ORIGINAL ARTICLE

Deflazacort and Nevridol 800 to prevent acute carpal tunnel syndrome in adult distal radius fractures

Luigi Meccariello

Department of Orthopaedics and Traumatology, AORN San Pio Hospital, Benevento, Italy;

ABSTRACT

Aim Acute carpal tunnel syndrome (ACTS) is a well-recognized and common condition following a distal radius fracture. The aim of this study was to test deflazacort associated with Nevridol®800 or deflazacort alone in order to prevent moderate or severe ACTS after the distal radius fracture in adults.

Methods Sixty-four patients suffering from extraarticular wrist fractures were divided into three groups. The first group (n=26) was treated by plaster cast. The second group (n=20) was treated by cast and deflazacort (heterocyclic glucocorticoids prodrug belonging to the class of oxazoline steroids) 30 mg/day for 15 days. The third group (n=18) was treated by cast and deflazacort 30 mg/day for 15 days + Nevridol (food supplements) 800 mg a day for 40 days. The criteria to evaluate the patients were: the complication of ACTS, the duration of symptoms, the functional results were evaluated according to The Disabilities of the Arm, Shoulder and Hand (DASH) life correlated with wrist function by the Short Form 12 Health Survey (SF-12), and positive Tinel and Phalen test. The correlation between ACTS signs and volar tilt in the latero-lateral at X-rays in the three studied groups was assessed. The endpoints were set on 7 days, 15 days, 1 months, 2 months and 3 months after a trauma.

Results In the first group, 12 of 26 (46.15%) and the second group 7 of 20 (35%) patients suffered from ACTS, while in the third group only two of 18 (11%) patients (p=0.033). After 3 months of treatment, the third group had better results in DASH (p=0.034), SF-12 (p=0.044), Tinel (0.045) and Phalen (0.048) tests.

Conclusion Deflazacort associated with Nevridol 800 may reduce the prevalence of postoperative median nerve dysfunction.

Key words: adjunctive therapy, alpha lipoic acid, borage oil, nerve dysfunction

Corresponding author:
Luigi Meccariello
Department of Orthopaedics and Traumatology, AORN San Pio
Via Cupa dell'Angelo, Block: Moscati
Floor: 2, 82100, Benevento, Italy
Phone: +393299419574;
Fax.: +390823713864
E-mail: drlordmec@gmail.com
ORCID: https://orcid.org/0000-0002-3669-189X

Original submission:
03 October 2023;
Revised submission:
03 November 2023;
Accepted:
14 November 2023
doi: 10.17392/1679-23

Med Glas (Zenica) 2024; 21(1):229-235

INTRODUCTION

Acute carpal tunnel syndrome (ACTS) is a common condition and a well-recognized phenomenon following a distal radius fracture (1). The treating surgeon should be vigilant in noticing the signs and symptoms. If ACTS is noted, surgical release of the carpal tunnel and fracture fixation should be performed urgently (1,2). If early carpal tunnel syndrome-symptoms are noted during distal radius fracture management, all potential causes should be evaluated (1-4).

The prevalence of ACTS associated with a distal radial fracture of 3-17% was noticed and could result in permanent median nerve dysfunction or complex regional pain syndrome (CRPS) if left unrecognised or untreated (3).

For patients who developed ACTS between two to six weeks, conservative management was used and the evolution of symptoms monitored closely, with definitive fixation and/or full Carpal Tunnel Decompression (CTD) considered if fracture displacement was thought to be the cause. For patients who developed ACTS after 6 weeks, treatment options included conservative measures (night splint), CTD, or a distal radius osteotomy with CTD (3).

Previous studies reported that distal radius malunion, particularly extension of the distal radius has been associated with ACTS especially in patients treated conservatively (10).

Delayed carpal tunnel syndrome presenting after a distal radius fracture is best managed in standard fashion. There is no prophylactic treatment carpal tunnel release at the time of distal radius fixation in a patient who is asymptomatic (1-6).

