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Challenges of pain masking in the management of soft tissue disorders: optimizing patient outcomes with a multi-targeted approach

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Abstract

Current approaches to managing soft tissue injuries often rely upon the use of non-steroidal anti-inflammatory drugs (NSAIDs). The use of NSAIDs in this manner is contentious, and some believe that the risks of using NSAIDs can outweigh any potential benefit. In this article the issues of toxicity, pain masking and return to full activity are reviewed, and an alternative strategy for the management of inflammation in soft tissue injuries is proposed. We consider that a multi-targeted approach has the potential to improve healing, reduce additional injury from premature return to full activity as a consequence of pain masking, and improve prognosis for many patients with soft tissue injuries.

Introduction

Soft tissue disorders are a common source of musculoskeletal pain, and chronicity and recurrence are common. While the precise incidence and prevalence of soft tissue disorders is difficult to establish, they are known to be the most common rheumatic causes of sickness absences from work[1]. Overuse injuries, also known as cumulative microtrauma, constitute 50–60% of all sports injuries[2,3]. Also repetitive strain injuries arise frequently in adults of working age[4].

Soft tissue disorders can be particularly challenging to manage. Conditions may be complicated by comorbidities, medications may be contraindicated; there may be drug interactions, age restrictions or side effects that restrict their use. Alternatively, patients may simply prefer not to use some medications for their own reasons, or they may be ineffective in some patients.

The cardinal symptom of a soft tissue disorder is pain, which can arise from many sources[1]. However, use of conventional analgesics can also lead to 'pain masking' whereby important pain signals are masked leading to a premature return to full activity levels, increasing the chances of re-injury. Furthermore, overuse injuries can be worsened if demands on tissues are not reduced to allow sufficient time for tissue to heal[5].

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in treating soft tissue disorders has been challenged; however, it is premature to suppose that the anti-inflammatory properties of NSAIDs are not useful to the treating physician[6]. While simple analgesics can be used to treat pain, excessive inflammation can also be detrimental to the healing of injuries, and should also be addressed. It is, therefore, apparent that alternative treatment strategies should be explored.

Excessive inflammation is painful, limits functional restoration, causes fibrosis, can cause joint or soft tissue destruction and can perpetuate the disease

process. There are many effective approaches to treating inflammation; however, many are associated with risks, and it is the risks that present the greatest challenge to management. The anti-inflammatory approach associated with the lowest risk is ICE (ice, compression, elevation), which should be utilized immediately after injury. Topical anti-inflammatories provide the next lowest level of risk. Depending upon the site of injury, oral NSAIDs (with or without proton-pump inhibitor [PPI] for gastroprotection), colchicine or corticosteroid injections may be utilized if considered clinically necessary. In unresponsive cases, oral steroids may be considered, although the level of risk associated with this approach needs to be carefully evaluated.

NSAIDs

NSAIDs are a mainstay of treatment of pain associated with many medical conditions, including musculoskeletal soft-tissue injuries. While oral NSAIDs are effective in relieving pain and reducing inflammation, their usefulness is limited in many patients by a high incidence of adverse events[7–10]. Notably, high systemic drug concentrations after oral NSAID therapy may result in potentially serious adverse events such as gastrointestinal ulceration or bleeding[11], hypertension and cardiovascular events[12], acute renal impairment[13] and hepatotoxicity[14,15].

NSAIDs, in general, inhibit the inflammatory response by inhibiting the enzyme cyclo-oxygenase (COX), thus decreasing prostaglandin production[7,16]. COX-2 is highly expressed in inflamed tissue, while COX-1 is expressed constitutively in various tissues[7,10,15]. It is inhibition of COX-1 that is thought to be responsible for most of the adverse events observed with NSAIDs. Therefore, as the beneficial actions of NSAIDs are thought to be provided by action on local tissues, which is not dependent on systemic absorption, topical application has the potential to provide effective local analgesia while minimizing the potential for adverse events[17].

