ORIGINAL ARTICLE

The ion resonance and bromelain-vitamin C vs bromelain-vitamin C to prevent ankle complications in post-operative bimalleolar surgery

Luigi Meccariello[1], Anna Iolanda Bello[2], Giovanni Bove[3], Nicola Gagliardo[4], D'Anna Raffaele[5], Luigi Matera[1]

[1]Department of Orthopaedics and Traumatology, AORN San Pio Hospital, Benevento, [2]Rehabilitation Unit, AORN San Pio Hospital, Benevento, [3]Department of Orthopaedics and Traumatology, PO Ferdinando Veneziale, Isernia, [4]Department of Orthopaedics and Traumatology, PO San Giuliano, Giugliano, [5]Department of Orthopaedics and Traumatology, AORN San Anna and San Sebastiano Hospital, Caserta; Italy.

ABSTRACT

Aim To investigate whether the use of ion resonance and bromelain-vitamin C or bromelain-vitamin C is the best to prevent ankle complications in post operative bimalleolar surgery.

Methods A total of 61 patients treated with bimalleolar surgery were enrolled. The patients were divided into three groups: the first group (n=22) treated only with the surgery, the second group (n=18) treated by ion resonance and bromelain-vitamin C, and the third group (n=21) was treated with bromelain-vitamin C. All patients in the second and third group underwent adjuvant therapy for 50 days. The criteria to evaluate the three groups during the clinical and radiological follow-up were as follows: complications and soft tissue status. Bone healing measured by the Radiographic Union Score Ankle (RUSA), and functional results were evaluated according to the American Foot & Ankle Score (AFAS).

Results In the first group nine (out of 22; 40.90%) patients developed complications, in the second group three (out of 18; 16.67%) and in the third group seven (out of 21; 33.33%) presented complications. There is no statistical difference between the three groups regarding the type of fractures, mean age, gender ratio. The worst radiographic and stiffness results in the first group were found (p=0.006). The second group showed better bone healing (p=0.049), better performance in functional recovery measured by AFAS (p=0.039).

Conclusion Ion resonance and bromelain-vitamin C group showed better outcomes to improve the functional outcome; it allows reduction of complications, consequently, an early return to quality life, and a corresponding improvement of the quality of life.

Key words: ankle, bromelain, complication, ion resonance, soft tissue, surgery, vitamin C

Corresponding author:
Luigi Meccariello
Department of Orthopaedics and Traumatology, AORN San Pio Hospital
Via Cupa dell'Angelo, Block: Moscati Floor: 2, 82100, Benevento,
Italy
E-mail: drlordmec@gmail.com
Phone: +39 3299419574;
Fax: +39 0823713864;
ORCID: https://orcid.org/0000-0002-3669-189X

Original submission:
28 October 2023;
Revised submission:
01 November 2023;
Accepted:
25 November 2023
doi: 10.17392/1691-23

Med Glas (Zenica) 2024; 21(1):236-243

INTRODUCTION

Ankle fractures account for about 9% of all fractures, with an incidence of 187 fractures per 100.000 people each year in the USA (1). They frequently occur in elderly as a result of a minor injury in younger age (1). Surgery of these fractures is associated with complications such as non-union, mal-union, complex regional pain syndrome (CRPS), post-traumatic osteoarthritis and especially skin and soft tissue problems ranging from wound healing delay to the exposure of the internal fixation (2).

The Food and Drug Administration (FDA) (3) recommends the supplement of vitamin C to reduce the prevalence of complex regional pain syndrome after wrist fractures. A daily dose of 500 mg for fifty days is recommended. The rationale for the use of vitamin C is based on a hypothetical pathogenesis for CRPS from oxidative stress (3). Vitamin C halts the progression of vascular permeability after burning (4), and reduces microvascular leakage of fluid and protein (5) and also reduces lipid peroxidation after burning (6). Vitamin C is a natural antioxidant that can scavenge hydroxyl radicals (7) and superoxide radicals that produce hydroxyl radicals (8,9), thus stopping free-radical reactions and the propagation of chain reactions (10-12).

