Efficacy of betamethasone valerate medicated plaster on painful chronic elbow tendinopathy: a double-blind, randomized, placebo-controlled trial

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Summary

Objective: **to investigate the efficacy and safety of a medicated plaster containing betamethasone valerate (BMV) 2.25 mg in patients with chronic elbow tendinopathy.**

Methods: **randomized, double-blind, placebo-controlled study with assignment 2:2:1:1 to BMV medicated plaster applied daily for 12 hours, daily for 24 hours or matched placebo. 62 patients aged ≥18 years with chronic lateral elbow tendinopathy were randomized. The primary efficacy variable was pain reduction (VAS) at day 28. Secondary objectives included summed pain intensity differences (SPID), overall treatment efficacy and tolerability.**

Results: **mean reduction in VAS pain score at day 28 was greater in both BMV medicated plaster groups, -39.35±27.69 mm for BMV12-h and -36.91±32.50 mm for BMV24-h, than with placebo,-20.20±27.32 mm. Considering the adjusted mean decreases, there was a statistically significant difference between BMV12-h and placebo (p=0.0110). Global pain relief (SPID) and overall treatment efficacy were significantly better with BMV. BMV and placebo plasters had similar local tolerability and there were few treatment-related adverse events.**

Conclusions: **BMV plaster was significantly more effective than placebo at reducing pain in patients with chronic elbow tendinopathies. The BMV plaster was safe and well tolerated.**

KEY WORDS: topical corticosteroids, betamethasone valerate, chronic elbow tendinopathy, treatment, pain.

Introduction

Lateral epicondylitis (LE) is the most common cause of elbow pain, affecting up to 3% of the adult population[1,2]. LE occurs in the dominant elbow in 70% of patients in particular during their fourth and fifth decade, without gender preference[3]. Usually it involves the extensor carpi radialis brevis tendon, whereas in 30% of cases the extensor digitorum communis tendon is also involved[4]. Although the etiopathogenesis is still not fully elucidated, it seems that the pathological condition arises by a combination between mechanical overloading and abnormal microvascular-response[5,6]. Histopathologically, it could be described as an angiofibroblastictendinosis with absence of inflammatory cells in chronic stages, as other site tendinopathies[7,8].

The most common symptom is pain that typically develops gradually and is exacerbated by activities that contemplate active wrist extension[9]. The manage-

ment of LE is generally conservative, as up to 90% of patients will recover without surgical intervention, however it is still debated which is the most efficient conservative intervention[10-12].

Different approaches could be proposed among which rest, activity modification, non-steroidal anti-inflammatory drugs (NSAIDs), forearm bracing, physiotherapy and local steroid injections are the most used in clinical practice[13]. The results obtained by topical and oral NSAIDs are limited although different trials suggest that topical NSAIDs may be beneficial in improving pain, without gastrointestinal effects caused by oral intake[14].

The short-term use of corticosteroid injections appears to be beneficial[15] while long-term use may be associated with significant harm to tendon tissues and tendon cells[16], probably due to the large excess of unbound, and therefore active, corticosteroids into the joint that may interfere with long-term healing process of the tendon[17]. Therefore, the lack of long-term benefit from corticosteroid therapy may have more to do with the delivery method than the medication.

Several studies have investigated the use of topically-applied steroids for tendon pain treatment[18-20], and directly comparing the effect of topically-applied corticosteroids with that of corticosteroid injections has demonstrated a significantly better outcome for patients treated with corticosteroid iontophoresis in the short-term and a statistically significant improvement in pain at the end of therapy, compared with injected corticosteroids[21].

A ready-to-use, self-adhering occlusive medicated plaster containing 2.25 mg of betamethasone 17-valerate (BMV, 0.1%) is currently marketed in several EU countries for the treatment of corticosteroid-responsive dermatoses (Betesil®; IBSA)[22]. The Betesil plaster is formulated to provide continuous sustained release of BMV, delivering an uniform concentration of the corticosteroid specifically to the affected area while acting as an occlusive barrier, ensuring good hydration and protecting against local trauma. The design of the plaster reduces the risk of excess medication absorption and avoids BMV dispersion on unaffected areas, reducing the risk of local adverse effects.

The BMV medicated plaster has been shown to significantly decrease pain and improve functional capacity in a pilot study in patients with chronic tendinopathies[23].

The aim of this multicentre, randomized, double-blind, placebo-controlled study was to evaluate the efficacy and safety of two treatment regimens (i.e., 12 or 24 hours of application/day) of the betamethasone valerate 2.25 mg medicated plaster during four weeks of treatment in patients with chronic tendinopathies of the upper and lower limbs.