In a pharmacokinetic study comparing the systemic exposure resulting from application of diclofenac sodium 1% gel (total dose applied to knee 16 g/day) and oral diclofenac (50 mg three times daily) in healthy human volunteers, mean plasma concentrations of diclofenac were approximately 17 times lower with topical administration compared with oral treatment. Furthermore, peak concentrations were approximately 150-fold lower[15,18]. It should, however, be noted that the effectiveness of topical formulations varies between patients, different NSAIDs, different formulations, and the site of application[15]. Importantly, percutaneous absorption may be strongly influenced by individual skin properties[19].

Thus, topical formulations can deliver effective analgesic concentrations at the site of inflammation while minimizing systemic concentrations. Lower systemic concentrations after topical administration should also lower the risk of drug–drug interactions. It has also been suggested that topical formulations can improve adherence to therapy due to the combination of improved tolerability and convenient dosing regimen[15,19].

Topical NSAIDs are often used for short-term pain relief in patients with acute soft tissue injuries, and there is good evidence to support their use[15,20]. The most widely studied topical NSAID is diclofenac (both gel and patches). Studies consistently report that topical diclofenac, compared with placebo, significantly reduces pain within 2–3 days of treatment. The tolerability profile of topical diclofenac has also been shown to be similar to that of placebo: the most common adverse events are mild application site reactions, such as erythema or pruritus. Importantly, no severe systemic gastrointestinal adverse events have been observed during studies with topical diclofenac[20].

While topical NSAIDs provide lesser risks to patients in terms of adverse events, oral NSAIDs are thought to be more effective, particularly when action in synovial fluid is required. Animal studies suggest that the application of diclofenac sodium gel allows penetration of diclofenac to a depth of 3–4 mm below the skin[21]. These support data suggest that diclofenac sodium gel has minimal penetration into the synovial fluid from topical delivery[15]. A study of patients with bilateral knee joint effusions compared diclofenac concentrations in the knee with diclofenac gel applied topically and the other knee, which was treated with a placebo gel preparation. Free unbound diclofenac concentrations in the synovial fluid were found to be similar in diclofenac- and placebo-treated knees, and not significantly different from plasma concentrations, leading to a conclusion that transport of diclofenac was primarily via the plasma, and not via direct transport or diffusion into the knee joint[22]. When diclofenac is administered orally, however, the short plasma half-life of diclofenac and the slow diffusion in and out of synovial fluid eventually result in higher concentrations in the synovial fluid and tissue, versus plasma[17,23].

The potential greater efficacy of oral preparations has to be balanced with the increase in risk to the patient of serious adverse events. At the end of the last century, NSAID toxicity was recognized as a significant cause of death with over 16,500 deaths attributed in the USA in 1997 (only slightly fewer than AIDS, but more than multiple myeloma, asthma, cervical cancer and Hodgkin's disease)[24]. These data were gathered before the recognition of the extent of increase in cardiovascular risk generated by NSAID use, which became well known following the introduction of the 'coxibs'.

A recent meta-analysis of individual participant data from randomized trials found that the vascular risks of high-dose diclofenac, and possibly ibuprofen, are

comparable to coxibs[7]. Indeed, the incidence of major vascular events (non-fatal myocardial infarction, non-fatal stroke or vascular death) was increased by a third by use of diclofenac versus placebo, chiefly due to an increase in major coronary events (non-fatal myocardial infarction or coronary death). The risk of a major coronary event is increased by the use of ibuprofen; however, the risk of a major vascular event is not increased versus placebo. Naproxen does not appear to significantly impact the risk of major vascular events; however, the risk of heart failure is roughly doubled by the use of any NSAID.

Another recent network meta-analysis also found naproxen to be the least harmful in terms of cardiovascular risk[8]. Coxibs were found to be associated with the highest risk of myocardial infarction, while ibuprofen and diclofenac were associated with the highest risk of stroke. Diclofenac was also associated with a high risk of cardiovascular death. The authors conclude that no NSAID can be considered safe in cardiovascular terms and that cardiovascular risk should always be considered when prescribing any NSAID. Similar findings on cardiovascular risk have also been found in community-based studies[25].

