was observed that low hemoglobin level correlated with low Glasgow Coma Value. Imaging could not be performed in patients, who were intubated in the emergency department. All patients had low hemoglobin and low Glasgow coma scores; and all were performed

surgery without performing tube thoracostomy. Mortality increases in proportion to the size of the resection resulting from the parenchymal injury of the lung (16). In our study, pneumonectomy was performed in 1 patient, while non-resection surgical procedures were performed in the other patients. The patient, who underwent pneumonectomy, died in the intensive care unit in the early period due to sepsis and multiple organ failure.

Many surgical approaches have been described in the literature for the repair of the lung parenchyma. The parenchymal injury to the lung, and the resection performed due to the parenchymal injury to the lung was not found to have an effect on survival in some studies. However, in our study it was found that the parenchymal injury and the size of the resection had a negative effect on survival (16, 17)

While median sternotomy is preferred when the cardiovascular injury is predominant in the patient evaluated in the emergency department, thoracotomy and video-assisted thoracic surgery (VATS) are highly preferred in patients with trauma (17). Similarly, in our study, the first choice was surgical incision sternotomy for injuries to the cardiac and the large vessel, and thoracotomy was the first choice for the injuries to the lung and the small vessel.

In our study, the mean length of stay in the hospital was 12.3 days. When compared with the literature, the length of stay in the hospital was similar. The mean length of hospital stay was 10.65 (range, 5–65) days (16).

Various mortality rates have been reported due to thoracic trauma in the literature. This could stem from the variety of the type of trauma. Mortality rates due to blunt and penetrating trauma have been evaluated both separately and together. However, the fact that patients have other systemic injuries diversifies the mortality rates. Zakharia (18) reported 1.7% mortality rate for the patients except for the patients with large vessel injuries. Onat et al. (16) reported 1.2% mortality rate for the patients with non-cardiac injury and 17.6% mortality rate for the patients with cardiac injury. Degiannis et al. (19) mentioned 30.8% mortality rate for the patients with cardiac injury; and Karmy-Jones et al. (20) reported 17% mortality rate for an emergency thoracotomy due to bleeding after penetrating chest trauma. Asensio et al. (21) reported a mortality rate of 59%, and Hirshberg et al. (22) stated a mortality rate of 41% for 82 patients requiring combined laparotomy and thoracotomy. In our study, a total of 9 patients had cardiovascular injuries. In patients with cardiovascular injury, the mortality rate was found as 11.11% in our study, which was a similar rate compared to the literature. The mortality rate in the group of patients with no cardiovascular injury and the total mortality rate of both groups was again 11.11%. This value was approximately similar to the literature.

The Revised Trauma Score is one of the most common physiological scoring methods recently. The trauma score of our patients who died was determined as 4. The overall mean was calculated as 8.5. With the help of our improving healthcare system, emergency health services and the ambulance infrastructure, we believe that the continuation of treatment in competent centers after immediate and rapid intervention decreases the mortality rates of the patients, despite it is below 11.

In conclusion, tube thoracostomy is sufficient for most of the patients with thoracic trauma. Nonetheless, surgery should be considered immediately in cases with a drainage of 1000-1500 ml when the thoracic tube is first inserted, in cases with a drainage of 200-250 ml/hour in the 3-hour follow-up. Deterioration of the hemodynamic state, massive hemothorax causing shock, symptoms of pericardial tamponade, massive air leak or radiographic evidence are all indications for emergency surgery.

Declarations

Financial Declaration: No financial or personal support was received from any company with a direct interest in the topic, that could influence the interpretation of the data and the results of the study.

Conflict of Interest: The authors have no conflicts of interest to declare.

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CASE REPORT

Ideal Surgery Time in COVID-19 Process: A Case Report of Pulmonary Hydatid Cyst in Covid Patient

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Abstract

In order to reduce the risk of postoperative mortality and pulmonary/thromboembolic complications during the COVID process, surgery is recommended 4-7 weeks after the diagnosis of COVID in elective cases. We are sharing a case of a patient with a parasitic disease such as hydatid cyst, which was detected incidentally with the diagnosis of COVID-19, who was operated on eight weeks after the diagnosis of COVID-19 and experienced postoperative pulmonary complications.