Patients and methods

Study design

This randomized, double-blind, placebo-controlled, parallel-group multicenter study was performed between 24 April 2013 and 6 February 2014 in a total of 9 sites, all located in Italy. The study was registered with the EU Clinical Trials Register (Eudra CT Number: 2012-005030-11; available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-005030-11/IT). The original study protocol provided for the enrollment of patients with chronic tendinopathy of both the upper and lower limbs, and more precisely chronic LE and chronic Achilles tendinopathy. These two groups of patients were allocated to treatments according to different randomization lists – one for LE and one for the Achilles – and the results were analyses both separately and for the pooled population. Based on the known significant etiopathogenetic differences between the two diseases considered, we decided that it was more appropriate to report here the results relevant to the LE sub-group of patients, while those relevant to the Achilles tendinopathy will be separately reported elsewhere.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP). All patients provided informed consent prior to entry into the study and were able to understand the nature and aims of the study, including possible risks and side effects, to cooperate with the Investigator, to comply with the study requirements, and to attend all planned study visits.

The study protocol, patient information leaflet and the informed consent document were submitted to the reference Independent Ethics Committee (IEC) of each center participating in the study before any study-related procedure was started, and approval obtained from the IEC of each participating center before the study commenced. The study met the ethical standards of the Muscle, Ligaments and Tendons Journal[24].

Patient population

Male and female patients aged ≥18 years in the symptomatic phase of chronic lateral elbow tendinopathy, of ≥12 weeks duration and confirmed by ultrasound echographic scan were enrolled in the study. Symptomatic phase was defined as a pain score ≥50 mm on a 0-100 mm Visual Analogue Scale (VAS) as perceived when performing a standardized movement, according to the tendinopathy localization. Females of childbearing potential were required to be using an appropriate method of contraception.

Pregnant or breast-feeding women, patients with known hypersensitivity to the active substance and ingredients of the medicated plaster or to the rescue medication (paracetamol) were excluded from the study. Prior receipt of local corticosteroid injection or intra-articular corticosteroid injection for their tendinopathy within the preceding six months or systemic corticosteroids or local corticosteroid injection for another medical condition within one month, recent or chronic systemic NSAID, opioid or narcotic analgesic use, physiotherapy, electro-medical Tecar therapy,

laser therapy, iontophoresis therapy or eccentric training within the preceding three months were not allowed.

Randomization and treatment

Following a screening and enrolment visit (V1 - day 1), eligible patients were randomized according to a 2:2:1:1 randomization scheme to one of four treatment groups:

- BMV plaster, applied daily for 24 hours
- BMV plaster, applied daily for 12 hours
- Matched placebo plaster, applied daily for 24 hours
- Matched placebo plaster, applied daily for 12 hours.

Randomization was conducted according to a pre-defined, computer generated randomization list, prepared by the sponsor, IBSA Institut Biochimique SA, Switzerland, using validated SAS software. The randomization list was stored as an Excel file accessible only to Authorized personnel not involved in the conducting of the study to ensure full confidentiality. Patients meeting the eligibility requirements were sequentially assigned the next available study medication number by the Investigator for each site. Allocated treatment groups corresponding to individual patient identification codes (randomization numbers) were contained in sealed envelopes and concealed from Investigators and participants until after the study was completed.

The control plasters were identical to the active form in terms of size, shape, color and method of application. One plaster was applied whole, once daily, on the skin at the affected body site. Patients assigned to the 24-hour application regimen removed the plaster not less than 20 hours and not more than 23.5 hours after its application. Patients assigned to the 12-hour application regimen removed the plaster in the evening approximately 12 hours after its application. In the case of insufficient pain relief, patients were allowed to take paracetamol oral tablets as rescue medication to a maximum dose of 4 g/day. In the event that the patient needed to take rescue medication on the day when a control visit was scheduled, a minimum wash-out period of 4 hours before the visit was followed. The use of any kind of occlusive bandage over the medicated plaster was not allowed.

A flow chart describing the progress of patients throughout the study is presented in Figure 1.

Outcomes

The primary objective of this study was to investigate the ability of BMV 2.25 mg medicated plaster, as compared to placebo plaster (same formulation but without active ingredient), to reduce pain when topically applied daily, according to two different dose regimens (i.e., 12 or 24 hours of application/day), and during a period of 4 weeks, in patients suffering from chronic lateral elbow tendinopathy. The primary efficacy variable was defined as pain reduction at the day 28 (V5) post-baseline end-of-treatment visit while performing a standardized movement as scored by the 0-100 mm VAS, where 0 mm represented 'no pain' and 100 mm represented 'worst imaginable pain'.