Conservative management plays a primary role, especially in the acute phase. Steroids are effective at reducing swelling on the account of their anti-inflammatory action (7). It is thus reasonable to use oral steroids in the treatment of acute carpal tunnel syndrome (8). Deflazacort (DFZ) is a synthetic glucocorticoid that has few adverse effects on glucose and calcium metabolism and fewer deleterious effects on the neuronal population (9). The structural characteristics of deflazacort can explain some of its peculiar pharmacological activities, including strong anti-inflammatory/immunosuppressive activity, and lower interference with carbohydrate metabolism and phosphocalcium metabolism (and, therefore, on the growth and bone turnover) in comparison with older corticosteroids (10).

A low dose of deflazacort is also useful in nerve injury or diseases; in fact, the efficacy of proposed low dose deflazacort in comparison to the standard dose did not meet the prespecified criteria for non-inferiority in Duchenne disease (11).

Nevridol 800 is a food supplement based on α-Lipoic acid (ALA), curcumin, borage oil and *Salvia miltiorrhiza*; ALA is an antioxidant that has been widely studied for the treatment of pain symptoms in diverse conditions (12). Nevridol 800 may be proposed for controlling symptoms and improving the evolution of ACTS, especially in an earlier stage of the disease (12).

Given the data present in the literature, we decided to investigate the advantages of the combined use of a cortisone with food supplements in ACTS prevention.

The aim of this study was to investigate whether the use of deflazacort associated with nevridol 800 or deflazacort alone is the best choice in order to prevent acute carpal tunnel syndrome after the distal radius fracture in adults.

PATIENTS AND METHODS

Patients and study design

Sixty-four patients suffering from extra-articular wrist fractures (Colles' fracture) were recruited for this study in the period between July 2022 and May 2023 at San Pio Hospital, Benevento, Italy.

Inclusion criteria were patients aged between 18 and 75 years with distal radius fractures. Patients with a history of upper extremity surgery or with food allergies were excluded.

Patients with wrist fractures were divided into three groups: the first group (n=26) was a group treated by cast, the second group (n=20) treated by cast and deflazacort 30 mg a day for 15 days, and the third group (n=18) was a group of patients treated by cast and deflazacort 30 mg a day for 15 days + Nevridol 800 mg a day for 40 days (Table 1).

The patients' division depended on the free choice of patients to adhere to one of the relative and absolute contraindications and treatments for the therapies.

The cast was retained for 35 days by all patients in the three groups. All patients gave their informed consent prior to being included into the study. All procedures involving human participants were made in accordance with the 1964 Helsinki Declaration and its subsequent amendments.

This paper did not need an approval of the ethical committee because active ingredients of the drugs used have the correct indication for the treated pathology.

Methods

The chosen criteria to evaluate the three groups during the clinical follow-up were: the complication of ACTS, the duration of symptoms; the functional results were evaluated according to The Disabilities of the Arm, Shoulder and Hand (DASH) (13), quality of life was correlated with wrist function by the Short Form 12 Health Survey (SF-12) (14), and with positive Tinel and Phalen tests (15), and Non Union Scoring System (NUSS) (16).

The disabilities of the arm, shoulder and hand (DASH) questionnaire is a self-administered region-specific outcome instrument developed as a measure of self-rated upper-extremity disability and symptoms. The DASH consists mainly of a 30-item disability/symptom scale, scored 0 (no disability) to 100 (13).

The 12-Item Short Form Health Survey (SF-12) was developed for the Medical Outcomes Study (MOS), a multi-year study of patients with chronic conditions. The resulting short-form survey instrument provides a solution to the problem faced by many investigators who must restrict the survey length. The instrument was designed to reduce respondent burden while achieving minimum standards of precision for the purposes of group comparisons involving multiple health dimensions (14).

Phalen's test is a series of movements and positions that help a healthcare provider to diagnose carpal tunnel syndrome. The patient will move your hands and wrists into a position that puts light pressure on the median nerve in your wrist. If he feels tingling or numbness in your hands or fingers, he probably has carpal tunnel syndrome (15).

