Case Report

PALMITOYLETHANOLAMIDE M/UM REPRESENTS AN INNOVATIVE NUTRITIONAL APPROACH IN THE MANAGEMENT OF POST-OPERATIVE BONE PAIN: PRELIMINARY RESULTS

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ABSTRACT

Distal radius fractures are among the most common skeletal injuries of the wrist. Although the surgical treatment with a volar plate allows rapid and complete functional recovery, most patients experience significant pain when performing movements in the post-operative period. Two clinical cases of patients undergoing reduction and osteosynthesis surgery with volar-locking plate after wrist fracture and treated with micronized (PEAm) and ultramicronized PEA (PEAum) (300 mg + 600 mg) twice daily for 30 days. Pain and functional recovery were assessed 1, 7, 14, 21 and 30 days are here reported after surgery and, subsequently, 30 days after the end of treatment by the NRS scale and DASH questionnaire, respectively. Pain and functional recovery significantly improved in both patients during the treatment. Further improvement was detected at the follow-up 30 days after therapy. No patient reported adverse effects related to PEAm/um treatment. The use of PEAm/um may represent an appropriate approach to promote the recovery of patients with post-operative pain, thanks to its ability to alleviate painful symptoms and improve functional recovery.

KEYWORDS: *micronized and ultramicronized PEA, wrist fracture, surgery, pain, functional recovery*

INTRODUCTION

Distal radius fractures are among the most common skeletal injuries of the wrist: they account for about 44% of all hand and forearm fractures and represent about 20% of all fractures (1). In the last decade, surgical techniques and related implants have advanced considerably. Among them, the volar plate is widely used in patients with unstable distal radius fractures, as it provides secure fixation, early post-operative mobility, and rapid recovery of wrist function (2). During post-operative rehabilitation, particularly in the immediate post-operative period, most patients experience significant pain when performing both active and passive movements (3). Surgical trauma is characterized by stiffness and suffering of bone's sensitive nerve fibers (4-6). Peripheral nerve sensitivity is regulated by mast cells in the bone whose hyperactivation, caused by surgical trauma, results in neuroinflammation associated with bone oedema and post-traumatic pain (7). Evidence on the role of mast cells in the development of bone pain suggests that therapies able to

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modulate mast cell activation may represent an innovative approach. In this perspective, a possibility could be represented by Palmitoylethanolamide (PEA): an endogenous molecule belonging to the N-acylethanolamine family, which is produced "on-demand" in order to restore tissue homeostasis and which exerts its action thanks to the ALIA ("Autacoid Local Injury Antagonism") mechanism, mediating neuroprotective, anti-inflammatory and analgesic effects through mast cell control (8).

This article describes the cases of two patients with wrist fractures who underwent volar plate surgery and were subsequently treated with PEA in its micronized and ultra-micronized form, increasing its bioavailability and biological efficacy.

MATERIALS AND METHODS

We analyzed two patients with wrist fractures who underwent surgery with reduction and fixation using a volar plate and treated with micronized (PEAm) and ultra-micronized (PEAum) PEA (Normast ® MPS, Food for Special Medical Purpose, Epitech Group SpA, Saccolongo, Padua) 300mg + 600mg, 2/daily for 30 days (2 sachets/die for the first 20 days, followed by oral tablets for the remaining 10 days).

The fracture was classified according to the AO classification: type A represents extra-articular fracture, type B partial-articular, and type C complete articular fracture.

Evaluations were performed on day 1 after surgery (T0), 7 (T1), 21 (T3) and 30 (T4) days after surgery. A subsequent follow-up was performed 30 days after the end of treatment (T5).

The parameters considered were:

- pain intensity assessed by Numeric Rating Scale (NRS), an 11-point scale where 0 represents "no pain "and 10 "the most intense pain imaginable" (9), performed at all time points;
- functional recovery through the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, administered at T0, T3, T4 and T5. The questionnaire is divided into 3 modules: symptom/disability module consisting of 30 questions investigating aspects of daily life; occupational module and sports/recreational activities module (optional). Additional items are used for workers and individuals whose occupation or sports or recreational activity requires a high level of physical performance. Each question has 5 possible answers, from 1 (no difficulty) to 5 (unable to perform a specific activity). The sum of the individual scores results in an overall score, which is converted into a scale from 0 to 100 (100 indicates severe disability) (10).
- The safety of the treatment was monitored by collecting observed and patient-reported adverse events. Written informed consent for the data's publication was obtained for the Declaration of Helsinki and Good Clinical Practice (GCP).

RESULTS

Case 1

A 47-year-old man with a 2R3B fracture underwent surgery for reduction and fixation with a volar plate (Fig. 1). The patient had no comorbidities or other bone related diseases and was not taking concomitant medications and other bone-related diseases. On the first day after surgery, the patient presented a pain score of 7/10 on the NRS scale.