Secondary efficacy objectives of the study were as follows: 1) summed pain intensity difference (SPID), defined as total pre-/post-treatment difference at each pre-defined control visit during the treatment period; 2) proportion of successes based on patient's self-perceived level of improvement at each control visit assessed as: completely recovered/much improved/improved/no change/worse/much worse; 3) functional disability, as assessed by the patient by means of the Patient-Rated Tennis Elbow Evaluation (PRTEE) score at 'end-of-treatment' visit, compared to the pre-treatment score; 4) overall treatment efficacy, as judged by the Investigator on a 5-point scale (4 = excellent; 3 = good; 2 = fair; 1 = poor; 0 = none) at the end of treatment; 5) total dose of rescue medication (paracetamol 500 mg) used and proportion of patients using the rescue medication during the study.

The safety variables of the study were designed to evaluate the local tolerability at the site of plaster application, with particular attention to any atrophic change of the skin, and the appreciation of the general safety of the tested medication, adverse events (AEs), serious AEs (SAEs) and treatment-emergent AEs (TEAEs) occurring at any time during the study; vital signs; skin irritation at the plaster application site, presence of visible atrophic changes of the skin (VAS score, where 0 mm represented 'no atrophic changes' and 100 mm represented 'severe atrophic changes'), overall treatment tolerability independently judged by the Investigator and the patient (4=excellent; 3=good; 2=fair; 1=poor; 0=none), and compliance to the tested medication.

Statistical analysis

All statistical analyses and data processing were performed using SAS® software release 8.2 for Windows® (SAS Institute, Inc., Cary, North Carolina, USA). Data analyses for both efficacy (primary and secondary) and safety outcomes were performed using an intention-to-treat (ITT) approach basis that included all randomized patients. The two placebo groups were pooled for data analysis.

A secondary analysis of the primary efficacy variable was performed on the per-protocol (PP) population, which included all subjects who completed the treatment period without any major deviation from the protocol.

Descriptive statistics were provided for all variables by treatment group. Continuous variables were summarized by using number, mean, median, standard deviation (SD) and range. Categorical variables were summarized by using frequency distributions and percentages. Results were considered statistically significant if the rounded p-value was ≤ 0.05.

Between-group comparisons were made using an analysis of covariance model (ANCOVA) with base-