There is also variation in the associated risks of upper gastrointestinal complications (ulcer perforations, obstructions and bleeding) associated with the use of individual NSAIDs. A meta-analysis of published observational studies suggests that the relative risk of upper gastrointestinal complications is 1.8 with ibuprofen, 3.3 with diclofenac, 3.9 with ketoprofen and 4.1 with naproxen[9]. It can, therefore, be seen that, while naproxen may be associated with lower risk for cardiovascular events, the risk of gastrointestinal complications is higher. Balancing these potential risks in the individual is challenging, but essential to good management.

Returning to normal activities

The goal of management of soft tissue disorders is to return patients to normal activity levels. Following from that goal is the sustainability of treatment success. Ideally, the patient should not suffer any sequelae, or flares of their condition. However, for many reasons, including, but not limited to, poor initial management of the injury, failure to appropriately resolve inflammation, poor patient adherence to the treatment regimen (particularly rehabilitation exercises) and returning to full activity too rapidly, acute flares of injuries are not uncommon.

While the outcome of inflammation is to replace or repair injured tissues with healthy, regenerated tissue, continuous activity with injured and inflamed tissue can result in a vicious cycle of injury, chronic or systemic inflammation, fibrosis, and tissue breakdown[26,27]. Repetitive activities resulting in overuse injury may potentially cause pathology along the route of tissue injury, tissue reorganization and central nervous system reorganization. Pathomechanical complexity may contribute to an end point of pain, loss of function, sickness behaviors, depression, and/or anxiety[26]. If an activity is low enough to avoid tissue injury, then inflammation is avoided and tissue reorganization moves into a beneficial adaptive remodeling. There is suggestion of a threshold of activity below which the tissue response (with or without inflammation) leads to adaptive rather than degenerative long-term tissue changes[26].

The first principles of management are that most acute flares of musculoskeletal conditions have a significant inflammatory component, and a proactive approach is vital for best outcomes. Furthermore, more than one pathology can be present, so it is important to consider the differential diagnosis to ensure the right condition is being treated. Identifying the cause of the flare is also important to ensure that it is managed appropriately and can be prevented from occurring again in the future.

Acute flares should always be considered as an opportunity to optimize longer-term management, to intervene and educate the patient. Rehabilitation should be reviewed, ensuring that the patient is not overloading, as that could be pro-inflammatory. In cases of overloading, the patient should undertake relative rest, and mechanics and weight should be reviewed. If excessive inflammation is present then that should be addressed.

Pain masking

Pain masking is another potential problem that can hinder the long-term recovery from injury. High rates of musculoskeletal injury recurrence are observed in many sports and thought to be due to premature return to full activity[28]. Furthermore, there are concerns that NSAIDs could, in fact, be detrimental to the long-term healing of some injuries, and, thus it could be hard to justify their use in order to facilitate a faster return to activity[29]. While pain masking is not often discussed in the literature, it is a real and known problem within clinical practice[30].

There is universal agreement that previous injury is a risk factor for recurrent muscle injury. Furthermore, a recent history of strain of one muscle group confers an increased risk of injury to surrounding muscle groups. This could be due to compensation by surrounding muscles to protect the injured or weakened muscle group[31].

While returning to activity is vital to the recovery of an injury, doing so too soon has the potential to worsen an injury or delay recovery. Immediately after injury, RICE (rest, ice, compression and elevation) should be used to minimize pain, swelling, inflammation and hemorrhage, offering the best possible conditions for the healing process. The damaged tissue area should also be protected and immobilized to prevent additional bleeding to the

injury site, secondary injuries, and early distension and lengthening of injured structures. Mobilization of the damaged tissue too early and intensively may result in re-ruptures and weaker tissue than that produced during an optimal period of immobilization. This can affect the long-term outcomes, with weaker tissue formation leading to an increased risk of future re-injury[32].

It is often advised that analgesics are used to reduce pain in order to facilitate rehabilitation. However, overuse of analgesics could mask pain allowing the patients to 'push things too far' and worsen the existing injury, or even create *de novo* injury. The ideal is to manage pain such that rehabilitation can proceed, but not to eliminate pain, as pain is an indicator that activity should be reduced. The golden rule is summarized in the acronym REST – Resume Exercise below Soreness Threshold.

