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REVIEW

Traumeel – an emerging option to nonsteroidal anti-inflammatory drugs in the management of acute musculoskeletal injuries

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Christian Schneider

Praxis für Ganzheitsmedizin, Herrsching, Germany; Schön Klinik München Harlaching, München, Germany

Abstract: Musculoskeletal injuries are on the rise. First-line management of such injuries usually employs the RICE (rest, ice, compression, and elevation) approach to limit excessive inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also commonly used to limit inflammation and to control pain. Traumeel®, a preparation with bioregulatory effects is also used to treat the symptoms associated with acute musculoskeletal injuries, including pain and swelling. Traumeel is a fixed combination of biological and mineral extracts, which aims to apply stimuli to multiple targets to restore normal functioning of regulatory mechanisms. This paper presents the accumulating evidence of Traumeel's action on the inflammatory process, and of its efficacy and tolerability in randomized trials, as well as observational and surveillance studies for the treatment of musculoskeletal injuries. Traumeel has shown comparable effectiveness to NSAIDs in terms of reducing symptoms of inflammation, accelerating recovery, and improving mobility, with a favorable safety profile. While continued research and development is ongoing to broaden the clinical evidence of Traumeel in acute musculoskeletal injury and to further establish its benefits, current information suggests that Traumeel may be considered as an anti-inflammatory agent that is at least as effective and appears to be better tolerated than NSAIDs.

Keywords: Traumeel, inflammation, acute musculoskeletal injuries, nonsteroidal anti-inflammatory drugs

Introduction

Inactivity is recognized as an important predictor of mortality and morbidity, and the benefits of regular physical activity are well documented.[1] A moderate amount of physical activity on most days can have substantial health benefits.[2] However, participation in sports and other physical activities increases the risk of injury. The most common injuries are at the ankle, which, with an incidence of 1 per 100,000 people a day, account for about 20% of all sports injuries and usually comprise moderate ligament sprains.[1] Moreover, there are additional risks of musculoskeletal injury from innate factors, such as in people who are overweight,[3] through excessive load, or who are elderly and prone to falls.[4]

Generally, the principle of the management of acute musculoskeletal injuries is to provide symptomatic relief so that a return to activity and rehabilitation can begin,[5] and the pre-injury level of function is regained without overtly compromising tissue healing.[6,7] In this respect, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to limit inflammation and to control pain, and appear to facilitate the return to function.[7] However, these drugs are not always well tolerated and alternatives may

Correspondence: Christian Schneider
Schön Klinik München HarlachingPrivatAmbulanz,
Harlachinger Str 51,
81547 München, Germany
Tel +49 89 6211 4060
Fax +49 89 6211 4062
Email chschneider@schoen-kliniken.de

need consideration.[7] Such concerns are likely to contribute to the increase in complementary and alternative medical (CAM) practices.[8]

A frequently used preparation for the symptoms associated with acute musculoskeletal injuries, including inflammation and pain, is Traumeel® (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany), a fixed combination of biological and mineral extracts.[9] The aim of this paper is to describe the conventional management of acute musculoskeletal injuries, focusing on NSAIDs and their use and limitations, and to consider Traumeel as an emerging option to NSAIDs for individuals who, for whatever reason, either cannot or prefer not to take NSAIDs.

Acute musculoskeletal injuries

Acute musculoskeletal injuries, such as sprains, strains, tendinopathy, and stress fractures, are a range of disorders involving ligaments, muscles, tendons, bones, and associated neurovasculature. Common causes include sudden impact, physical muscular overloads, or repetitive use of a joint or particular muscle group. Such injuries are associated with significant short-term disability and constitute a significant demand on primary and hospital care.

Conventional management of acute musculoskeletal injuries

Tissue processes following acute musculoskeletal injuries involve an acute inflammatory response at the injury site. Conventional management aims to control the pain, minimize secondary tissue injury, and restore the range of motion and voluntary muscle control.[10] Decisions about the care of acute problems are made mostly on patients' symptoms,[11] and visits to a general practitioner are generally influenced by the perceived seriousness and duration of the injury.[12] The availability of over-the-counter (OTC) medications makes it possible for consumers to treat many ailments without consulting a healthcare professional,[13] and OTC pain medication (eg, salicylates and paracetamol-based products) are frequently used to cope with minor aches, pains, and injuries.