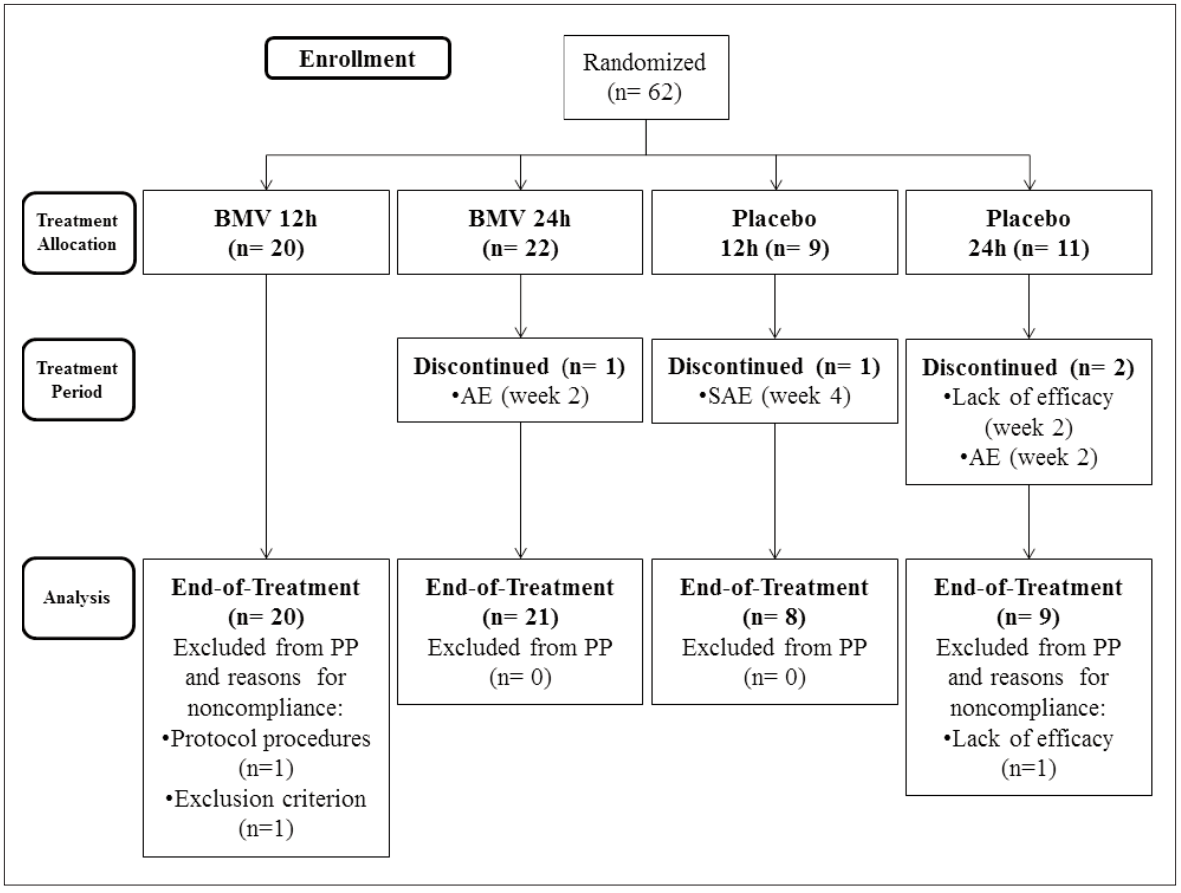

Figure 1. Flow chart describing the progress of patients throughout the study. AE, adverse event; BMV, betamethasone medicated plaster; PP, per protocol; SAE, serious adverse event.

line VAS pain value and centre as covariates. Pairwise comparisons were performed for the BMV plaster applied for 24 hours/day, BMV plaster applied for 12 hours/day and (pooled) placebo plaster. For continuous variables, differences between groups were analyzed by means of analysis of variance (ANOVA) with treatment group as a class variable. For non-ordered categorical variables, the groups were compared using Chi-square test.

Safety parameters were analyzed in the safety population, which was defined as all randomized patients who received at least one dose of either the active or the placebo treatments. The incidence of adverse events (AEs) and serious AEs (SAEs) in the treatment groups was analyzed using descriptive statistics. The difference between treatment groups in patients who experienced AEs and SAEs was evaluated using the Chi-square test.

The sample size was calculated *a priori* based on the ANCOVA analysis of the primary endpoint in the pooled LE and Achilles tendon patients. By considering a 30% improvement in pain at day 28 from pretreatment status as significant for patients with mild-to-moderate acute pain[25,26], and assuming a common standard deviation of 20 mm and a 0.05 two-sided significance level, a sample of 29 patients in each group would have a 80% power to detect a difference between active and placebo of 15 mm (i.e., about 30% of the minimum 50 mm pain level required to be eligible for the study).

Results

Patient population

A total of 62 patients with chronic elbow tendinopathy were randomized to treatment with BMV 12-hour (n=20), BMV 24-hour (n=22) or placebo (n=20, considering both 12-hour and 24-hour regimens).

The flow of patients through the study is shown in Figure 1. Overall, 58 patients completed the study and 4 patients discontinued treatment; none in the BMV 12-hour group, 1 in the BMV 24-hour group (AE), 1 in the placebo 12-hour group (SAE) and 2 in the placebo 24-hour group (lack of efficacy and AE, respectively). All 62 randomized patients took at least one dose of the study medication and were included in the ITT and safety populations and 60 in the PP population.

All patients were Caucasian and well matched at baseline for demographic parameters, except for

height and weight (p=0.0034, and p=0.0231, respectively, Tab. 1), but not for BMI. The characteristics of tendinopathy at baseline (Tabs. 1, 2, 3) showed significant differences for the VAS pain score, with a less value for BMV 12-houras compared to BMV 24-hour *vs* (p=0.0043) as for the PRTEE total score (p=0.0315).

Efficacy

VAS pain score decreased in all groups, with a mean (± SD) decrease of -39.35 ± 27.69 mm in the BMV 12-hour group, -36.91 ± 32.50 mm in the BMV 24-hour group and -20.20 ± 27.32 mm in the pooled placebo groups. The pain reduction effect of the BMV medicated plaster compared with placebo was also greater at all time-points (Tab. 2).