It is clear that the patient's return to full activity requires careful management. Achieving the right balance between allowing sufficient activity to promote healing with strong tissue growth, while not allowing the patient to overload, potentially leading to weaker healed tissue that is more prone to re-injury, or conversely, not allowing long periods of inactivity which can also hinder healing, is particularly challenging. It is important that the patient is informed of the potential long-term risks of trying to return to full activity too early, as well as the risks of using analgesics to mask pain in order to facilitate this. Pain masking and associated flares or re-injury can obviously set back recovery and prevent the patient achieving the long-term goal of returning to sustained full activity.

Pain management: a multi-targeted approach

Inflammation is a good example of a physiological process that involves different networks with its complex cascade of molecular machineries. Multi-component medications with multi-target ingredients provide a logical choice to treat complex networks. Traumeel* (Tr14) provides such a multi-component, multi-target approach to the treatment of inflammation. Tr14 is a combination formula of 12 botanical and two mineral substances.

Tr14 acts differently to NSAIDs, its anti-inflammatory effect results from the synergistic interaction between its components on the different phases of the inflammatory response[33]. The mechanism of action of Tr14 does not appear to be the result of COX or lipoxygenase enzyme inhibition, as is the case with NSAIDs. In the rat model of blood-induced inflammation, Tr14 significantly reduced hind-paw induced edema and decreased IL-6 production. The authors suggested that Tr14 seems to act by speeding up the healing process instead of blocking the development of edema from the beginning[34]. Tr14 has been proven to be effective, with fewer side effects and with similar or better tolerability than NSAIDs, with no known drug interactions, and no restriction with regards to patient's age and comorbidities. Additional basic research is currently underway to further elucidate Tr14's mechanism of action.

*Traumeel is a registered trade name of Biologische Heilmittel Heel GmbH, Baden-Baden, Germany

Evidence for the use of Tr14

Tr14 has been investigated in five randomized controlled trials: three in comparison with placebo, one in comparison with placebo and diclofenac, and one in comparison with diclofenac[35–39].

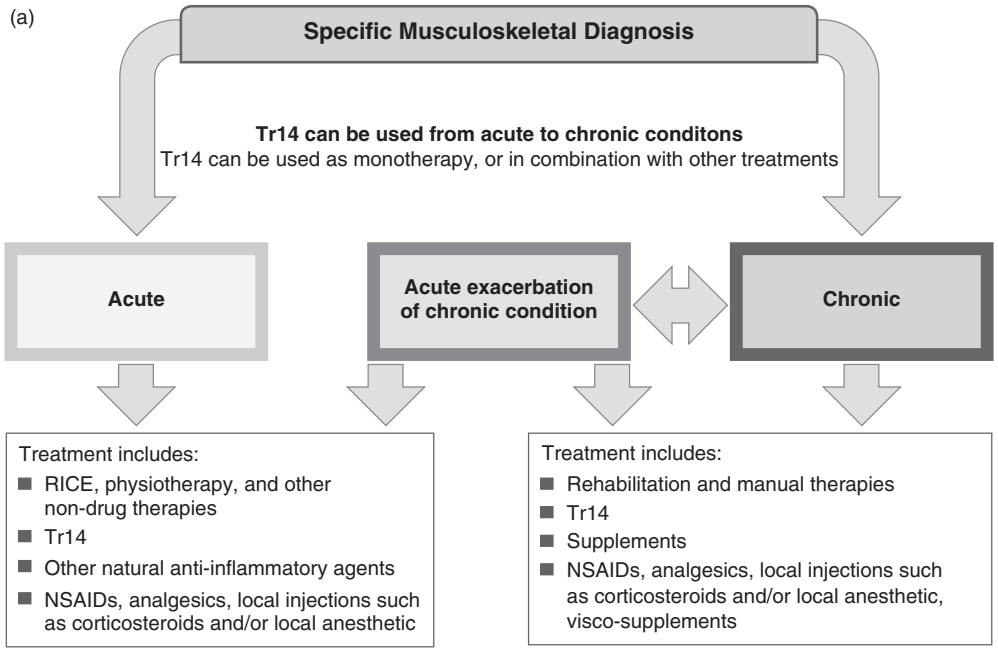
The first randomized-controlled study that was performed investigated the use of Tr14 in activity-related ankle sprains. Patients were randomized to receive either 10–12 g Tr14 ointment ($n = 33$) or placebo ($n = 36$) administered in a double-blind fashion by applying a compression ointment bandage on days 1, 3, 5, 8, 10, 12 and 15 as necessary until symptoms had resolved. By day 10 there was significant improvement between Tr14-treated patients and placebo-treated patients in the difference in total angulation of the joint between affected and non-affected joints ($p = 0.015$). The proportion of patients with no pain upon movement was also significantly greater in the Tr14 group by day 10 compared with the placebo group ($p \leq 0.0003$). Indeed, it was found that the probability of successful treatment was significantly greater with Tr14 than placebo ($p = 0.03$)[35].