The anti-inflammatory effects of boswellia and boswellic acids (substance of bromelain) have been shown to be linked to their ability to inhibit leukotriene biosynthesis (13). At the joint level, their action is not only symptomatic but also curative, as they reduce the thinning of the articular cartilage by inhibiting proteolytic enzymes such as hyaluronidase and elastase (13-21). The usefulness of bromelain in preventing the ankle soft tissue complications was reported by Rollo et al. (22).

For many years electromagnetic fields (EMFs) have been used clinically with various settings as an exogenous stimulation method to promote fracture healing. However, underlying mechanisms of action and EMF parameters responsible for certain effects remain unclear (13-20). The physiologic mechanism of the response of skeletal cells to extremely low frequency (ELF)- pulsed electromagnetic fields (PEMF) is the synthesis of extracellular matrix (ECM) structural and signalling molecules in the context of the reparation. In a well-characterized *in vivo* model, ELF-PEMF stimulation has been shown to increase the synthesis of cartilage and bone matrix growth factors and to enhance the proliferation and differentiation of osteoblast-like primary cells (13-21). In 1987, American FDA authorized the first medical application of ion resonance to treat bone fractures consolidation delays (23). The ion-resonance is based on two parallel magnetic fields, one static and one variable over time (23). It was demonstrated that the Ca2+ and Mg2+ ICR-like frequencies can stimulate cartilage and bone development and improve the soft tissue quality (13-17,23).

From scientific literature it is highlighted that the single use of vitamin C, bromelain and magnetic fields has a good result for this injury (24-29).

The aim of this study was to investigate whether the use of ion resonance and bromelain-vitamin C or bromelain-vitamin C is the best way to prevent ankle complications in post operative bimalleolar surgery.

PATIENTS AND METHODS

Patients and study design

Sixty-one patients who underwent bimalleolar surgery (over 18 years old) were prospectively enrolled. The patients were treated with internal fixation by lateral malleolus plating and medial malleolus fixed by cannulated screws in the AORN SAN Pio Hospital Benevento, Giugliano, and San Anna and San Sebastiano Hospital, Caserta (Italy) during the period between October 2021 and May 2023. The patients were divided into three groups (Table 1).

The first group (n=22) included patients treated only with surgery, the second group (n=18) was treated with ion resonance and bromelain-vitamin C, and the third group (n=21) of patients was treated with bromelain-vitamin C.

Patient division was done giving free choice to patients to adhere to one of the relative and absolute contraindications and treatments for the therapies.

The chosen criteria to evaluate the three groups during the clinical and radiological follow-up were: soft tissue, complex regional pain syndrome (CPRS), stiffness, and all complications (skin, soft tissues, stiffness, etc).

All patients gave an informed consent prior to being included into the study. All procedures involving human participants were in accordance

with the 1964 Helsinki Declaration and its later amendments. This paper did not need an approval of the Ethics Committee's.

Methods

The patients were treated with internal fixation by lateral malleolus plating and medial malleolus fixed by cannulated screws. In the post surgery period, plaster cast was worn only for 3 days, then the patient began rapid mobilization.

The weight bearing was due after 30 days.

All patients in the second and third groups underwent adjuvant therapy for 50 days by ion resonance, bromelain, and vitamin C.

The patients of the second group received ion resonance therapy for 30 days (Seqex, SISTEMI SRL, Trento, Italy). The patients were exposed for 54 min/day for 30 days to variability frequencies (1-80 Hz), variability of intensities (1-100 μT) and complex waveforms simultaneously whit various parallel static magnetic fields tuned to calcium.

The Y balance test (YBT) was used to measure dynamic balance and a person's risk of injury. The test can be performed on both the upper and lower quarters of the body.

The type of bimalleolar fracture was determined according Weber Classification (22).

Type A - below the level of the syndesmosis (infrasyndesmotic), usually transverse, tibiofibular syndesmosis intact, deltoid ligament intact, medial malleolus occasionally fractured.