Keywords: Acute Lung Injury, COVID, Hydatid Cyst, Postoperative Complication.

INTRODUCTION

While the COVID-19 pandemic has caused increased morbidity and mortality all over the world, it has also caused serious changes in surgical operating principles because of COVİD related complications (1). While millions of elective surgeries are postponed during the peak times of the pandemic, studies are being conducted on the appropriate surgical time for patients with COVID-19 during the period when elective surgery can be performed (2-4).

Hydatid cyst is a parasitic disease in which echinococcus granulosus is the most common causative agent, and the primary treatment is surgery in the lung, which is the second most common organ (5).

We present a case of pulmonary hydatid cyst with postoperative pulmonary complications, diagnosed during the examinations for COVID-19.

CASE REPORT

Seventeen years old woman patients, who applied to the COVID outpatient clinic with a positive family history of COVID-19 and cough, showed consolidation in the right lower zone with bilateral infiltrates in the chest X-ray (Figure 1A). Due to positive PCR test and active

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complaints, a 10X9 cm lesion in the right lower lobe with bilateral ground-glass areas on thorax CT taken during hospitalization was thought to be compatible with hydatid cyst (Figure 1B). For the non-ruptured cyst in accordance with surgical principles, right thoracotomy, cystotomy, and capitonage were performed due to the complete regression of infiltrates in the chest X-ray at the 8th week after COVID diagnosis. While there was no pathological finding in the chest X-ray taken on the first postoperative day, increased bilateral infiltrations, increased infection parameters, loss of appetite, and dyspnea occurred on the postoperative second day (Figure 1C). Broad-spectrum antibiotics were started on the patient who had two control PCR tests that resulted negative, no eosinophilia in hemogram and no production in the sputum culture, and widespread infiltration suggestive of acute lung injury was observed in the thorax CT taken on the 3rd postoperative day (Figure 2A). Then, steroid treatment was added, and the patient, who had dyspnea and decreased infiltration and infection parameters in the follow-up, was discharged on the 8th day in health (Figure 2B). The patient's pathology was confirmed as a hydatid cyst, did not have any active complaints in the 1st week and 1st-month follow-ups after discharge, and no obvious pathology was observed in the chest X-ray (Figure 2C).

Figure 1. A. Chest X-ray at the time of COVİD diagnosis. B. Thorax CT at the time of diagnosis C. Postoperative 2th day chest X-ray

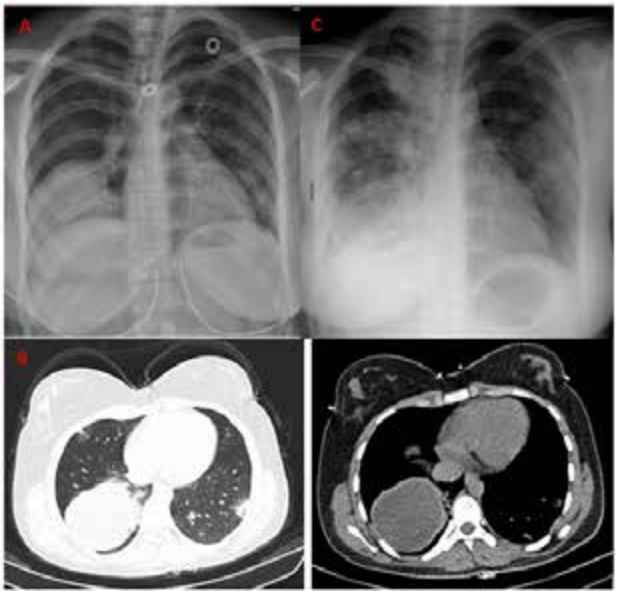
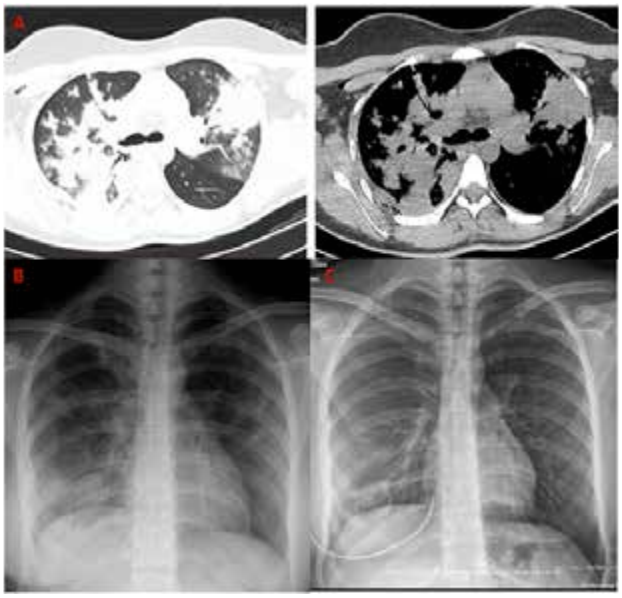