(The Non-Union Scoring System (NUSS) aims to classify non-unions according to their severity and relate them to four treatment categories (16).

Hand Grip Dynamometry was used to define the strength of the hand. Kilogram force (Kfg) was measured, defined as the weight force exerted by a mass of 1 kilogram subjected to an acceleration of gravity of 9.81 m/s2.

The correlation between ACTS signs and volar tilt (VT) in the latero-lateral at X-rays has been evaluated (16).

The comparison between the three groups was made according to three different radiological parameters: radio-capitate distance (RCD), volar tilt (VT) and volar prominence height.

The RCD (mm) represents the effective distance between the capitate and radius. The VT (°) is an angle determined by the perpendicular line to the axis of the radius and the line that passes through the dorsal volar rims of radius. The volar prominence height (VPH) (mm) is considered as the distance between the prominence of the distal radial epiphysis and the line of the radial diaphysis.

All parameters were defined using lateral-view radiographs of wrist fractures.

The evaluation endpoints were set on 7 days, 15 days, 1 months, 2 months and 3 months after trauma.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study group and subgroups, including means and standard deviations of all continuous variables.

The t-test was used to compare continuous outcomes.

The $\chi 2$ test or Fisher's exact test (in subgroups smaller than 10 patients) was used to compare categorical variables. The statistical significance was defined as $p<0.05$.

Pearson correlation coefficient (r) was used to compare the predictive scores. 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 at the second decimal was approximated Pearson correlation coefficient (r).

Cohen's kappa coefficient (κ) was used to measure inter-rater agreement for qualitative (categorical) item: The concordance between different qualitative values of the X-rays wrist alignment and the ACTS Signs.

RESULTS

The three subgroups studied were quite similar in average age. The most affected by Colles' fracture were patients above 50 years of age. The most common cause of Colles' fracture in the three groups was domestic trauma. In all three groups the NUSS <25 points (Table 1).

Table 1. Clinical details of 64 adults with Colles' wrist fracture

Variable	Group of patients according to the treatment*			p
	Cast	Deflaza-cort	Deflazacort+ Nevridol	
Number of patients	26	20	18	
Average±SD (range) of age (years)	36.4±15.3 (18-55)	37.7±14.2 (18-55)	37.6±14.8 (18-55)	>0.05
Age groups (No, %) (years)				
18-25	5 (19.23)	1 (5.00)	1 (5-56)	>0.05
26-35	7 (26.92)	5 (25.00)	3 (16.67)	>0.05
35-50	7 (26.92)	6 (30.00)	6 (33.33)	>0.05
>50	7 (26.92)	8 (45.00)	8 (44.44)	>0.05
Gender ratio (M:F)	0.53 (9:17)	0.54 (7:13)	0.5 (6:12)	>0.05
Type of accident (No, %)				
Domestic fall	12 (46.16)	8 (40.00)	6 (33.33)	>0.05
Traffic accident	4 (15.38)	4 (20.00)	4 (22.22)	>0.05
Work accident	6 (23.08)	6 (30)	6 (33.33)	>0.05
Other accidents	4 (15.38)	2 (10)	2 (11.12)	>0.05
Type of occupation/work (No, %)				
Agriculture sector	12 (46.16)	6 (30)	5 (27.78)	>0.05
Industrial sector	4 (15.38)	6 (30)	6 (33.33)	>0.05
Service sector	6 (23.08)	5 (25)	4 (22.22)	>0.05
Not employed	4 (15.38)	3 (15)	3 (16.67)	>0.05
Average NUSS score at moment of wrist fracture±SD (range)	16.74±15.8 (1-32)	18.63±35.6 (3-35)	17.33±16.3 (1-35)	>0.05

*cast, patients treated by cast; deflazacort, patients treated by cast and deflazacort 30 mg a day for 15 days; Deflazacort+Nevridol, patients treated by cast and deflazacort 30 mg a day for 15 days + Nevridol 800 mg a day for 40 days;
SD, standard deviation; NUSS; Non Union Scoring System;

Among 64 patients suffering from extra-articular wrist fracture, 21 (32.81%) patients suffered from ACTS. According to patient's choice regarding the therapy, 12 of 26 (46.15%) patients were in the first group, in the second group seven of 20 (35%), while in the third group only two patients of 18 (11%) suffered from ACTS (p=0.033) (Table 2).