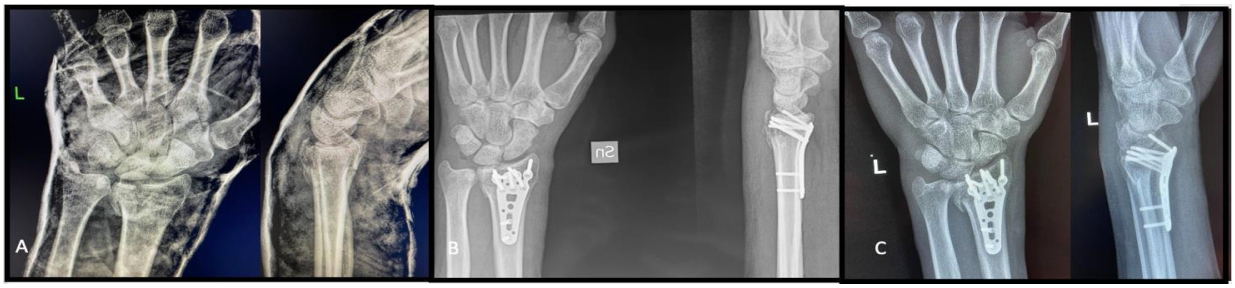

Fig. 1. *Pre-operative (A); Post-operative (B); 1 month follow-up (C).*

At subsequent assessments on days 7, 14 and 21 after surgery, the patient reported continuous progress in the perception of pain, which decreased to 2 points on the NRS scale after 30 days of treatment (T4), resulting clinically insignificant. This intensity was maintained at the post-treatment follow-up (Table I).

Table I. *Pain and functional recovery over time.*

Observation times	*NRS*	*DASH Symptom/Disability Module*
T0 – 1st day after surgery	7	100
T1- 7th day after surgery	6	
T2 - 14th day after surgery	4	
T3 – 21st day after surgery	4	49.2
T4 - 30th day after surgery (end of treatment)	2	20.8
T5 – 30 days after end of treatment	2	9.2

The assessment of the main form of the DASH questionnaire concerning symptoms and disability showed, on the first day after surgery, total disability in performing daily activities. Twenty-one days after surgery, the questionnaire score decreased, with a further reduction at T4. At the last follow-up (T5), the patient reported a further improvement in disability (Table I). The patient completed the planned treatment with PEAm/um without taking analgesics and/or anti-inflammatories during the weeks following surgery and without reporting any side effects.

Case 2

A 58-year-old woman with a 2R3B fracture underwent surgery for reduction and fixation with a volar plate (Fig 2). The patient had no comorbidities or bone-related diseases.

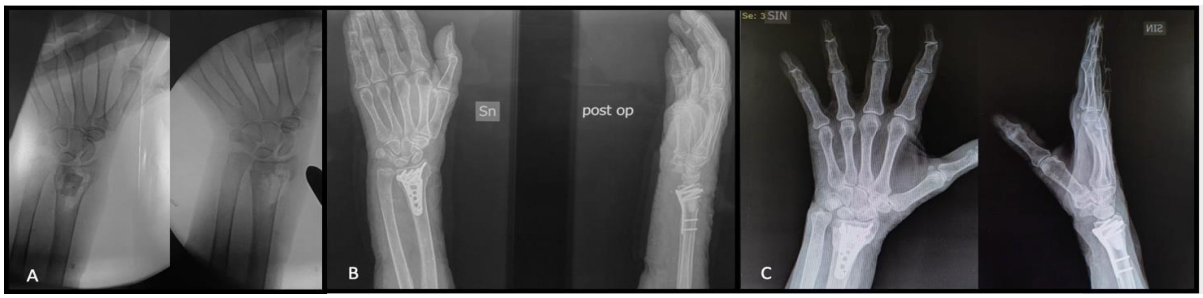

Fig. 2. *Pre-operative (A); Post-operative (B); 1-month follow-up (C).*

At T0, the patient presented severe pain, with an NRS score of 7/10, also reported 7 and 14 days after surgery. Twenty-one days after surgery, the patient reported an improvement in pain intensity with an NRS score of 5, which was maintained until T4. 30 days after surgery and after the end of treatment, the patient reported no more pain.

The assessment of functional recovery, carried out by filling out the main and occupational forms of the DASH questionnaire, showed a significant improvement in performing daily and occupational activities over time. Thirty days after the end of treatment, the DASH score was further reduced significantly regarding symptoms and the ability to perform various activities, including occupational ones (Table II). During the 30 days of treatment, the patient took no analgesics or anti-inflammatory drugs and reported no adverse effects.

Table II. *Pain and functional recovery over time.*

Observation times	*NRS*	*DASH Symptom/Disability Module*	*DASH Occupational Module*
T0 – 1st day after surgery	7	83.3	93.98
T1- 7th day after surgery	7		
T2 - 14th day after surgery	7		
T3 – 21st day after surgery	5	62.5	87.5
T4 - 30th day after surgery (end of treatment)	5	39.2	62.5
T5 – 30 days after end of treatment	0	5.0	0.0

DISCUSSION

PEA's anti-inflammatory, analgesic and neuroprotective effects have been confirmed in models of chronic inflammation and chronic and neuropathic pain: PEA was effective in preserving peripheral nerve morphology, reducing

mast cell activation and producing pro-inflammatory mediators at the site of injury; this confirms the direct intervention of PEA in the inflammatory process and pain response (11, 12).