Another double-blind study investigated the use of Tr14 ointment for acute musculoskeletal injuries. Treatment with Tr14 was assessed by physicians as either 'good' or 'very good' in a much greater proportion of patients than placebo (74% versus 35%), although it probably should be noted that a greater proportion of patients randomized to Tr14 (20/34, 58.8%) had contusions than those randomized to placebo (11/34, 32.4%) with the remainder of patients suffering sprains. In no case was treatment with Tr14 rated by physicians as 'poor' compared with 35% of cases treated with placebo. There was also greater improvement in swelling, maximum muscle force and pain with Tr14 versus placebo. No adverse effects were reported with either placebo or Tr14[36].

Tr14 was found to produce fast regression of the blood effusion in an assessment of Tr14 injection ($n = 37$) versus physiological saline solution ($n = 36$) for the treatment of hemarthrosis of the knee. After a single injection, only 13.5% of Tr14 patients required further punctures compared with 25% of those receiving placebo. In addition, there were greater improvements in degree of movement, swelling and pain reduction observed with Tr14 compared

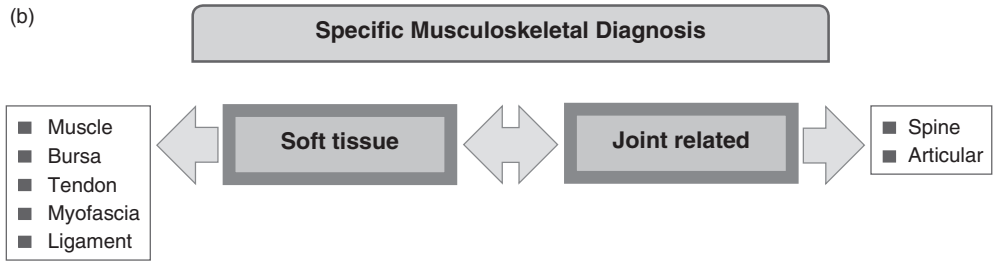
with placebo, such that by day 36, 95% of Tr14 patients questioned had resumed normal activities compared with only 58% of placebo patients. No adverse effects were reported with either placebo or Tr14[37].

The first randomized, active-controlled study was conducted in elite athletes with various tendinopathies and compared Tr14 ointment ($n = 89$) with both topical diclofenac ($n = 87$) and placebo ($n = 76$). The topical preparation was applied four times daily for at least 21 days by all participants. Treatment with Tr14 was associated with a significantly greater reduction in pain ($p = 0.001$) and percentage reduction in the echographic assessment of the



Developed by: Luc Vanden Bossche, Belgium; Andrey Garkavi, Russia; Charles Kahn, USA; Cathy Speed, UK; Carlos González de Vega, Spain; Bernd Wolfarth, Germany.

RICE; rest, ice, compression, elevation. NSAIDs; non-steroidal anti-inflammatory drugs. Tr14; Traumeel.