No patients showed complex regional pain syndrome.

At the endpoint of 3 months from the trauma, the third group had better results based on the specific evaluated parameters: DASH score in cast group was 14.78±5.7 (2-18), in deflazacort 13.44±3.4 (2 -18), and in Deflazacort+Nevridol cast group, 7.44±1.8 (2-8) (p=0.034); SF-12 score, 90.3±3.2 (84 -100), 92.7±6.9 (86 -100) and 96.4±3.4 (91-100), respectively (p=0.044); Tinel test was positive in 12 (46.15%), nine (45%) and

Table 2. Clinical results and complications for all three groups, 21 patients with acute carpal tunnel syndrome (ACTS) according to treatment

Complication	Group of patients according to the treatment*			p
	Cast	Deflazacort	Deflazacort +Nevridol	
ACTS (No,%)	12 46.15)	7 (35)	2 (11.12)	0.033
Complex regional pain syndrome (No, %)	0	0	0	1
Stiffness (No, %)	6 (23.07)	4 (20.00)	4 (22.22)	0.057
Avarage±SD RUS score bone healing at 3 months after trauma (range)	29.4±1.2 (26 -30)	29.3±1.2 (27-30)	29.5±1.6 (27 -30)	0.87
Average±SD points of Quick-DASH score at 3 months after trauma (range)	14.78±5.7 (2-18)	13.44±3.4 (2 -18)	7.44±1.8 (2-8)	0.034
Average±SD points of VAS score at 3 months after trauma (range)	2.2±0.6 (0 -6)	0.9±0.7 (0-4)	0.4±0.8 (0-1)	0.029
Average±SD points of SF-12 after trauma (range)	90.3±3.2 (84 -100)	92.7±6.9 (86 -100)	96.4±3.4 (91-100)	0.038
Average±SD Kgf hand Grip by Dynamometer at 3 months after trauma (range)	20.5±6.3 (15-40)	32.4±12.7 (20-40)	33.8±9.7 (25-40)	0.029
Average±SD score Hand Grip value at 3 months fitted a linear regression with VAS, at 3 months after trauma (range)	r2=0.86±0.08 (0.72-1)	r2=0.91±0.05 (0.86-1)	r2 =0.93±0.06 (0.87-1)	0.036
Tinel's positive sign at 3 months after trauma (No, %)	12 (46.15)	9 (45)	4 (22.22)	0.045
Phanel's positive test at 3 months after trauma (No, %)	12 (46.15)	9 (35)	5 (27.78)	0.048
Average±SD score of Cohen's inter-correlation between wrist radiographic alignment and DASH at 3 months after trauma (range)	k=0.72±0.22 (0.59-1)	k=0.94±0.05 (0.89-1)	k=0.90±0.12 (0.81-1)	0.001

*cast, patients treated by cast; deflazacort, patients treated by cast and deflazacort 30 mg a day for 15 days; Deflazacort+Nevridol, patients treated by cast and deflazacort 30 mg a day for 15 days + Nevridol 800 mg a day for 40 days;
RUS, radiol-ulnar synostosis; Quick-DASH, Quick Disability of the Arm, Shoulder and Hand Questionnaire; SF-12, short form health survey 12; VAS, Visual Analogic Scale;

four (22.22%) patients, respectively (p=0.045), and Phalen test was positive in 12 (46.15%), nine (45%) and five (27.78) patients, respectively (p=0.048), tests with respect to the treatment with cast or with cast + Daflazacort (Table 2).

There was no correlation between ACTS signs and VT in the latero-lateral X-rays. Comparison between the three studied groups according to different radiological parameters showed statistically significant difference in radiocapitate distance (in mm) between three groups, cast, Deflazacort and Deflazacort+Nevridol: –7.32±1.67 (–10.07−4.33), –7.37±1.95 (–10.27−4.53) and– 8.28±1.95 (–11.20−5.20), respectively (p=0.038).