During the treatment period with micronized/ultra-micronized PEA, both patients' post-surgical pain intensity and functional wrist recovery improved significantly. The first patient experienced almost complete pain relief at the follow-up, while the second reported a complete symptom resolution. In addition, the improvement of daily functions, observed in both patients through the Symptom/Disability Module of DASH and the Occupational Module for patient 2, was higher than the "Minimal Clinically Important Difference" reported by both the DASH website (15 points) and the literature data (10.83 points) (13, 14) at each assessment compared to the previous one.

The management of pain and the restoration of wrist function demonstrate the efficacy of this approach, which is supported by the clinically significant improvement achieved already after 21 days of treatment and at each evaluation time compared to the previous one, as well as by the further reduction of both the evaluated parameters 30 days after the end of treatment. In order to confirm these results, a larger, controlled, randomized, double-blind versus placebo study is planned.

CONCLUSIONS

Patients reported benefits after using a combination of PEAm/um in reducing pain and functional wrist recovery following a surgically treated fracture, encouraging its use as an effective, safe and well-tolerated alternative to manage post-operative bone pain.

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REFERENCES

1. Yao H, Zhang W, Xu W, Liu K, Xu Y. A new method to predict the outcome of the volar locked plate treatment for distal radius fracture. *BMC Musculoskelet Disord.* 2019;20(1):538. doi:https://doi.org/10.1186/s12891-019-2931-3
2. Solarino G, Vicenti G, Abate A, et al. Volar locking plate vs epibloc system for distal radius fractures in the elderly. *Injury.* 2016;47 Suppl 4(S84-S90. doi:https://doi.org/10.1016/j.injury.2016.07.056
3. Luo P, Lou J, Yang S. Pain Management during Rehabilitation after Distal Radius Fracture Stabilised with Volar Locking Plate: A Prospective Cohort Study. *Biomed Res Int.* 2018;2018(5786089. doi:https://doi.org/10.1155/2018/5786089
4. Zhao Y, Zhang H, Li N, Li J, Zhang L. Chronic Pain after Bone Fracture: Current Insights into Molecular Mechanisms and Therapeutic Strategies. *Brain Sci.* 2022;12(8):doi:https://doi.org/10.3390/brainsci12081056
5. Molfetta L, Saviola G, Fornasari D, Grossi PA, Corcione A, Frediani B. Osteoarticular pain: therapeutic approach by paradigms. *Eur Rev Med Pharmacol Sci.* 2022;26(11):4054-4068. doi:https://doi.org/10.26355/eurrev_202206_28975
6. Urso G. Le rigidità articolari: riabilitazione. *Riv Chir Mano.* 2001;38(2):170-179.
7. Ragipoglu D, Dudeck A, Haffner-Luntzer M, et al. The Role of Mast Cells in Bone Metabolism and Bone Disorders. *Front Immunol.* 2020;11(163. doi:https://doi.org/10.3389/fimmu.2020.00163
8. Petrosino S, Di Marzo V. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. *Br J Pharmacol.* 2017;174(11):1349-1365. doi:https://doi.org/10.1111/bph.13580
9. Haefeli M, Elfering A. Pain assessment. *Eur Spine J.* 2006;15 Suppl 1(Suppl1):S17-24. doi:https://doi.org/10.1007/s00586-005-1044-x
10. Padua R, Padua L, Ceccarelli E, et al. Italian version of the disability of the Arm, Shoulder and Hand (DASH) questionnaire. Cross-cultural adaptation and validation. *J Hand Surg Br.* 2003;28(2):179-186. doi:https://doi.org/10.1016/s0266-7681(02)00303-0
11. Paladini A, Fusco M, Cenacchi T, Schievano C, Piroli A, Varrassi G. Palmitoylethanolamide, a Special Food for Medical Purposes, in the Treatment of Chronic Pain: A Pooled Data Meta-analysis. *Pain Physician.* 2016;19(2):11-24.
12. Scarano A, Degidi M, Iezzi G, et al. Maxillary sinus augmentation with different biomaterials: a comparative histologic and histomorphometric study in man. *Implant Dent.* 2006;15(2):197-207. doi:https://doi.org/10.1097/01.id.0000220120.54308.f3
13. Franchignoni F, Vercelli S, Giordano A, Sartorio F, Bravini E, Ferriero G. Minimal clinically important difference of the disabilities of the arm, shoulder and hand outcome measure (DASH) and its shortened version (QuickDASH). *J Orthop Sports Phys Ther.* 2014;44(1):30-39. doi:https://doi.org/10.2519/jospt.2014.4893
14. Gummesson C, Atroshi I, Ekdahl C. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. *BMC Musculoskelet Disord.* 2003;4(11. doi:https://doi.org/10.1186/1471-2474-4-11