Although inflammation is a homeostatic mechanism and part of the body's response to injury, excessive inflammation can slow the healing process and cause tissue damage. Excessive inflammation of acute musculoskeletal injuries can be limited by following the RICE (rest, ice, compression, and elevation) approach. The objective of RICE is to stop the injury-induced bleeding into the muscle tissue, thereby minimizing the injury extent.[14] Additional medication is often required to achieve effective symptomatic relief. Treatments including hyaluronidase, low-dose heparin, aprotinin, and corticosteroids have been used in the management of various injuries, although there is little evidence of long-term effectiveness or to support their use.[15,16] Moreover, these approaches are associated with risks of adverse effects.[15,17,18] Newer agents, such as Actovegin (calf-derived deproteinized hemodialysate), injection of autologous red cells in and around a symptomatic tendon, sclerosant injections, topical glyceryl trinitrate, and polysulphated glycosaminoglycans may also be useful in tendon disorders, but their efficacy needs to be substantiated in larger controlled trials.[17,18]

NSAIDs have become synonymous with the management of acute musculoskeletal injuries.[7] They are some of the most widely used medications, and are reliable and effective when used appropriately for pain relief and to reduce inflammation. NSAIDs reduce pain through their influence on the peripheral nervous system, achieved through incomplete inhibition of the enzymes, cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2), which inhibit prostaglandin biosynthesis. Cox-2 is involved in inflammatory processes mediated by prostaglandins.

Side effects associated with NSAIDs are common (Table 1) and are generally a result of the inhibition of the "housekeeping" functions of prostaglandins by Cox-1, which is present in a variety of cell types. Most frequent are the effects on the gastrointestinal tract, the most common being gastritis and upper gastrointestinal ulcer and bleeding.[19–22] There may be effects on prostaglandin-mediated renal[23–25] and platelet function, an increased risk of myocardial infarctions, hypertension and heart failure, as well as liver damage, blood dyscrasias, rashes, and hearing and vision impairment.[23,26–29]

A report of two US surveys of over 9602 respondents concluded that OTC NSAID analgesics were widely used, frequently taken inappropriately and potentially dangerous, and users were generally unaware of the risk of adverse events.[30] A retrospective study of US medical records of about 12,000 patients on naproxen and 38,500 patients on ibuprofen found that the "real-world" risk of these patients sustaining a serious gastrointestinal event was 1.38- and 1.54-times greater, respectively, than for those not taking such medications.[31]

Complications secondary to NSAID use are increasingly recognized in patients who are elderly; or with a previous history of gastrointestinal complications;[23,26,32] pre-existing renal dysfunction, diabetes or heart failure; or with cardiovascular

Table 1 Typical adverse events of nonsteroidal anti-inflammatory drugs

System/organ	Adverse event
Cardiovascular system	Thrombotic vascular incidents, including myocardial infarction
Gastrointestinal tract	Nausea, vomiting, dyspepsia, gastritis, bleeding, ulceration
Hematopoiesis	Thrombocytopenia, hypoprothrombinemia, anemia, granulocytopenia
Hypersensitivity reactions	Rashes, erythema, drug-induced eruptions, urticaria, angioedema, broncospasm, aspirin-induced asthma, Stevens–Johnson syndrome (very rarely)
Kidneys	Renal failure, hematuria, proteinuria, sodium and water imbalance (fluid retention), interstitial nephritis, nephrotic syndrome, papillary necrosis
Liver	Hepatic damage, abnormalities on liver function tests (eg, increased aminotransferase activity)
Nervous system	Headache, dizziness, nervousness, depression, drowsiness, insomnia
Sense organs	Hearing disturbances, vertigo, photosensitivity, eye changes

risk factors, such as obesity, dyslipidemia, and hypertension.[29] Moreover, there is the risk of drug interactions,[33,34] particularly in the elderly who are likely to have other medical conditions and therefore taking multiple medications.