Type B - distal extent at the level of the syndesmosis (trans-syndesmotic), may extend some distance proximally, usually spiral, tibiofibular syndesmosis usually intact, but widening of the distal tibiofibular joint (especially on stressed views) indicates syndesmotic injury medial malleolus may be fractured; deltoid ligament may be torn, indicated by widening of the space between the medial malleolus and talar dome; variable stability, dependent on the status of medial structures (malleolus/deltoid ligament) and syndesmosis; may require open reduction and internal fixation (ORIF); Weber B fractures could be further subclassified as B1- isolated,

B2 - associated with a medial lesion (malleolus or ligament) and B3 - associated with a medial lesion and fracture of posterolateral tibia.

Type C - above the level of the syndesmosis (suprasyndesmotic); tibiofibular syndesmosis disruption with widening of the distal tibiofibular articulation; medial malleolus fracture or deltoid ligament injury often present; fracture may arise as proximally as the level of fibular neck and not visualized on ankle films, requiring knee or full-length tibia-fibula radiographs (Maisonneuve fracture); unstable - usually requires ORIF; Weber C fractures can be further subclassified as C1 - diaphyseal fracture of the fibula, simple; C2 - diaphyseal fracture of the fibula, complex; C3 - proximal fracture of the fibula; fracture above the syndesmosis results from external rotation or abduction forces that also disrupt the joint; usually associated with an injury to the medial side,

None of the patients received anti-osteoporotic therapy during the study.

The radiographic union scale for ankle fractures (RUSA) (24) has been recently developed to assess healing of the ankle fractures after open reduction and internal fixation (ORIF). Using a numerical value for each tibial cortex (anterior, posterior, medial, and lateral), the RUSA uses bridging callus and fracture line visibility to assess fracture healing, both of which have been found to be the most reliable signs of bone healing between observers. The validity and reliability of the RUSA score have been previously evaluated (24), and functional results were evaluated according to the American Foot & Ankle Score (AFAS) (25) (developed in 1994, the clinician-based AFAS covers four different regions of the foot: ankle-hindfoot, midfoot, metatarsophalangeal (MTP)-interphalangeal (IP) for the hallux, and MTP-IP for the lesser toes. Each measure is comprised of nine questions and covers three categories: pain (40 points), function (50 points), and alignment (10 points). These are all scored together for a total of 100 points. The survey includes both subjective (level of pain) and objective (the alignment category – to be answered by the physician) questions. The function category consists of 5-7 questions and requires completion by both the patient and the physician. Unlike other outcome measures which fall into a single category, (AFAS) (25) is a clinician reporting tool that requires both patient and provider participation to be fully complete. The AFAS is not a patient-reported outcome measure (PROM) and when created, it was designed for physicians

to help standardize the assessments of patients with foot or ankle disorders. Since its inception, however, it has gained widespread popularity. Unfortunately, some concerns have been raised with regard to its validity and reliability (25).

Life style correlated with ankle function by the Short Form 12 Health Survey (SF-12) (25). It was developed for the Medical Outcomes Study (MOS), a multi-year study of patients with chronic conditions. The SF-12 instrument provides a solution to the problem faced by many investigators who must restrict survey length. The instrument was designed to reduce respondent burden while achieving minimum standards of precision for the purpose of group comparisons involving multiple health dimensions (25), as well as the correlation between complications and AFAS (26,27).

The Non Union Scoring System (NUSS) (22) aims to classify non-unions according to their severity and relate them to four treatment categories. The YBT assessments were measured in the morning (11:00 AM). The body weight and height were used to calculate the body mass index (BMI). The leg length was measured bilaterally in centimetres and was used to normalize reach distances because leg length has been shown to be a factor affecting YBT performance (28).

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study group and subgroups, including mean and standard deviation (SD) of all continuous variables.

The t-test was used to compare continuous outcome. The $\chi 2$ test or Fisher's exact test (in subgroups smaller than 10 patients) were used to compare categorical variables. The statistical significance was defined as $p<0.05$. Pearson correlation coefficient (r) to compare the predictive scores was used. Mean ages (and their range) of the patients were rounded at the closest year. The predictive score of outcomes was approximated at the first decimal while Pearson correlation coefficient (r) was approximated at the second decimal. Cohen's kappa coefficient (κ) was used to measure inter-rater agreement for qualitative (categorical) items allowing calculation of the concordance between different qualitative values of the AFAS and the complications.