Statistically significant difference between the three groups was found also for volar tilt (in °): –7.87±6.99 (–19.40−1.30), – 8.57±6.94 (–19.53−1.52) and – 9.36±7.63 (–21.67−1.87), respectively (p=0.036), as well as for volar prominence height (in mm): 3.64±1.64 (2.45–7.43) , 2.76–8.67 (4.77±1.67) and 5.68±2.82 (3.27–9.64), respectively (p=0.029) (Table 3).

Table 3. Comparison between the three studied groups according to different radiological parameters

Variable	Cast	Deflazacort	Deflazacort +Nevridol	p
Number of patients	26	20	18	
Radiocapitate distance ±SD (range) (mm)	–7.32±1.67 (–10.07−4.33)	–7.37±1.95 (–10.27−4.53)	– 8.28±1.95 (–11.20−5.20)	0.038
Volar tilt ±SD (range) (°)	–7.87±6.99 (–19.40−1.30)	– 8.57±6.94 (–19.53−1.52)	– 9.36±7.63 (–21.67−1.87)	0.036
Volar prominence height ±SD (range) (mm)	3.64±1.64 (2.45–7.43)	2.76–8.67 (4.77±1.67)	5.68±2.82 (3.27–9.64)	0.029

*cast, patients treated by cast; deflazacort, patients treated by cast and deflazacort 30 mg a day for 15 days; Deflazacort+Nevridol, patients treated by cast and deflazacort 30 mg a day for 15 days + Nevridol 800 mg a day for 40 days;

DISCUSSION

Median nerve injuries are the primary causes of access in emergency department for peripheral nerve injuries. In the United States, there are about 8,000,000 reported cases of injuries per year (17). Carpal tunnel syndrome is the most frequently encountered entrapment neuropathy of the upper extremity and is prevalent in up to 3% of the general population. The incidence of carpal tunnel syndrome is 105 cases per 100,000 person-years (18). The prevalence of median nerve neuropathy in association with a distal radial fracture is not insignificant and has been estimated to be between 4% and 8%. Also, ACTS is much higher of the 25%-45% in the perilunate fracture and ACTS incidence is the highest in the perilunate fracture dislocation and more complex carpal injuries (3).

The median nerve can be affected by acute trauma after wrist fractures and develop acute tunnel carpal syndrome. The etiology of carpal tunnel syndrome after a distal radial fracture is likely multifactorial and has been linked to changes in the carpal tunnel anatomy after a traumatic event (16,19), as we found in our study too. In 2010, Itsubo et al. (7) reported carpal tunnel syndrome was defined occurring >12 weeks after distal radius fracture or injury. Our patients had signs of ACTS within the first 3 weeks after the trauma.

ALA showed efficacy for the treatment of headache, carpal tunnel syndrome and burning mouth syndrome (20). Compared to placebo, ALA treatment decreased the total symptom score (20). The use of ALA reported a decrease of stabbing pain, burning, paraesthesia, and numbness in ALA-treated patients compared to placebo (20-28). In addition, both routes of administration, intravenous and oral, demonstrated the efficacy to reduce total symptom score (20-28). Therefore, ALA should be used to treat diabetic polyneuropathy pain symptoms.

Another potential candidate seems to be curcumin, a polyphenol extracted from *Curcuma longa* roots and endowed with anti-inflammatory properties; the latter is due to modulation of different transcription factors, which in turn are responsible for the decreased synthesis of proinflammatory cytokines (interleukin - IL-1, IL-2, IL-6, and tumour necrosis factor-α) and play a role in cyclooxygenase 2 and NO synthase inhibition (21-23). Unfortunately, curcumin exhibits poor oral bioavailability, caused by limited intestinal absorption and massive liver metabolism through phase 2 enzymes (24). Its conjugation with a lipid vector (25-28) and the association with piperine reduces the kinetic limitations of curcumin and makes its oral use more effective.