Although effective at reducing pain and inflammation, NSAIDs may not be appropriate particularly for those frequently participating in sports. Masking pain may enable an individual to continue their sport or daily activities in the short term, but may lead to a worsening of the injury without realization of the damage being inflicted. Moreover, animal studies have demonstrated that anti-inflammatory treatment may not promote healing;[7,35] NSAIDs have been shown to impair the return of mechanical strength following acute injury to bone, ligament, and tendon.[7] Prostaglandin synthesis is required for factors regulating muscle regeneration, and Cox inhibition can affect expression of such factors.[36]

Patient choice

Patient preferences have been shown to have a direct impact on the outcome of therapy through psychological factors, such as belief in the medication and media coverage, or indirectly via patient rates of adherence to treatment.[37] Preference for a medication is based on several factors, including speed and degree of pain relief, symptom recurrence, functional disability, consistency of effect, ease of administration, and adverse events.[38] A study to investigate patient preferences for osteoarthritis treatment found the attributes significantly influencing treatment preference were the degree of joint aches, the level of physical mobility, and the risk of experiencing serious treatment-related adverse events.[39] Thus, while some patients may find their treatment ineffective or prefer to avoid the risk of adverse effects,[39] it is reasonable to assume that others may prefer an alternative treatment option. It therefore seems prudent to consider patients' preferences[29] to encourage adherence.

Self-care is becoming increasingly popular,[13] and government policies are developing to support and empower people to treat themselves appropriately.[40] Additionally, people want the opportunity for shared decision-making.[41] In addition to standard conventional medical care, use of CAM therapies for routine healthcare is becoming increasingly popular.[41] CAM therapies include dietary supplements, herbal medicine, acupuncture, and biofeedback. Data suggest that many people have a holistic view of health, and believe that a combination of CAM and conventional medicine is superior to either approach alone.[41] Notably, some prefer to avoid prescription medicines whenever possible, using them as a last resort. In the UK, patients have demonstrated such preference by purchasing alternative therapies privately, despite the provision of conventional medicines by their healthcare providers.[42]

Traumeel – an option in acute musculoskeletal injury management

What is Traumeel?

Traumeel is a fixed combination of diluted plant and mineral extracts (Table 2). It has been available over the counter in Germany for over 60 years and in Austria for over 40 years, and is currently available in approximately 50 countries, including the USA. The combination is currently used to treat acute musculoskeletal injuries, such as sprains and traumatic injuries, and as supportive therapy in pain and inflammation of the musculoskeletal system. It can be used in the form of tablets, drops, injection solution, ointment, and gel.

The ingredients of Traumeel have been used for many years for therapeutic purposes, such as for pain (*Atropa belladonna*), inflammation (*Echinacea*), bruising (*Arnica montana*), wound healing (*Matricaria recutita, Calendula officinalis*), bleeding (*Achillea millefolium*), edema (*Mercurius solubilis*), and infections (*Hepar sulfuris*). Based on such observations, Traumeel was developed by the German physician, Dr Hans-Heinrich Reckeweg in the 1930s; he combined botanical and mineral substances to produce this natural medicine to treat musculoskeletal injuries and inflammation.

Table 2 Components of Traumeel (eg, ointment, tablets, and ampoules)

