Chapter 11

Local Therapies for Osteoarthritis — An Update and a Review of the Literature

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1. Introduction

Osteoarthritis (OA) is the most common chronic joint condition affecting an estimated 8 million people in the UK alone. It manifests as localised joint pain, stiffness and occasionally swelling. Osteoarthritis can be secondary to pre-existing joint damage - commonly inflammatory arthropathy or previous injury - or primary with no known pre-existing damage. Risk factors for primary OA include old age, female sex and family history and obesity.

The disease can be restricted to a particular joint or generalised, affecting multiple joints. In severe cases, it can be progressive eventually leading to loss of function and deformity.

Treatment has mainly focused on symptomatic relief from pain, physical approaches such as rehabilitation and physiotherapy, disease modifying treatment (such as hydroxychloroquine) and surgery. Pain relief with systemic drugs has drawbacks. In particular the use of non-steroidal anti-inflammatories (NSAIDs) has been associated with significant adverse events including gastritis and increased risk of cardiovascular disease. In view of this, there has been increased interest in localised treatments for OA.- i.e. therapies that are administered to the joint itself, or in the region of the joint. These can be divided into topical treatment, such as anti-inflammatory gels and creams and thermotherapy, and more invasive local treatment including joint aspiration, and intra-articular joint injection with corticosteroid and hyaluronans.

2. Topical treatments

2.1. Thermotherapy

Thermotherapy refers to the application of either heat or cold (cryotherapy) to affected joints in an attempt to improve pain, stiffness and swelling.

Ice massage and ice packs application have both been studied in knee osteoarthritis [5-10]. In one review [7], cryotherapy was found to reduce pain, stiffness and oedema. Regular ice massage, given 5 times a week, was found to have a clinically significant effect on all three symptoms as well as function (11% improvement relative difference), strength (29% improvement) and range of movement (8% relative difference) over a short period of time [8]. However, these improvements were not replicated with less frequent applications (3 times per week) [9] and there are no data to indicate a more long term effect of cold therapy on osteoarthritis as these studies looked at short term results. It is likely that most of the effects of cryotherapy are related to the induction of local vasoconstriction and the reduction of local blood flow resulting in reduced swelling.

Common methods of superficial heat administration are electrical heating pads, application of hot packs, towels or wax, or immersion in warm water or wax baths. In some early trials, heat application was not found to improve function or symptoms [8,9]. In recent years, however, there has been an explosion of studies looking at different modalities of local heat therapy[10-13]. These include the application of heat packs [12], ultrasound [13 11] and diathermy. The application of local heat packs has been found to provide short-lived benefit in terms of pain relief [12, 14]; and in particular, wet heat has been found to be better than dry heat [15] for symptomatic improvement. In one study [12] 18 patients were treated with either steam generating heat sheets for 6 hours daily or with quadriceps strengthening exercises only for a total of 12 weeks. At the end of the study, patients in the heat treated group reported statistically significant improvements in symptoms as well as the Timed Up and Go time (a measure of function). The mechanism of heat therapy in osteoarthritis is unclear, although *ex vivo* studies of cartilage [15, 16] have indicated raising chondrocyte temperature might increase their metabolism and production of proteoglycans. This in part, maybe secondary to increased blood flow to the chondrocytes.

On the whole, the data suggest that thermotherapy maybe useful as an adjunct in the treatment of osteoarthritis although long-term benefits have not been established.

2.2. Local ultrasound therapy

The role of ultrasound (US) in diagnosis of musculoskeletal problems has been well established. Its popularity in large part due to the low cost and non-invasive nature of the modality. In recent years, there has been growing interest in its application for therapeutic purposes [13,18-20]. In theory direct treatment with US leads to local heating of the tissue at depths not achieved by applying heat packs. There are two methods for doing this: continuous US which leads to a rise in temperature of the treated tissues; and pulsed wave treatment which harnesses other properties of US. *In vitro* and animal studies [18, 19] have suggested that pulsed wave US can increase collagen production and reduce expression of membrane metallo-proteinase, suggesting a protective role. This has failed to translate to clinical benefit as recent randomised controlled studies [13, 20] comparing continuous, pulsed and sham US on knee osteoarthritis symptoms and joint function, have shown no difference in pain scores nor 15m-walk time. In general, the safety of US has been established but evidence is scarce for any therapeutic advantage [13,20].