As shown in Figure 2 (adjusted mean reduction), the VAS pain score reduction at day 28 (end of treatment) in the ITT population, the primary efficacy endpoint, was statistically significantly greater in the BMV 12-hour than in the placebo groups (p=0.0110). The results for the primary efficacy variable were confirmed in the PP population (p=0.0015). In both ITT and PP population, although the decrease of VAS pain score at day 28 was markedly higher with both BMV regimens than with placebo, it did not reach statistical significance for BMV 24-hour. The SPID results additionally showed that the difference between both BMV 12-hour and BMV 24-hour groups *vs* placebo was statistically significant (p=0.0042 and p=0.0432, respectively, Tab. 2).

As shown in Table 3, the proportion of success, according to the patient's self-assessment, was higher in the two BMV groups than in the placebo groups at all weekly assessment time points from day 7 to day 28 although without statistically significant differences (% of success at day 28 were 67 and 53% in pooled BMV 12-hour and BMV 24-hour groups and placebo group, respectively). Further, the proportion of patients with an overall treatment efficacy rating of good or excellent at day 28 was more than two-fold higher in the two BMV groups than in the placebo groups, with a statistically significant difference between groups (p= 0.0317).

The extent of the mean decrease in total score of PRTEE was higher in the two BMV groups than in the placebo groups, resulting statistically significant for the comparison between BMV 24-hour and placebo (p=0.0383).

There were no statistically significant between-groups differences in the proportion of patients who used rescue medication. Moreover, the mean number of

Table 1. Demographic and clinical characteristics of the intention-to-treat (ITT) population at baseline.

	BMV 12-hour (n=20)	BMV 24-hour (n=22)	Placebo (n=20)	*p* value (ANOVA)
Gender, n (%)				
Male	13 (65.0)	13 (59.1)	6 (30.0)	0.0588*
Female	7 (35.0)	9 (40.9)	14 (70.0)	
Age, years	47.90 ± 7.87	48.45 ± 10.17	49.05 ± 33.00	0.9218
Weight, kg	80.15 ± 15.08	77.36 ± 15.61	66.85 ± 46.00	0.0231
Height, m	1.75 ± 0.09	1.73 ± 0.11	1.65 ± 1.50	0.0034
BMI, kg/m^2	26.01 ± 3.94	25.81 ± 3.78	24.54 ± 17.97	0.4957
Duration of tendinopathy, weeks	49.40 ± 57.63	49.18 ± 72.84	48.95 ± 57.24	0.9997

*Chi-Square test.
Unless otherwise noted, data are mean ± standard deviation (SD).
BMI, body mass index, BMV, BMV medicated plaster.

Table 2. Mean VAS Pain score changes (mm) over time in the intention-to-treat (ITT) population.

	BMV 12-hour (n=20)	BMV 24-hour (n=22)	Placebo (n=20)	*p* value (BMV 12-hour vs. 24-hour)
Baseline - day 0	64.00 ± 7.82	71.50 ± 8.52	67.30 ± 8.16	
*p value (vs placebo)**	*0.2073*	*0.1020*		*0.0043*
Reduction at day 7	-23.70 ± 18.55	-19.50 ± 23.29	-5.20 ± 13.02	
Reduction at day 14	-29.60 ± 20.85	-29.64 ± 28.41	-13.95 ± 21.95	
Reduction at day 21	-34.95 ± 25.20	-37.91 ± 25.96	-20.20 ± 24.93	
Reduction at day 28	-39.35 ± 27.69	-36.91 ± 32.50	-20.20 ± 27.32	
SPID	127.60 ± 86.35	123.95±104.01	59.55±77.36	
p value (vs. placebo)	*0.0042*	*0.0432*		*0.3734*

Values are mean ± standard deviation (SD).BMV, BMV medicated plaster; VAS, visual analogue scale; SPID, Summed Pain Intensity Difference. *ANOVA.