Source of extract	Characteristics[a]	Ointment (per 100 g)	Tablets (per 300 mg)	Ampoules for injection (per 2.2 mL)
Achillea millefolium (milfoil)	Hemorrhages, especially precapillary arteriovenous (anastomosis), oozing hemorrhages	90 mg	0.015 mg	0.0022 μL
Aconitum napellus (monkshood)	Fever with hot, dry skin, neuralgia, inflammatory rheumatism; improvement of the vasotonia; analgesic, hemostatic	5 mg	0.03 mg	0.0132 μL
Arnica montana (mountain arnica)	To stimulate the healing of wounds, fractures, dislocations, contusions, hemotomas, myocardial weakness, neuralgia, myalgia, analgesic, hemostatic	1.5 mg	0.15 mg	0.022 μL
Atropa belladonna (deadly nightshade)	Localized reaction phases, cerebral sensitivity with cramp and delirium	5 mg	0.0075 mg	0.022 μL
Bellis perennis (daisy)	Dislocations, contusions, sensation of soreness in the abdominal wall/cavity, exudative processes, resorption of edema	100 mg	0.06 mg	0.011 μL
Calendula officinalis (calendula)	Slowly healing wounds, promotes granulation, analgesic	450 mg	0.15 mg	0.022 μL
Matricaria recutita (chamomile)	Anti-inflammatory; stimulates granulation, promotes healing in difficult healing wounds and ulcers; fistulae, hemorrhoids, mastitis, intertrigo, aphthous stomatitis, conditions of restlessness and excitation, disorders of dentition, otitis media, glandular swellings	150 mg	0.024 mg	0.0022 μL
Echinacea angustifolia (narrow-leaved cone flower)	Increase in the mesenchymal defences; inflammation of all kinds and locations; septic processes; hyaluronidase inhibiting, anti-inflammatory action	150 mg	0.06 mg	0.0055 μL
Echinacea purpurea (purple cone flower)	Increase in the mesenchymal defences; inflammation of all kinds and locations; septic processes; hyaluronidase inhibiting, anti-inflammatory action	150 mg	0.06 mg	0.0055 μL
Hamamelis virginiana (witch hazel)	Venous stasis, varicose veins, (thrombo-) phlebitis, crural ulcers, hemorrhoids, venous hemorrhages, anti-inflammatory, analgesic	450 mg	0.15 mg	0.022 μL
Calcium sulphide (otherwise: Hepar sulfuris)	Tendency to suppuration, especially on the skin and lymph glands (furuncles, pyodermia, panaris, phlemons), tonsillar abscesses, chalazions, hordeolums, hemicrania, urinary disorders, hypersensitivity to cold and draughts	0.000025 mg	0.0000003 mg	0.0000022 μL
Hypericum perforatum (St John's wort)	Neural and cerebral injuries, eg, commotio cerebri neural pains upon or after injuries hemostatic	0.00009 mg	0.03 mg	0.0066 μL
Mercurico-amidonitrate (otherwise: *Mercurius solubilis Hahnemanni*)	Suppurations, abscesses, gingivitis, stomatitis, nasopharngeal catarrh, catarrh of the sinuses, cholangitis, shrinking action on edematous conditions	0.00004 mg	0.0000003 mg	0.0000011 μL
Symphytum officinale (comfrey)	To accelerate callus formation in fractures periostitis, causalgia, disorders arising from amputation stumps contusions	0.01 mg	0.00000024 mg	0.0000022 μL
Excipients	–	Cetostearyl alcohol, paraffin, 13.8% alcohol	6 mg lactose, 1.5 mg Mg-stearate	0.9% saline solution

Notes: In some countries the number of ingredients and their concentration may vary slightly. [a]Characteristics with reference to: Reckeweg H-H. *Materia Medica – homoeopathia antihomotoxica*. 4th edition. Baden-Baden. Germany: Aurelia Verlag 2007.

Mechanism of anti-inflammatory action

The anti-inflammatory effect of Traumeel results from the activity of the various components on the different phases of the inflammatory response. For example, *Aconitum napellus*, *Matricaria recutita*, *Hamamelis virginiana*, and *Hypericum* may reduce pain associated with inflammation; *Mercurius solubilis* may be anti-inflammatory; while *Arnica montana, Calendula officinalis*, *Echinacea,* and *Symphytum* may accelerate wound healing.[43] Study of single components of Traumeel has shown that *Arnica montana, Hamamelis virginiana, Achillea millefolium, Aconitum napellus, Atropa belladonna*, and *Mercurius solubilus* exert a considerable inhibitory effect on edema, while other components have a pro-inflammatory effect (*Calendula officinalis, Echinacea purpurea, Matricaria recutita*); yet others are reported not to influence the development of edema (*Symphytum, Hypericum, Hepar sulfuris*).[43] However, the effect of Traumeel was found to be greater than the 'sum' of the active components, suggesting a synergistic interaction between all components of the preparation have a bearing on the final effect.[43]

Despite its long history of use as an anti-inflammatory agent, little was known until relatively recently regarding Traumeel's effects on immune cell function. Preclinical evidence is provided by an in vitro study investigating the effects of Traumeel on human T-cells, monocytes, and gut epithelial cells in terms of their ability to secrete pro-inflammatory mediators interleukin-1beta (IL-1β), tumor necrosis factor alpha (TNFα), and interleukin-8 (IL-8).[44] Traumeel was found to modulate the secretion of these mediators, inhibiting secretion in resting and activated cells by up to 54%–70% ($P < 0.01$ for all cells). These findings suggest that Traumeel acts on cells of the 'mobile' arm of the immune system (blood-borne leukocytes) and also on the first line of defense of the 'nonmobile' gut-associated immune system (gut epithelial cells).