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2.3. Laser therapy

Laser beam therapy directs intense light to treated tissue. Two types of laser therapy have been trialled in osteoarthritis: low-level and high intensity. Low- level laser therapy uses red and infra-red light whilst high intensity laser therapy uses higher wavelengths of radiation for deeper tissue penetration. Low level laser therapy has been found to reduce pain, possibly by modulating the local inflammatory process In a rat model of osteoarthritis, laser therapy caused a reduction in neutrophil migration, oxidative stress, altered levels of cyclo-oxygenase-2 and other pro-inflammatory mediators) [21]. Other than providing symptomatic relief, there is also some evidence that laser promotes fibroblast proliferation, collagen synthesis and bone regeneration [22-26]. In a rabbit model of osteoarthritis, six weeks of treatment with laser therapy not only resulted in improved pain but also histological evidence of reduced inflammation as well as a reduction in cartilage damage [27]. This suggests that laser therapy could have disease-modifying as well as symptomatic benefits.

So far, the results of early clinical trials have been mixed [28]. More recent studies have tended to be more positive with those treated with laser therapy and exercise doing better than those treated with exercise alone on pain measurements as well as function [29, 30]. These studies suggest that laser in combination with standard physiotherapy could have advantages over standard therapy. We have little evidence regarding long term effect and whether the cellular effects noted results in halting disease progression. The use of low-level laser therapy has now been approved by the US Food and Drug Agency (FDA) and so we are likely to see an expansion in its use in the coming years.

2.4. Topical non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDS) work by blocking the action of cyclo-oxygenases responsible for prostaglandin synthesis, the latter being known mediators of inflammation [31]. Locally this reduces pain, swelling and heat. NSAIDs also have central analgesic actions, possibly by reducing brain prostaglandin synthesis although alternative mechanisms include the induction of endogenous opioid peptides and blockade of serotonin release. From this, it can be seen why systemic NSAIDs have long been used for osteoarthritis. However, significant side effects including gastritis, renal impairment and increased risk of cardiovascular disease has meant that their long-term use has been limited. It is on this background that topical NSAID use has been promoted, theoretically providing analgesic and anti-inflammatory benefits without systemic adverse effects.

There are many types of topical NSAID. There are preparations containing diclofenac, ibuprofen, piroxicam, ketoprofen or felbinac as the active ingredient. Some include a penetration enhancer such as menthol or dimethylsulfoxide (DMSO). Gels and sprays tend to be more penetrative than cream preparations. Once applied, a topical NSAID must be absorbed by the underlying tissue or enter the local blood stream. Studies have shown that the absorption of NSAIDs into the underlying tissue gives rise to therapeutic local concentrations of the drug without significant systemic absorption [32,33]. An estimated 3-7% of the applied dose is thought to be absorbed systemically [33] with plasma concentrations being approximately 5% of those achieved with oral administration [33].

The skin seems to act as a reservoir from which the drug disseminates to the deeper tissue. Peak concentrations in the skin are achieved 2 hours after application with a further spike at about 19 hours later, likely secondary to systemic absorption. Further proof of their local action is the absence of analgesic effect at joints distant to the point of application [34].

There have been many studies looking into the effectiveness of topical NSAIDs in treating osteoarthritis [35-41]. These on the whole have found that topical NSAIDs were superior to placebo in the treatment of chronic pain. Most of the initial studies found no benefit beyond two weeks of treatment [35-41] but larger randomised controlled trials found long term benefit for up to 3 months when compared to placebo [42-43].