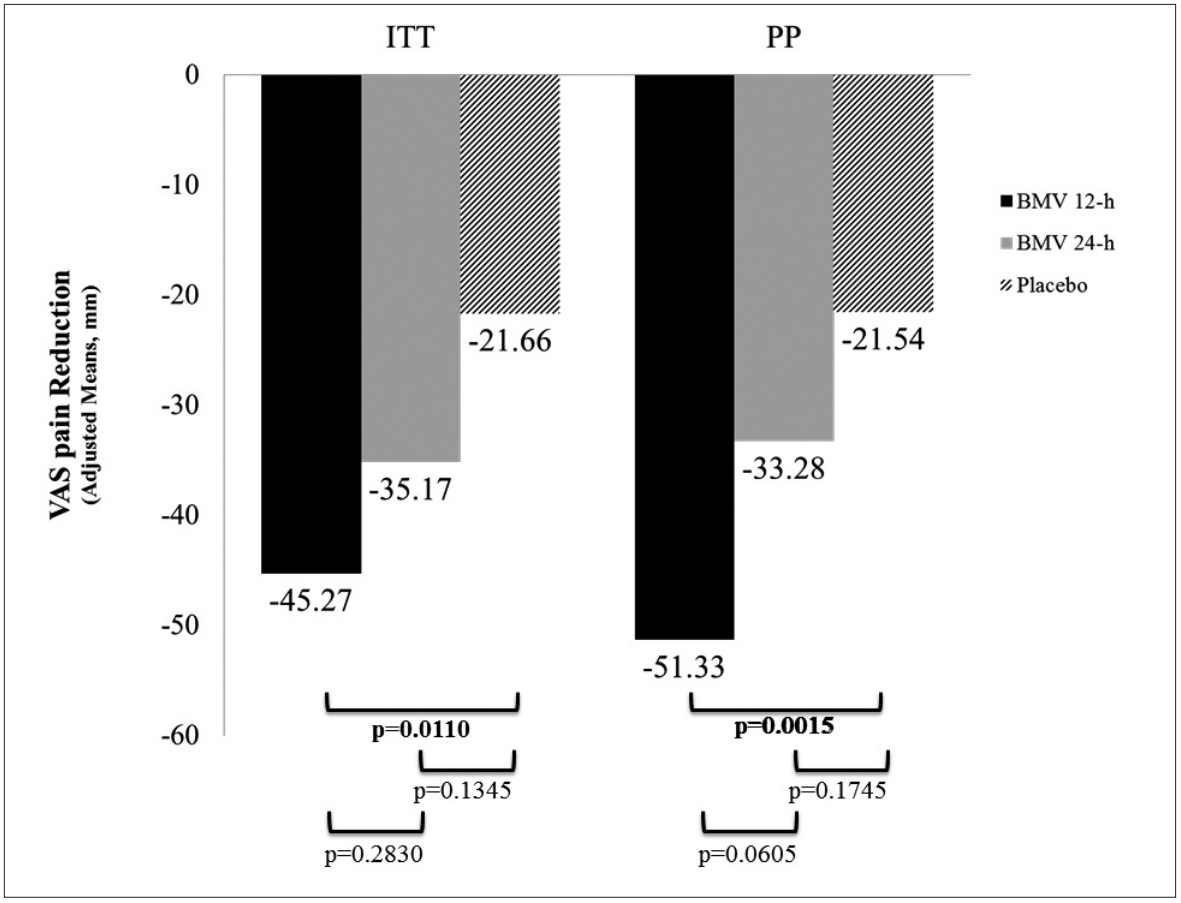

Figure 2. Pain reduction after 28 days of treatment with betamethasone valerate medicated plaster (BMV) or placebo plaster in 12-hour or 24-hour application regimens using a 0-100 mm visual analogue scale (VAS). Adjusted mean values from the ANCOVA models that included baseline VAS pain and study site as covariates. ITT, intention-to-treat; PP, per-protocol.

tablets used in those patients was approximately 8 tablets during the entire 4-week study period (data not shown).

Safety

Local tolerability was assessed by both the investigators and the patients as good or excellent in about 75% of cases in the placebo group and in over 90% of cases in the BMV groups, without statistically significant differences between groups (Tab. 3).

TEAEs were reported in a total of 19 patients (30.6%), without statistically significant difference between groups (p=0.3860). Eight AEs were considered treatment-related; 6 in the BMV 24-hour group and 2 in the placebo group. There were no treatment-related AEs in the BMV 12-hour group (Tab. 4).

The most common TEAE was headache, which was reported by 2 patients (10.0%) in the BMV 12-hour group, 4 (18.0%) in the BMV 24-hour group and 4 (20.0%) in the placebo group. Application site erythema and oedema were reported in 2 patients in the BMV 24-hour group, skin rash in 2 patients in the placebo group. No substantial changes from baseline in vital signs were observed in any group.

At day 28, only 3 patients in the BMV 24-hour group reported mild-to-moderate skin irritation. In 2 of these patients clinically relevant signs of skin atrophy after 4 weeks of treatment were also reported, with VAS scores of 39 for the first patient and of 17 for the second patient who experienced also application site erythema and oedema (data not shown). These results indicate mild-moderate and transient skin irritation and atrophic changes at the plaster application area only with the 24h/day treatment.