Other preclinical evidence suggest that Traumeel reduces microvascular leakiness to albumin in the mesenteric microcirculation and subsequent mast cell degranulation in rats exposed to daily 15-min episodes of 90-dB SPL noise for 3–5 weeks.[45] Compared to controls, the number and area of leaks per venule in the rats that received Traumeel were significantly smaller and mast cell degranulation was significantly lower than those in rats exposed to noise only. This result is consistent with the in vitro study showing that Traumeel inhibited secretion of pro-inflammatory mediators from immune cells such as monocytes and T cells,[44] and it is suggested that Traumeel may act by stabilizing immune cells.

There is evidence to suggest that Traumeel does not act in the same way as NSAIDs.[46] While reducing acute local inflammation (first phase of adjunct arthritis) in vivo, the preparation did not affect granulocyte function (eg, superoxide anion production and adhesion) or human platelet adhesion in vitro, indicating that the normal defensive and homeostatic functions of these cells are preserved. Traumeel appears to act by regulating the orchestration of the overall process of acute local inflammation rather than by interacting with a specific cell type or biochemical mechanism. Further studies concluded that Traumeel also seems to act by speeding up the healing process instead of blocking edema development from the start.[43]

Additionally, Traumeel may play a role in situations where regulatory lymphocytes actively help control inflammatory reactions by producing the messenger, transforming growth factor beta (TGF-β).[47] Low potencies of plant extracts (including *Bellis perennis* and *Atropa belladonna*) used in Traumeel have demonstrated stimulatory effects on lymphocyte synthesis of the inhibitory cytokine TGF-β in whole blood cultures. Through TGF-β synthesis, other pro-inflammatory T-lymphocytes (via, for example, TNFα and IL-1) are prevented from supporting the inflammatory process. This action has been supported by results in vivo.[48]

The nuclear factor-κB (NF-κB) family of transcription factors has a crucial role in the expression of genes that control the inflammatory response.[49] In acute inflammation, NF-κB is activated rapidly in response to a wide range of stimuli (including pro-inflammatory cytokines, particularly TNF and IL-1) and increases the expression of several pro-inflammatory cytokines and chemokines. Traumeel, therefore, indirectly inhibits the activation of NF-κB by its effects on pro-inflammatory cytokines. There is evidence that it may also directly inhibit helenalin, an anti-inflammatory sesquiterpene lactone found in the asteracea plant family (which includes *Arnica montana* and *Bellis perennis*, components of Traumeel) and has been shown to selectively inhibit NF-κB.[50]

The concept of 'U'- or 'J'-shaped dose-response curves (the dose-response hypothesis of which is also referred to as hormesis) is well established.[51] The pharmacokinetic response of Traumeel, which comprises low concentrations of each component, is biphasic – high dilutions have no effect, but an effect is seen within a certain range of low concentrations, after which higher doses have the opposite effect. Between dilutions of 10^{-1} to 10^{-7}, Traumeel has a selective inhibitory effect on the pro-inflammatory mediators, IL-1β, TNFα, and IL-8.[44]

Evidence of effect – randomized controlled clinical trials (RCT)

There are several studies reported in the literature on the use of Traumeel for traumatic injuries (Table 3). A PubMed search was carried out to identify trials on Traumeel use in adults (full publications, in English or with English translation), associated with sports injuries, musculoskeletal traumatic injuries, and injuries accompanied by inflammation. Studies in pediatrics, inflammatory disorders, such as stomatitis and asthma, and use in surgery and dentistry, were excluded. The manufacturer was also contacted to ensure all relevant fully published studies were included. The studies of Traumeel use in adults identified with traumatic injuries are reviewed below.

In general, the studies required treatment to be within a few days of injury. They excluded patients already undergoing treatment for the injury (including medications), and patients with multiple injuries, previous injury of the same joint, degenerative joints, fractures, and open wounds. Additionally, treatment groups in terms of patient population and injury characteristics were generally comparable at baseline.