Effectiveness of natural borage oil as sources of gamma-linolenic acid to correct peripheral nerve conduction velocity abnormalities in diabetic rats was reported in literature (29).

Salvianolic acid A (SalA) is the main efficacious, water-soluble constituent of *Salvia miltiorrhiza Bunge*. Oral administration of SalA was performed daily for 10 weeks after modeling by Yang et al. (30). SalA increased peripheral blood perfusion and vascular activities; improved peripheral nerve function, and decreased advanced glycation end products (AGEs) levels, vascular endothelial NOS (eNOS) expression, and blood glucose, lipid, von Willebrand factor (vWF) and malondialdehyde levels in diabetic rats. Based on these findings, many authors proposed the therapeutic use of SalA to prevent the development of diabetic foot problems (16-30).

There are no articles in the literature for the pharmacological treatment of ACTS. We analysed diabetic patients because the neuropathic pain and nerve damage is similar to that of ACTS.

In conclusion, according to our results, routine usage of the deflazacort associated with Nevridol 800 from the time of fracture may reduce the prevalence of ACTS.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest**:** None to declare

REFERENCES

1. Gillig JD, White SD, Rachel JN. Acute carpal tunnel syndrome: a review of current literature. Orthop Clin North Am 2016;47:599–607.
2. Holbrook HS, Hillesheim RA, Weller WJ. Acute carpal tunnel syndrome and median nerve neurapraxia: a review. Orthop Clin North Am 2022; 53:197–203.
3. Leow JM, Clement ND, McQueen MM, Duckwhort A. The rate and associated risk factors for acute carpal tunnel syndrome complicating a fracture of the distal radius. Eur J Orthop Surg Traumatol 2021; 31:981-7.
4. Lane JCE, Craig RS, Rees JL, Gardiner MD , Green J, Prieto-Alhambra D, Furniss D. Serious postoperative complications and reoperation after carpal tunnel decompression surgery in England: a nationwide cohort analysis. Lancet Rheumatol 2020; 3:e49–57.
5. Tosti R, Ilyas AM. Acute carpal tunnel syndrome. Orthop Clin North Am 2012; 43:459-65.
6. Singh S, Sanna F, Singh N, Adhikari R, Kumar V. An unusual case of acute carpal tunnel syndrome. Cureus 2021; 13:e20852.
7. Itsubo T, Hayashi M, Uchiyama S, Hirachi K, Minami A, Kato H. Differential onset patterns and causes of carpal tunnel syndrome after distal radius fracture: a retrospective study of 105 wrists. J Orthop Sci 2010; 15:518-23.
8. Paolucci T, Piccinini G, Nusca SM, Marsilli G, Mannocci A, La Torre G, Saraceni VM, Vulpiani MC, Villani C. Efficacy of dietary supplement with nutraceutical composed combined with extremely-low-frequency electromagnetic fields in carpal tunnel syndrome. J Phys Ther Sci 2018; 30:777-84.
9. Chang MH, Ger LP, Hsieh PF, Huang SY. A randomised clinical trial of oral steroids in the treatment of carpal tunnel syndrome: a long term follow up. J Neurol Neurosurg Psychiatry 2002; 73:710-4.
10. Markham A, Bryson HM. Deflazacort. A review of its pharmacological properties and therapeutic efficacy. Drugs 1995; 50:317–33.
11. Saviola G, Abdi Ali L, Shams Eddin S, Coppini A, Cavalieri F, Campostrini L, Sacco S, Bucci M, Cirino G, Rossini M. Compared clinical efficacy and bone metabolic effects of low-dose deflazacort and methyl prednisolone in male inflammatory arthropathies: a 12-month open randomized pilot study. Rheumatology (Oxford) 2007; 46:994-8.
12. Di Geronimo G, Fonzone Caccese A, Caruso L, Soldati A, Passaretti U. Treatment of carpal tunnel syndrome with alpha-lipoic acid. Eur Rev Med Pharmacol Sci 2009; 13:133-9.
13. Stock LA, Brennan JC, Johnson AH, Gelfand J, Turcotte JJ, Jones C. Disparities in Hand Surgery Exist in Unexpected Populations. Cureus 2023;15:e39736.
14. Maempel JF, Jenkins PJ, McEachan JE. The relationship of mental health status to functional outcome and satisfaction after carpal tunnel release. J Hand Surg Eur Vol 2020; 45:147-52.
15. Paiva Filho HR, Costa AC, Paiva VGN, Severino NR. Diagnostic contradictions in carpal tunnel syndrome. Rev Bras Ortop (Sao Paulo) 2022; 58:290-4.
16. Elwakil W. Correlation between delayed carpal tunnel syndrome and carpal malalignment after distal radial fracture. J Orthop Surg Res 2023; 18:365.
17. Lad SP, Nathan JK, Schubert RD, Boakye M. Trends in median, ulnar, radial, and brachioplexus nerve injuries in the United States. Neurosurgery 2010; 66:953-60.
18. Bland JD, Rudolfer SM. Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, 1991-2001. J Neurol Neurosurg Psychiatry 2003; 74:1674-9.
19. Medici A, Meccariello L, Rollo G, De Nigris G, Mccabe SJ, Grubor P, Falzarano G. Does routine carpal tunnel release during fixation of distal radius fractures improve outcomes? Injury 2017; 48(Suppl 3):S30-3.
20. Reddy C, Patil AN, Suthar R, Sankhyan N, Sirari T, Kumar A, Bhattacharjee S, Saxena S, Saini AG, Sahu JK. Deflazacort dose optimization and safety evaluation in Duchenne muscular dystrophy (DOSE): a randomized, double-blind non-inferiority trial. Eur J Paediatr Neurol 2022; 38:77-84.