	Frequency[1]	Duration[2]
Tr14 Injection*	1 – 3 times per week	2 – 12 weeks
Tr14 Tablets	3 x 1 tablet daily Acute; up to 12 tablets per day	Up to 3 months
Tr14 Topical	2 – 4 times daily	Up to 3 months

*Intra-articular,[3] peri-articular, intra-lesional, peri-lesional

1. The regimens should be tailored to individual requirements
2. Treatment may be continued long term following review and evaluation of the treatment plan
3. Intra-articular injection should not be given more than once per week

There is a contraindication for known hypersensitivity to one or more of Tr14's ingredients.
Tr14 has no known negative interactions with other medications based on pharmacovigilance.
Tr14; Traumeel

Figure 1. Treatment algorithm for musculoskeletal disorders (Tr14). (a) Tr14 in the treatment paradigm. (b) How to treat specific indications with Tr14. ©Aspen Medical Media 2014. Updated from Wolfarth and González de Vega. Curr Med Res Opin 2013;29(Suppl 2):15-19[40].

peritendinous diameter and edema ($p = 0.001$) than both placebo and diclofenac. It is of particular importance that the mean number of days until return to activity was significantly fewer in Tr14-treated patients than either diclofenac- or placebo-treated patients ($p = 0.001$): return to activity was 4.3 days sooner than with diclofenac and 10.3 days sooner than with placebo. Four patients dropped out, these were all in the diclofenac group due to allergic skin reactions[38].

The recent Traumeel in Acute Ankle Sprain Study (TAASS) compared topical Tr14 (ointment and gel) with diclofenac 1% gel for the treatment of acute ankle sprain. This randomized, controlled, three-arm, multicenter study included 449 physically active patients aged 18–40 years with unilateral sprain of the lateral ligaments of the ankle joint (grades 1 and 2). Patients were randomized to Tr14 ointment ($n = 152$), Tr14 gel ($n = 150$) or diclofenac 1% gel ($n = 147$) and instructed to apply 2 g of product topically three times a day for 14 days. Statistical analysis showed that on the primary end points of pain and function both Tr14 formulations were non-inferior to diclofenac 1% gel after 7 days of treatment. At 6 weeks, all patients reported total pain relief and normal functioning. The median time to return to normal activity for Tr14 ointment, Tr14 gel and diclofenac groups, respectively, was 19.09, 19.35 and 19.39 days. Adverse events were mostly mild or moderate in severity, none was serious and all treatments were equally well tolerated. Both Tr14 gel and ointment were also found to be non-inferior to diclofenac on all secondary outcome variables including reduction in swelling and global assessment of efficacy[39].

Treatment algorithm

In light of the new findings from TAASS, and the established evidence base, a treatment algorithm has been developed to assist clinicians in the appropriate utilization of Tr14 in clinical practice (Figure 1)[40,41]. An expert panel evaluated the place of Tr14 in therapy based on clinical trial evidence and personal experience of the product. The experts concluded that Tr14 could be considered a therapy of choice in the following conditions: acute, acute exacerbation of chronic condition, and chronic[40].

The treatment algorithm supports better management of musculoskeletal disorders, provides multiple treatment options for a broad range of musculoskeletal disorders and demonstrates Tr14 as a part of the general armamentarium to manage these conditions.

Conclusions

Management of acute soft tissue disorders can be challenging. The goal of management is to return the patient to normal activities and decrease recurrence and avoidance of chronicity. The risks associated with anti-inflammatory approaches need to be considered carefully, with risks and benefits balanced appropriately for the individual patient. Furthermore, when managing pain, care should be taken to ensure that important pain signals are not masked. Pain masking can result in worsening of existing injury, setting back recovery, or potentially result in new injury.

Tr14 provides a different approach to the management of inflammation and consecutive pain. Recently, topical Tr14 has been proven to be as effective as topical diclofenac in reducing pain and improving function in acute ankle sprain. To facilitate the appropriate utilization of Tr14 in clinical practice, a treatment algorithm has been developed by a group of international experts. Investigation of the efficacy and place in therapy of Tr14 is ongoing with further randomized controlled trials underway.

Transparency

Declaration of funding

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Declaration of financial/other relationships

B.W. has disclosed that he is Chairman of the Traumeel Scientific Advisory Board for Biologische Heilmittel Heel GmbH, and has received honoraria for giving scientific talks. C.S. has disclosed that she is a consultant/advisor to the Traumeel Scientific Advisory Board for Biologische Heilmittel Heel GmbH.

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