High quality research on therapies other than those considered to be conventional is considered to be lacking.[52] The effectiveness and tolerability of Traumeel for acute musculoskeletal injuries has been evaluated in four RCTs. The first was a placebo-controlled, double-blind study in 73 patients (69 evaluated) with ankle sprains incurred during sports activities.[53] Patients were treated with Traumeel ointment (n = 33) or placebo (n = 36) seven times within a 2-week period. Compression bandages were applied over the ointment, and electrotherapy was also administered as basic therapy. Ankle mobility (joint angulation), which would occur naturally over time, had improved after 10 days of treatment in both treatment groups, but improvement was faster and more frequent with Traumeel than with placebo (Fischer's Exact Test; $P = 0.03$). Additionally, significantly more patients in the Traumeel group reported no pain with movement on Day 10 (28 versus 13 patients; Fischer's Exact Test $P \leq 0.0001$, $P \leq 0.0003$ with Bonferroni adjusted).

Traumeel ointment has also been evaluated in a placebo-controlled, double-blind study in 68 outpatients with a range of musculoskeletal sports injuries.[54] An occlusive dressing and cold compresses were applied for half an hour after application. After 15 days of twice-daily treatment, the reduction in swelling ($P = 0.0214$), as measured by joint circumference, and pain ($P = 0.0005$), assessed by a pain index score, was significantly greater in patients using Traumeel than in those receiving placebo. These findings were clinically highly significant. There was no statistical difference in skin temperature between the two groups. Both patients and physicians rated the overall effectiveness of Traumeel superior to placebo ($P \leq 0.001$).

Use of Traumeel injection solution for the treatment of traumatic hemarthrosis of the knee was studied in a placebo-controlled double-blind trial in 73 outpatients.[55] Three 2 mL intra-articular injections (and, where necessary, subsequent puncture of the joint to enable escape of fluid) were given over a period of 8 days. A support dressing was applied, and cold compresses were permitted. After a single injection, 13.5% of patients treated with Traumeel required further punctures compared with 25% of the placebo group. The punctuate was still bloody on Day 8 for 5.4% and 19.4% of patients in the Traumeel and placebo groups, respectively. Therapeutic success – improvement in the degree of joint movement between the healthy knee and injured (treated) knee of 0 to 10 degrees, plus an improvement in the difference in circumference of the joints of 0.5 cm maximum – was reported for 64.9% of the Traumeel group and 36.1% of the placebo group on Day 8; with mean differences in mobility reducing from 48.4° to 8.3° and from 41.4° to 18.2°, respectively, and with mean differences in joint circumference reducing from 2.02 to 0.54 and from 2.18 to 1.06 cm, respectively, on Day 8. Reductions in pain over time were greater in the Traumeel group than in the group receiving placebo, with 89.2% and 63.9% of patients reporting no pain after 8 days, respectively.

Nonrandomized observational studies and surveillance studies

While the randomized clinical trial is considered the "gold standard" for evaluating clinical therapies, patients enrolled into such trials (which exclude patients not meeting certain predefined criteria) may not be representative of the broad range of individuals treated in clinical practice.[56] As such, the addition of observational, nonrandomized studies is considered to be complementary to these trials,[57] particularly with regards to tolerability data. Their limitations (possible selection and evaluation bias) and advantages (more closely related to clinical practice) are well recognized; however, it is also reasonable to assume that physicians would like to see the best results for their patients regardless of treatment.

Traumeel has been compared with conventional therapy in multicenter, observational, nonrandomized studies where