RESULTS

Among 61 patients undergoing bimalleolar surgery there was no statistical difference between the three groups regarding mean age, gender ratio, type of accident, occupation and type of fracture ($p>0.05$). The more frequent type of accident in all three groups was traffic and work accidents ($p>0.05$). The more frequent types of bimalleolar fracture in all three groups were types B1 and B2 ($p>0.05$). The NUSS did not have a significant variation between the three groups (Table 1).

Table 1. Clinical characteristics of 61 patients suffering from bimalleolar fracture

Variable	Patients group*			p
	OS	I+B+C	B+C	
Number of patients	**22**	**18**	**21**	p>0.05
Average age ±SD (years)	42.3±17.4	43.7±17.2	42.6±17.1	p>0.05
Range of age	18-64	18-64	18-64	p>0.05
Gender ratio (M:F)	1.2 (12:10)	1.2 (10:8)	1.1 (11:10)	p>0.05
Type of bimalleolar fracture according Weber Classification (No; %)				
A	5 (22.72)	5 (27.78	4 (19.05)	
B1	7 (31.82)	5 (27.78)	7 (33.33)	p>0.05
B2	7 (31.82)	5 (27.78)	7 (33.33)	
B3	3(13.64)	3 (16.66)	3 (14.29)	
Type of accident (No; %)				
Domestic Fall	5 (22.72)	5 (27.78)	4 (19.05)	p>0.05
Traffic	7 (31.82)	5 (27.78)	7 (33.33)	p>0.05
Work	7 (31.82)	5 (27.78)	7 (33.33)	p>0.05
Other	3 (13.64)	3 (16.66)	3 (14.29)	p>0.05
Employment (No; %)				
Primary sector	6 (27.27)	5 (27.78)	5 (23.81)	p>0.05
Industrial sector	6 (27.27)	5 (27.78)	6 (28.57)	p>0.05
Tertiary sector	6 (27.27)	5 (27.78)	6 (28.57)	p>0.05
No employed	4 (18.19)	3 (16.66)	4 (19.05)	p>0.05
Average±SD of NUSS score at moment of wrist fracture (range)	17.64±14.7 (1-34)	17.77±15.6 (3-35)	17.45±16.8 (1-35)	p>0.05

*OS, only synthesis; I+B+C, ion resonance+bromelain+vitamin C; B+C, bromelain+vitamin C; SD, Standard Deviation; NUSS; Non Union Scoring System;

Table 2. Clinical results and complications for three groups

Variable	Patients group*			p
	OS	I+B+C	B+C	
Number of patients	22	18	21	p>0.05
Complications (No, %)	9 (40.91)	3 (16.67)	7 (33.33)	p= 0.022
Skin or wound problems	4 (18.18)	1 (5.55)	2 (9.52)	p= 0.033
Complex regional pain syndrome	1 (4.54)	0	1 (4.76)	p= 0.001
Ankle stiffness	4 (18.18)	2 (11.11)	4 (19.05)	p= 0.049
Average RUS score±SD bone healing at 3 months after trauma (range)	26.3±1.2 (26 -30)	29.3±1.2 (27-30)	29.5±1.6 (27 -30)	p= 0.019
Average points ±SD of AFAS score at 1 month after trauma (range)	44.76±12.6 (28-60)	58.76±11.7 (32-76)	52.32±11.74 (76-96)	p = 0.039
Average points of AFAS ±SD score at 3 months after trauma (range)	84.76±9.8 (76-96)	92.56±5.4 (92 -100)	90.4±6.8 (82-98)	p= 0.041
Average points of VAS ±SD score at 3 months after trauma (range)	1.4±0.6 (0 -6)	0.3±0.4 (0-2)	0.8±0.6 (0-3)	p= 0.029
Average points of SF-12 ±SD after trauma (range)	89.5±4.6 (84 -100)	94.8±3.8 (88-100)	92.3±4.6 (86-100)	p= 0.038
Average score ±SD of Cohen's inter-correlation between ankle complications and AFAS at 3 months after trauma (range)	k=0.84±0.09 (0.76-0.96)	k=0.91±0.05 (0.84-1)	k=0.89±0.7 (0.81-1)	p= 0.032