Discussion

Although the BMV medicated plaster was effective in reducing pain and improving functional limitation in a small pilot study of patients with relapses of chronic tendinopathies[23], to the best of our knowledge this is the first controlled study in a size able number of patients to investigate the BMV medicated plaster in patients with chronic lateral epicondylitis (LE).

Our study showed that the BMV medicated plaster

Table 3. Secondary efficacy results in the intention-to-treat (ITT) population.

	BMV 12-hour	BMV 24-hour	Placebo	*p value*
Success, %#	**(n=19)**	**(n=20)**	**(n=19)**	
Day 7	47.37	55.00	22.22	*0.1054**
Day 14	57.89	75.00	42.11	*0.1135**
Day 21	52.63	80.00	47.37	*0.0805**
Day 28	63.16	70.00	52.63	*0.5319**
Overall treatment efficacy	**(n=19)**	**(n=21)**	**(n=16)**	
Good\Excellent, %	57.89	57.14	18.75	*0.0317**
Investigator's opinion on local tolerability	**(n=19)**	**(n=20)**	**(n=16)**	
Good\Excellent, %	94.74	95.00	87.50	*0.6614**
Patient's opinion on local tolerability	**(n=18)**	**(n=21)**	**(n=16)**	
Good\Excellent, %	94.44	95.24	75.00	*0.3080**
PRTEE total score, mean (SD)	**(n=20)**	**(n=22)**	**(n=20)**	
Baseline - day 0	48.45 ± 13.85	59.16 ± 14.88	60.38 ± 17.35	*0.0315***
Reduction at day 28	-16.93 ± 12.15	-20.91±16.52	-10.63±12.80	
p value (vs placebo)	*0.2074****	*0.0132****		*0.2706*** (BMV 12-hour vs. 24-hour)*

BMV, BMV medicated plaster;PRTEE, Patient-Rated Tennis Elbow Evaluation score.
* Chi-Square; **ANOVA; ***ANCOVA,#Proportion of patients self-assessing their level of improvement as completely recovered, much improved or improved.

when applied daily for 28 consecutive days in patients with LE was significantly more effective at reducing pain than placebo plaster, even when applied for only 12 hours a day. After 4 weeks of daily plaster application, the improvement in pain observed in the active plaster groups was about 2-fold as compared to the placebo group (approximately 38 mm *vs.* 21 mm), independently from the dose regimen. This actually corresponds to ~80% incremental pain reduction in favor of the active plaster. Analysis of both primary and secondary efficacy endpoints, including self-assessments of pain by the patient, at different times of the day, as well as cumulative reduction along the 4-week treatment period (SPID), confirmed in general that the BMV medicated plaster provided a greater reduction in global amount of pain, that was rapid and sustained as compared with placebo. Both patient and investigator assessments of overall treatment efficacy judged the BMV plaster more effective than placebo, with consistent differences between BMV and placebo across the secondary efficacy parameters. The BMV medicated plaster was well tolerated, with an overall safety and local safety placebo-like profile, particularly for the 12 h application regimen. Compliance to study medication was excellent, with almost 100% compliance observed in all groups. Furthermore, the use of rescue medication was very limited and, considering the small number of paracetamol tablets taken during the study period, without relevance for study outcome.

Topically-applied steroids for the treatment of tendon pain have been shown to be of benefit in terms of pain reduction in patients with acute pain from epicondylitis[18,21]. However, these studies have aimed to induce a healing response by enhancing the absorption of the topical corticosteroid using iontophoresis to drive the topically applied medication into the damaged tissue. This approach has been shown to be as or more effective than corticosteroid injections in patients with lateral epicondylitis[21]. In contrast, absorption of betamethasone from the BMV medicated plaster is mediated by the occlusive hydrogel adhesive base of the dressing and the continuous controlled release of the medication to the underlying tissue during the 12- or 24-hour treatment period.

Our findings demonstrate that the BMV medicated plaster is significantly superior to placebo in patients with LE, additionally providing an improvement in pain considered by patients to be clinically meaningful, as measured by the internationally recognized PRTEE questionnaire: in fact, PRTEE total score mean reduction was of about 17-21 points (-35% *vs* baseline) with the active drug, as compared to only 11 points (-16% *vs*. baseline) with placebo, at the end of the 4-week study period. The difference for the active group can be considered clinically significative[27].