Table 3 Clinical trials on Traumeel in acute musculoskeletal injury

Study design	Indication	Number of patients[a]	Therapies	Main outcomes
Randomized, double-blind trials				
Zell et al,[53] Single center study in Germany 2-weeks duration	Ankle sprains	N = 73 n = 69	Traumeel ointment vs placebo ointment	More rapid and more frequent improvement in upper-ankle mobility in the Traumeel group vs placebo at 2 weeks.
Böhmer and Ambrus,[54] Single center study in Germany 15-days duration	Varied musculoskeletal sport injuries	N = 68 n = 68	Traumeel ointment vs placebo ointment	Reduction in swelling and pain significantly greater in patients using Traumeel vs placebo after 15 days. No difference between the groups in skin temperature. Overall effectiveness of Traumeel was superior to placebo. Traumeel was well tolerated with all patients rating the treatment as "good" or "very good".
Thiel and Borho,[55] Single center study in Germany 8-days duration	Post traumatic hemarthrosis of the knee	N = 80 n = 73	Traumeel injections vs physiological saline injections	Greater degree of movement and greater reductions in pain and swelling with Traumeel vs saline after 3 injections over 8 days. No treatment-related adverse events.
Observational studies				
Birnesser et al,[58] Multicenter study in Germany; nonrandomized 2-week duration	Epicondylitis	N = 184 n = 163	Traumeel injections vs unspecified NSAID (mainly diclofenac)	Noninferior effects of Traumeel on three pain relief and two joint mobility variables. Global outcome rated as "good" and "very good" by 71% of Traumeel patients and 44% of NSAID patients. Tolerability assessed as "very good" by 88% of Traumeel patients and 45% NSAIDs patients.
Schneider et al,[9] Multicenter study in Germany; nonrandomized 28-days duration	Tendinopathy of varying etiology (based on excessive tendon load rather than inflammation)	N = 457 n = 357	Traumeel ointment vs diclofenac 1% gel	Traumeel noninferior to diclofenac on all pain and mobility variables after 28 days. In the Traumeel and diclofenac groups, respectively, the mean (±standard deviation) reduction in summary score for pain-related variables was 5.3 ± 2.7 and 5.0 ± 2.7 units, and for mobility-related variables was 4.2 ± 3.8 and 3.7 ± 3.4 units. Global evaluation of therapies rated as "very good" or "good" by 88% of Traumeel cases and 82% of diclofenac cases.
Schneider et al,[62] Multicenter study in Germany; prospective; nonrandomized Up to 3 months duration	Various musculoskeletal injuries	N = 133 n = 132	Traumeel (tablets and gel) vs conventional management	Rates of complete symptomatic resolution at the end of therapy were similar between treatment groups, occurring in 59.4% of Traumeel-treated patients and 57.8% of the conventionally treated group. No adverse events reported in the Traumeel group vs six (6.3%) mild-moderate events in the conventional group. Physician-rated tolerability was "very good" for 90% of Traumeel cases vs 50% of conventional cases ($P = 001$).
Surveillance studies				
Zenner and Weiser,[61] Multicenter study in Germany, Italy, and Portugal; prospective; randomized; standardized questionnaires	Variety of injuries (eg, sprains, post-traumatic edema), and degenerative and inflammatory conditions (arthrosis, and epicondylitis)	N = 1359	Traumeel tablet or drop forms (69% tablets, 29% drops, 2% both). One-third of patients were treated without other therapies (drug and nondrug)	Symptom improvement occurred in about half of all patients within the first week of treatment and an additional 34% of patients within 1 to 3 weeks. Treatment rated as "very good" or "good" by 83% of cases.

(*Continued*)

Table 3 (*Continued*)

Study design	Indication	Number of patients[a]	Therapies	Main outcomes
Zenner and Metelmann,[59] Multicenter, drug monitoring trial	Variety of injuries, and degenerative and inflammatory conditions	N = 3241	Traumeel injection. Used exclusively by 17% of patients; adjuvant medications taken by 47% of patients; 65% received nonmedication therapies	Used most frequently in arthrosis (19%), particularly in inflammation of the knee and degenerative joint diseases, myogelosis (12%), sprains (12%), periarthropathia humeroscapularis (10%), epicodylitis (10%), and tendinovaginitis (8%). Traumeel, used exclusively, was highest for sprains (27%). Outcomes of Traumeel therapy was assessed as "very good" or "good" by 79% of patients.
Zenner and Metelmann,[60] Multicenter, drug monitoring trial	Variety of injuries, and degenerative and inflammatory conditions	N = 3422	Traumeel ointment. Used exclusively by 38% of patients; adjuvant medications taken by 30% of patients; 52% received nonmedication therapies	Used most frequently for sprains (21%), hematomas (8%), myogelosis (8%), contusion (8%), tenosynovitis (8%), and arthrosis (9%). Traumeel was used exclusively by half or more of patients with hematomas, contusions and sprains. Outcomes of Traumeel therapy was assessed as "very good" or "good" by 87% of patients.