*OS, only synthesis; I+B+C, ion resonance+bromelain+vitamin C; B+C, bromelain+vitamin C; SD, standard deviation; RUS, Radiographic Union Score; AFAS, American Foot & Ankle Score; VAS, Visual Nalogic Scale; SF-12, Short Form Health Survey-12

There was statistical difference for developing complications: in the second group only three (out of 18; 16.67%) (p=0.022), in the third group seven (out of 21; 33.33%), and in the first group nine (out of 20; 40.90%) patients developed complications (Table 2).

The worst radiographic and stiffness results were found in the first group (p=0.006).

The second group showed better bone healing (p=0.049), better performance in functional recovery measured by AFAS at one month after trauma (p=0.039), as well as after 3 months following trauma (p=0.041), and better quality of life at 30 days (p=0.034) and at 90 days after the surgery (p=0.041).

The correlation between complications and AFAS showed better results for the second group (p=0.032) at the 90 days from the surgery (Table 2).

The YBT for the first group was 0.84 (±0.08; 0.78-0.89), in the second group it was 0.93 (±0.09;0.83-1), and in the third group it was 0.91 (±0.7; 0.78-0.89) (p=0.046).

DISCUSSION

Complications of a bimalleolar ankle fracture can range in severity and include wound infection, wound hematoma, delay of wound healing, dislocation, arthrosis, inadequate reduction, complex regional pain syndrome, compartment syndrome, impingement syndrome, limited range of motion, malunion, malunion, and Charcot arthropathy, mainly in diabetic patients (2,22). The long-term complications include deformity, infection, ulceration, ankle osteoarthritis, and amputation (2,22).

Until any patient reached full weight-bearing, they must take thromboprophylaxis to prevent the development of deep vein thrombosis or pulmonary embolism (27).

The main problem of ankle fractures is soft tissue oedema and hematoma (22). Concomitant oedema has a major impact on the timing of surgery and may increase the risk of wound complications and postoperative infection. Various methods can be used, including cryotherapy, compression bandages, pulsed intermittent compressions and especially the use of nutraceuticals. Many follow-up studies (1-12, 22) examining patient outcomes between 14 months and 6 years after fracture found that few patients had optimally recovered the range of motion (ROM); in particular, 52% had difficulties in sporting activities, 51% complained of stiffness and swelling, pain when walking and reduced ability to climb stairs (22). This problem occurs very often due to post-traumatic stiffness from long immobilization which favours bone oedema. Furthermore, early mobilization of the ankle in the post-operative period is not possible since it is very often linked to the considerable oedema and filling of the soft tissues, which can lead to a dehiscence of the surgical wound, and the presence of the plaques is a predisposing factor to infection to post-operative complications (22).

Bromelain is an effective fibrinolytic agent (16-21). The fibrinolytic activity of bromelain is attributed to the increased conversion of plasminogen to plasmin, an event which favours the degradation of fibrin. This minimizes venous stasis, facilitates drainage, increases permeability and restores continuity to biological tissues reducing what can lead to dehiscence and infection of the surgical wound (22-27). Results obtained in some studies showed a significant improvement in perception of pain at rest, during daily activities and physical exertion and in all post-surgery outcomes in patients treated with bromelain/daily (28).