Our study has some limitations. Although the treatment groups were otherwise homogeneous in terms of demographics and medical history and reflected the characteristics expected for the target population, there were statistically significant differences among treatment groups at baseline in terms of height and weight, which were significantly lower in the placebo group and reflected the numerically higher proportion of female in that group, as compared to the two active plaster groups. However, when the patients BMI was compared no statistically significant intergroup difference were found.

Table 4. Summary of treatment-emergent adverse events (TEAEs) in the safety population.

	BMV 12-h (n=20)	BMV 24-h (n=22)	Placebo (n=20)	*p* value
Patients with TEAEs, n (%)	**4 (20.00)**	**7 (31.82)**	**8 (40.00)**	**0.3860**
Total Nr. of TEAEs	**6**	**12**	**9**	
Tachycardia	0	1	0	
Nausea	2	0	0	
Oral disorder	1	0	0	
Application site erythema	0	1	0	
Application site oedema	0	1	0	
Pyrexia	0	2	0	
Influenza	0	0	1	
Blood pressure increased	0	1	0	
Back pain	1	0	1	
Musculoskeletal chest pain	0	1	0	
Headache	2	4	4	
Transverse sinus thrombosis	0	0	1	
Erythema	0	1	0	
Rash	0	0	2	
Patients with ADRs, n (%)	**0 (0.0)**	**3 (13.64)**	**2 (10.00)**	**0.2495**
Total Nr. of ADRs	**0**	**6**	**2**	
*Tachycardia**	0	1	0	
Application site erythema	0	1	0	
Application site oedema	0	1	0	
*Blood pressure increased**	0	1	0	
*Headache**	0	1	0	
Erythema	0	1	0	
*Rash**	0	0	2	
Patients with SAEs, n (%)	**0 (0.0)**	**0 (0.0)**	**2 (10.00)**	**0.1142**
Total Nr. of SAEs	**0**	**0**	**2**	
Transverse sinus thrombosis	0	0	1	
*Rash**	0	0	1	
Patients with TEAEs leading to withdrawal, n (%)	**0 (0.0)**	**1 (4.55)**	**2 (10.00)**	**–**
Total Nr. of TEAEs leading to withdrawal	**0**	**3**	**2**	

ADR, adverse drug reaction; BMV, BMV medicated plaster; SAE, serious adverse event; TEAE, treatment-emergent adverse event. *leading to withdrawal.

It is of interest that the mean pre-treatment VAS pain score was significantly higher in the BMV 24-hour group than in the other groups. However, baseline VAS score was included in the covariates used in the ANCOVA model of the primary efficacy analysis to compensate for its potential confounding effect. These differences observed at baseline are mostly due to the limited sample size: a consequence of both the design of this early phase clinical investigation, which main goal was to identify the more advantageous between the two dose regimen – 12h and 24h daily application – of the medicated plaster, and further exacerbated by the choice to separately report the results of the two disease sub-group, elbow and Achilles chronic tendinopathy. This latter decision also had a negative impact on the power of the statistical comparisons, which failed in some cases to reach a clear significance, despite the difference observed in terms of extent of improvement between active and placebo appeared to be clinically relevant.

Strength of the study is the prospective, multicenter, double blind, placebo-controlled study design. Furthermore, as said above, the study was sufficiently powered to detect a clinically relevant improvement in pain at the end of treatment, and superiority over placebo was demonstrated for BMV medicated plaster applied for 12 hours in patients with LE. The results of the efficacy and safety assessments indicate that the 24-hour BMV medicated plaster regimen does not offer any further benefits in comparison with the 12-hour regimen.

The BMV medicated plaster, in both the 12-hour and 24-hour application duration regimens, was safe and well tolerated. Particularly, when applied for 12 h-a-day, the BMV medicated plaster had a local safety and tolerability profile perfectly similar to the placebo plaster, and the incidence of TEAEs and adverse drug reactions was globally lower in the two BMV groups than with placebo. Only 3 patients, in the BMV 24-hour group, and 2 patients in the placebo groups

reported treatment-related events during the study period.

Conclusion

Topical treatment with the BMV 2.25 mg medicated plaster was significantly more effective than placebo at reducing pain scores in patients with chronic lateral epicondylitis (LE). Rapid and sustained reduction in pain levels was achieved, and the BMV medicated plaster was safe and well tolerated.
The results of this study demonstrate that the BMV medicated plaster can be beneficial in reducing pain from chronic LE. An additional aim of this non-invasive approach for pain control could be to permit patients to effectively adopt corrective behavior modifications, without pain, during the long-term recovery and healing process.

Conflict of interests

The Authors declare that they have no conflict of interests regarding the publication of this paper.

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