Notes: [a]N = recruited patient population, n = efficacy population.
Abbreviations: NSAID, nonsteroidal anti-inflammatory drugs.

treatment groups were comparable at baseline (Table 3). Traumeel has demonstrated noninferiority to NSAIDs (unspecified; 52%, diclofenac) in patients with diagnosed epicondylitis[58] and to diclofenac, specifically, in patients with tendinopathy[9] on all pain relief (eg, pain at rest, local pressure pain, pain with movements, and at muscle load and contraction) and joint mobility (eg, extensional and torsional joint mobility) variables.

Multicenter drug surveillance studies have indicated that Traumeel is frequently used for a variety of injuries, including bruises, sprains, hematomas, and post-traumatic edema, as well as degenerative and inflammatory conditions, such as arthrosis, frozen shoulder, carpal tunnel syndrome, and epicondylitis.[59–61] Assessed in 3241 cases, Traumeel injection solution was used most frequently in arthrosis (19%), particularly in inflammation of the knee and degenerative joint diseases, and also for myogelosis (12%), sprains (12%), periarthropathia humeroscapularis (10%), epicodylitis (10%), and tendinovaginitis (8%).[59] Traumeel injection was used as monotherapy by 19% of patients; the percentage of these patients was highest for sprains (27%). Of 3422 patients using Traumeel ointment, this was most frequently applied for sprains (21%), followed by hematomas (8%), myogelosis (8%), contusion (8%), tenosynovitis (8%), and arthrosis (9%).[60] Traumeel ointment was used as monotherapy by 38% of patients; it was applied as monotherapy in about half or more of patients with hematomas, contusions, and sprains. The effectiveness and tolerability of Traumeel is generally reported to be "very good" or "good".

Tolerability

Traumeel is reported to be well tolerated and without treatment-related adverse effects.[9,54,55,58–62] There are no reports of disease exacerbation or drug interactions, making Traumeel an interesting option for people (particularly the elderly) who have other medical condition(s) and are taking other medication(s).

Out of the treatment populations of the two aforementioned multicenter drug monitoring trials (n = 6913), there were only 32 (0.5%) reports of adverse reactions when using Traumeel.[59,60] These mainly involved mild, transient, local skin reactions (redness, pruritus, heat; interpreted as allergic reactions), which could not clearly be assigned to Traumeel as other therapies were also used. Tolerability was rated as "very good" in twice as many patients using Traumeel compared with conventionally-treated patients when assessed by patients[58] and physicians.[62]

The clinical safety of Traumeel tablets taken daily for 4 weeks was evaluated in 20 healthy individuals in a four-week study.[63] There were no significant differences in vital signs or laboratory data (hematology, blood biochemistry, occult blood in stool) at baseline and at study term. Adverse events were reported by about half of the subjects (n = 11) who reported a total of 36 events. Common ones included headache (15 events), diarrhoea/stomach discomfort/bloating (6 events), feelings of nausea, and perceptions of "feeling buzzed" (2 events). All adverse events were mild or moderate in severity, and resolved with continued use of Traumeel, and none was considered probably/definitely related to this therapy.

Conclusion

There is a growing evidence-base supporting the effectiveness of Traumeel, alone and in combination with other medicines and/or nonmedicine therapies, in treating acute musculoskeletal injuries. Traumeel appears to be well tolerated, with no signs of severe adverse events and no evidence of gastrointestinal bleeding.[63] NSAIDs may cause gastrointestinal ulceration and bleeding, and are a particular risk for patients with diseases, on co-medications, or who are elderly. A recent consensus by international experts on "muscle strains" concluded against automatic prescription of a NSAID for all muscle strains, as they may predispose to recurrences by masking pain.[64] However, they also agreed that controlling inflammation may be beneficial to minimize early damage and subsequent loss of function.[64] Traumeel may thus provide an alternative anti-inflammatory and analgesic agent for these patients.

There is also growing insight into the mechanisms of action of this therapy on immune cell function. However, research behind CAM therapies is indisputably lacking, with RCTs reported to comprise only about 10% of published original articles in sport and exercise medicine.[65] The level of scientific evidence supporting use of Traumeel is considered still to be low due to the lack of clinical trials. However, there is no more justification than expert opinion for the use of the vast majority of other practices for musculoskeletal injuries, including ice and compression.[64] Regardless, further double-blinded randomized trials are required to increase Traumeel's general acceptance as an emerging option to NSAIDs and other conventional drugs.

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