21. Ammon HPT, Wahal MA. Pharmacology of Curcuma longa. Planta Med 1991; 57:1-7.
22. Funk JL, Oyarzo JN, Frye JB, Chen G, Lantz RC, Jolad SD, Sólyom AM, Timmermann B. Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis. J Nat Prod 2006; 69:351–5.
23. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life Sci 2006; 78:2081–7.
24. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm 2007; 4:807–18.
25. Di Pierro F, Rapacioli G, Di Maio EA, Appendino G, Franceschi F, Togni S. Comparative evaluation of the pain-relieving properties of a lecithinized formulation of curcumin (Meriva), nimesulide, and acetaminophen. J Pain Res 2013; 6:201–5.
26. Steigerwalt R, Nebbioso M, Appendino G, Belcaro G, Ciammaichella G, Cornelli U, Luzzi R, Togni S, Dugall M, Cesarone MR, Ippolito E, Errichi BM, Ledda A, Hosoi M, Corsi M. Meriva®, a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy. Panminerva Med 2012; 54(Suppl 4):11-6.
27. Mazzolani F. Pilot study of oral administration of a curcumin-phospholipid formulation for treatment of central serous chorioretinopathy. Clin Ophthalmol 2012; 6:801–6.
28. Appendino G, Belcaro G, Cornelli U, Luzzi R, Togni S, Dugall M, Cesarone MR, Feragalli B, Ippolito E, Errichi BM, Pellegrini L, Ledda A, Ricci A, Bavera P, Hosoi M, Stuard S, Corsi M, Errichi S, Gizzi G. Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study. Panminerva Med 2011; 53(Suppl 1):43-9.
29. Dines KC, Cotter MA, Cameron NE. Effectiveness of natural oils as sources of gamma-linolenic acid to correct peripheral nerve conduction velocity abnormalities in diabetic rats: modulation by thromboxane A2 inhibition. Prostaglandins Leukot Essent Fatty Acids 1996; 55:159-65.
30. Yang XY, Sun L, Xu P, Gong LL, Qiang GF, Zhang L, Du GH. Effects of salvianolic scid A on plantar microcirculation and peripheral nerve function in diabetic rats. Eur J Pharmacol 2011; 665:40-6.