The timeframe for vitamin C administration in different studies (17) ranged from 42 to 50 days postinjury and/or surgical fixation . The effect size showed that vitamin C was associated with a decreased rate of complex regional pain syndrome type I (CRPS)-1 than placebo. No significant difference was found between vitamin C and placebo in terms of complications, functional outcomes and pain scores. Overall, vitamin C was associated with a decreased rate of CRPS-I than placebo, while no significant difference was found regarding complications, functional outcomes, and pain scores (16-20). These results hold true when stratifying fracture type (distal radius, ankle, and foot surgeries) and vitamin C dose (500 mg or 1 g) (28). Bone marrow oedema syndrome (BME) was associated with vitamin C deficiency. Current therapeutic interventions include conservative measures (mainly unloading), various osteoactive drugs and iloprost. A causal relationship between vitamin D or vitamin C status, osteopenia, and BME cannot be determined from the existing literature (13-34). Our results are very similar to those described in the literature. Ion resonance associated with bromelain and vitamin C had better effects on the skin (tissue regenerative capacity) and bone (osteoblast stimulation).

In 2022 Salas-Gomez et al. (28) reported that the people with ankle fractures (PwAF) presented balance deficits in their operated limb compared to their non-operated limb at both 6 and 12 months after surgery; however, these deficits were mainly observed when the balance was assessed in dynamic conditions. The most significant balance impairment was observed when participants performed the anterior reaching direction of the Y Balance Test (21) with a bilateral deficit of 9.4% and 5.6% at 6 and 12 months after surgery, respectively. Although evidence in PwAF is limited, our results are supported by previous findings showing the YBT can be a suitable and sensitive tool to detect balance impairments caused by ankle fractures (29,30) or less severe ankle injuries (29,30).

De Luna et al. (31) reported fracture-dislocations of the ankle are serious injuries of the bone and surrounding soft tissues of the ankle that are usually diagnosed after high-energy traumas, with some occurring after a low-energy trauma, especially in older women. At medium- to long-term follow-up, better radiographic results are generally related to a good reduction of the lesion; however, unsatisfactory functional results may be observed regardless of an anatomic reduction of the fracture-dislocation. In fact, in nine of our cases, the AOFAS score was <90 points, despite an excellent or good postoperative reduction.

Therapeutic applications of ion resonance with extremely low frequency electromagnetic fields have demonstrated a significant anti-inflammatory effect. Varani et al. (13) and Vianale et al. (14) observed an upregulation of A2A and A3A adenosine receptors at 72-75 Hz. Zou et al. (15). observed a direct reductive action on expression and secretion of IL-1β and TNF-α at 2 Hz. Mahaki et al.(26) confirmed an inhibitory effect on TNF-α, while also noting an upregulation effect on the anti-inflammatory cytokine IL-10 obtained by administration of extremely low frequency (ELF) electric and magnetic fields (EMF) at 50 Hz; increased IL-10 at 50 Hz was again confirmed by another study by Kaszuba-Zwoińska et al. (17). Ion resonance application at 50 Hz also appears correlated with inhibition of IL-8 (18), while at 40 Hz a similar effect has been demonstrated on the production and secretion of IL-6 (19). Inhibition and modulation of inflammatory cytokines had a greater improvement on stiffness and swelling (22).

In conclusion, the association of ion resonance and bromelain-vitamin C to treat bimalleolar fractures helps to reduce complications. Ion resonance and bromelain-vitamin C group has reported better outcomes in improving functional outcomes; it allows a greater reduction of complications, and consequently, an early return to and a corresponding improvement of the quality of life.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