Figure 2. A. Postoperative 4th day thorax CT. B. Discharge chest X-ray. C. Chest X-ray 1 month after discharge



DISCUSSION

Although there is no possibility to postpone emergency surgeries during the COVID-19 process, efforts have been made to plan elective surgeries together with the pandemic's intensity and establish a guideline to determine the appropriate surgery time, especially in patients with COVID-19. Despite the intensive vaccination programs in developed countries, there are millions of patients who have had COVID-19, and the intense impact of the pandemic still continues due to the low vaccination rates in underdeveloped and developing countries. The question seems to remain on the agenda for a while. (2).

Although there are many studies conducted to decide the time of surgery after COVID, different time periods are mentioned in the results of the study. In a study conducted on 140,000 patients, it was observed that waiting seven weeks from the time of diagnosis in asymptomatic patients and longer waiting times in symptomatic patients reduced the risk of postoperative pulmonary and thromboembolic complications to the same level as in the normal population (2). In addition, there is also a study stating that it is associated with an increased risk in postoperative pulmonary complications and 30-day mortality compared to after surgery to be performed within 4 weeks (3).

It has been reported that the most common postoperative pulmonary complications are seen after COVID (6). As a matter of fact, in our patient, after waiting 4 weeks after recovery and 8 weeks after diagnosis, respiratory pathology that would cause general deterioration was observed in the surgery, which resulted in a prolonged hospitalization period. Widespread infiltrations in the early postoperative period and rapid steroid response together with thorax CT and clinical findings suggest in favor of pulmonary complications, acute lung injury, especially after COVID.

Hydatid cyst is a parasitic disease in which echinococcus granulosus is usually the causative agent and causes cystic lesions, most commonly in the liver and then in the lung. The basic surgery of hydatid cyst in the lung is cystotomy and capitonage (7). Since it may cause serious complications such as anaphylaxis, hemoptysis, empyema, and pneumonia, especially with the rupture of the cyst, also the possibility of rupture of giant cysts, it is recommended that lung hydatid cysts should be operated as soon as possible after diagnosis (8) As a matter of fact, in a study, at least one ruptured cyst was found in 37% of lung hydatid cysts, and it was stated that rapid growth was observed in children due to high lung compliance (9). Although there is no recommendation specific to the COVID process, there is an opinion that surgery should be performed as soon as possible in light of the current literature.

In addition to all these, the fact that there are fewer studies in the literature about pediatric patients may also be due to the low rate of diagnosis and testing, although it is evaluated due to the fact that they do not have the disease as severely or asymptomatically as adults (10). However, despite the lack of studies, there are publications stating that elective surgeries with PCR testing can continue with the same complication rates in normal time in studies titled surgery during the COVID-19 process (11). However, since there is no literature on thoracic surgery performed in pediatric patients with COVID-19, it would be useful to consider recommendations for adult patients.

In conclusion, although it is a strong opinion in the literature to wait at least four weeks for elective surgery in patients with a diagnosis of COVID 19 since there are no guidelines yet, it should be evaluated on a case-by-case basis.in diseases such as hydatid cysts.

Declarations

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