REFERENCES

1. Juto H, Nilsson H, Morberg P. Epidemiology of adult ankle fractures: 1756 cases identified in Norrbotten County during 2009-2013 and classified according to AO/OTA. BMC Musculoskelet Disord 2018; 19:441.
2. Petruccelli R, Bisaccia M, Rinonapoli G, Rollo G, Meccariello L, Falzarano G, Ceccarini P, Bisaccia O, Giaracuni M, Caraffa A. Tubular vs profile plate in peroneal or bimalleolar fractures: is there a real difference in skin complication? A retrospective study in three level i trauma center. Med Arch 2017; 71:265-9.
3. Rohekar S. Daily vitamin C prevented development of complex regional pain syndrome in adults with wrist fractures. Evid Based Med 2008;13:48.
4. Belousoviene E, Pranskuniene Z, Vaitkaitiene E, Pilvinis V, Pranskunas A. Effect of high-dose intravenous ascorbic acid on microcirculation and endothelial glycocalyx during sepsis and septic shock: a double-blind, randomized, placebo-controlled study. BMC Anesthesiol 2023; 23:309.
5. Malkoc A, Jong S, Fine K, Wong DT. High-dose intravenous versus low-dose oral vitamin C in burn care: potential protective effects in the severely burned: a retrospective cohort study. Ann Med Surg (Lond) 2023; 85:1523-6.
6. Moore A, Khanna D. The role of vitamin C in human immunity and its treatment potential against COVID-19: A review article. Cureus 2023; 15:e33740.
7. Jovičić MŠ, Pušić M, Antunović M, Ledinski M, Librenjak L, Kolundžić R, Ribičić T, Trkulja V, Urlić I.. In vitro effects of ascorbic acid on viability and metabolism of patients' osteosarcoma stem cells. Acta Pharm-2022; 72:599-613.
8. Juneja D, Nasa P, Jain R. Current role of high dose vitamin C in sepsis management: a concise review. World J Crit Care Med 2022; 11:349-63
9. Tanaka H, Broaderick P, Shimazaki S, Matsuda H, Hansalia H, Hanumadass M, Reyes H, Matsuda T. How long do we need to give antioxidant therapy during resuscitation when its administration is delayed for two hours? J Burn Care Rehabil–1992; 13:567-72.
10. Buettner GH. The pecking order of free radicals and antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate. Arch Biochem Biophys 1993; 300:535–43.
11. Gerasimova E, Salimgareeva E, Magasumova D, Ivanova A. Kinetic potentiometry as a method for studying the interactions of antioxidants with peroxyl radicals. Antioxidants (Basel) 2023; 12:1608.
12. Tragni V, Primiano G, Tummolo A, Beltrame LC, La Piana G, Sgobba MN, Cavalluzzi MM, Paterno G, Gorgoglione R, Volpicella M, Guerra L, Marzulli D, Servidei S, De Grassi A, Petrosillo G, Lentini G, Pierri CL. Personalized medicine in mitochondrial health and disease: molecular basis of therapeutic approaches based on nutritional supplements and their analogs. Molecules 2022; 27:3494.
13. Varani K, Vincenzi F, Ravani A, Pasquini S, Merighi S, Gessi S, Setti S, Cadossi M, Borea PA, Cadossi R. Adenosine receptors as a biological pathway for the anti-inflammatory and beneficial effects of low frequency low energy pulsed electromagnetic fields. Mediators Inflamm 2017; 2017:2740963.
14. Vianale G, Reale M, Amerio P, Stefanachi M, Di Luzio S, Muraro R. Extremely low frequency electromagnetic field enhances human keratinocyte cell growth and decreases proinflammatory chemokine production. Br J Dermatol 2008; 158:1189-96.
15. Zou J, Chen Y, Qian J, Yang H. Effect of a low-frequency pulsed electromagnetic field on expression and secretion of IL-1β and TNF-α in nucleus pulposus cells. J Int Med Res 2017; 45:462-70.
16. Mahaki H, Jabarivasal N, Sardanian K, Zamani A. Effects of various densities of 50 Hz electromagnetic field on serum IL-9, IL-10, and TNF-α levels. Int J Occup Environ Med 2019; pii:1572.
17. Kaszuba-Zwoińska J, Ciećko-Michalska I, Madroszkiewicz D, Mach T, Słodowska-Hajduk Z, Rokita E, Zaraska W, Thor P. Magnetic field anti-inflammatory effects in Crohn's disease depends upon viability and cytokine profile of the immune competent cells. J Physiol Pharmacol 2008; 59:177-87.
18. Vianale G, Reale M, Amerio P, Stefanachi M, Di Luzio S, Muraro R. Extremely low frequency electromagnetic field enhances human keratinocyte cell growth and decreases proinflammatory chemokine production. Br J Dermatol 2008; 158:1189-96.
19. Ross CL, Harrison BS. Effect of time-varied magnetic field on inflammatory response in macrophage cell line RAW 264.7. Electromagn Biol Med 2013; 32:59-69.
20. Ehnert S, Falldorf K, Fentz AK, Ziegler P, Schröter S, Freude T, Ochs BG, Stacke C, Ronniger M, Sachtleben J, Nussler AK. Primary human osteoblasts with reduced alkaline phosphatase and matrix mineralization baseline capacity are responsive to extremely low frequency pulsed electromagnetic field exposure - clinical implication possible. Bone Rep 2015; 3:48-56.
21. Ehnert S, Schröter S, Aspera-Werz RH, Eisler W, Falldorf K, Ronniger M, Nussler AK. Translational insights into extremely low frequency pulsed electromagnetic fields (ELF-PEMFs) for bone regeneration after trauma and orthopedic surgery. J Clin Med 2019; 8:2028.
22. Rollo G, Russi V, Meccariello L. Effects of a combination of Bromelain and Boswellia Serrata Casperome on swelling, pain, stiffness and complications in ankle fracture. Minerva Orthopedics 2022; 73:518-22.
23. Yang J, Feng Y, Li Q, Zeng Y. Evidence of the static magnetic field effects on bone-related diseases and bone cells. Prog Biophys Mol Biol 2023; 177:168-80.
24. Cadossi R, Massari L, Racine-Avila J, Aaron RK. Pulsed electromagnetic field stimulation of bone healing and joint preservation: cellular mechanisms of skeletal response. J Am Acad Orthop Surg Glob Res Rev 2020; 4:e1900155.

25. de Graaf MT, de Beukelaar JW, Burgers PC, Luider TM, Kraan J, Smitt PA, Gratama JW. Contamination of synthetic HuD protein spanning peptide pools with a CMV-encoded peptide. Cytometry A 2008; 73:1079-85.
26. Hussaarts L, Kaisar MMM, Guler AT, Dalebout H, Everts B, Deelder AM, Palmblad M, Yazdanbakhsh M. Human dendritic cells with Th2-polarizing capacity: analysis using label-free quantitative proteomics. Int Arch Allergy Immunol 2017; 174:170-82.
27. Evola FR, Di Fede GF, Evola G, Barchitta M, Agodi A, Longo G. Locking plates for distal fibula fractures in young and elderly patients: a retrospective study. World J Orthop 2023; 14:540-6.
28. Salas-Gómez D, Fernández-Gorgojo M, Sánchez-Juan P, Pérez-Núñez MI, Laguna-Bercero E, Prat-Luri A, Barbado D. Measuring recovery and understanding long-term deficits in balance, ankle mobility and hip strength in people after an open reduction and internal fixation of bimalleolar fracture and their impact on functionality: a 12-month longitudinal study. J Clin Med 2022; 11:2539.
29. Koujan K, Saber AY. Bimalleolar Ankle Fractures. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
30. Seth I, Bulloch G, Seth N, Siu A, Clayton S, Lower K, Roshan S, Nara N. Effect of perioperative vitamin C on the incidence of complex regional pain syndrome: a systematic review and meta-analysis. J Foot Ankle Surg 2022; 61:748-54.
31. De Luna V, Caterini A, Casci C, Marsiolo M, Efremov K, De Maio F, Farsetti P. Clinical and radiological results after fracture-dislocations of the ankle: a medium- to long-term followup study. J Funct Morphol Kinesiol 2022; 7:30.
32. Eidmann A, Eisert M, Rudert M, Stratos I. Influence of vitamin D and C on bone marrow edema syndrome-a scoping review of the literature. J Clin Med 2022; 11:6820.
33. Plisky PJ, Gorman PP, Butler RJ, Kiesel KB, Underwood FB, Elkins B. The reliability of an instrumented device for measuring components of the star excursion balance test. N Am J Sports Phys Ther 2009; 4:92-9.
34. Falzarano G, Pica G, Medici A, Rollo G, Bisaccia M, Cioffi R, Pavone M, Meccariello L. Foot loading and gait analysis evaluation of nonarticular tibial pilon fracture: a comparison of three surgical techniques. J Foot Ankle Surg 2018; 57:894-8.