When compared to oral NSAID use, the results have been variable. A meta-analysis in 2004 [41] found that topical NSAIDs were less effective than systemic NSAIDs. Since then, however, there have been several studies showing comparable effectiveness. Two studies comparing oral diclofenac with a topical preparation of the drug [44,45] found that there was no difference in pain scores or physical function. They also found that those in the topical treatment arm had a much lower incidence of severe gastrointestinal side effects, deranged liver function tests and abnormal creatinine clearance [44,45]. These results were replicated in another study comparing oral and topical treatment with ibuprofen for knee osteoarthritis, which also found no difference in pain and function scores between the two arms [43].

On the whole, topical NSAID use is associated with fewer systemic adverse events [35, 39, 44, 45] as compared to oral preparations. The main adverse event associated with topical NSAID use is local skin irritation, which has been reported in up to 39.3% of patients [46]. However, these skin reactions occur with placebo gel application with equal frequency indicating that it may not be related to the drug itself [39]. Other studies also suggest that skin reactions may be more common with solutions containing DMSO than DSG [37]. There is some contradictory evidence regarding their safety in older patients as some studies have found the rate of GI side effects in the over 50s to be as high as 15% [46].

Overall the data suggest that topical NSAIDs may be considered as first line therapy for osteoarthritis as they appear to be efficacious and associated with fewer adverse events. There should be caution about their long term use in the elderly as these patients may be more prone to adverse events.

2.5. Other topical treatments

Topical capsaicin cream has been used to treat a multitude of different painful conditions including osteoarthritis, inflammatory arthritis and neuropathic pain. Derived from chilli peppers, capsaicin is a lipophilic alkaloid that acts as a local irritant. It activates local pain receptors (c-nociceptors) leading to the release of substance P [47]. This in turn causes local irritation in the initial phase of treatment. With repeated use, however, levels of substance P are depleted, leading to desensitisation of the pain fibres and hypoalgesia [48]. In clinical practice, capsaicin is better than placebo for the treatment of chronic pain but compares less favourably with other treatments. In a meta-analysis comparing capsaicin with plaster, capsaicin was found to be only marginally effective [49]. Other drawbacks include the need to

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apply the cream four times a day for maximum benefit, as well as local irritation and intense burning sensation (occurring in uto 40% of patients) [50]. These problems lead 10% of patients to discontinue treatment [49]. In view of this, topical capsaicin should be used in conjunction with more traditional treatments.

Other topical treatments include the use of salicylate or nicotine esters, which acts as a local counter-irritant or rubefacient. These cause localised vasodilatation and reddening of the skin. This results in a local sensation of warmth, which often palliates pain. Theories of mechanisms of action include irritation of the sensory nerve endings in underlying muscle and tissue [51] as well as activation of the transient receptor ion channels involved in relaying thermal and pain sensation [52,53]. Clinical studies have shown modest benefits with regular use [54,55]. Compared to placebo, 16% achieved ≥50% improvement in pain scores at 2 weeks [54]. However, when compared to topical NSAIDs, counter-irritants performed poorly [55]. On the whole, counter-irritants are well tolerated and may be useful as adjuvants to standard therapy or patients in whom standard analgesics are contra-indicated [55]. There are no data to support their long term use and they are not recommended as continuing therapy.

3. Local injections

3.1. Intra-articular corticosteroids

Intra-articular (IA) corticosteroid injections are frequently used to treat osteoarthritis. In common practice, they are diluted in local anaesthetic to provide immediate relief, ensure accurate drug delivery and allow even dispersal of the drug within the joint due to the larger volume [57]. Commonly used corticosteroids in IA injections include hydrocortisone acetate (HCA), methylprednisolone acetate (MPA) and triamcinolone acetonide (TCA). These vary in solubility with the former being more soluble than the latter. Less soluble preparations are longer acting and theoretically provide more long term relief. In one randomised control trial comparing MPA (more soluble and shorter acting) and TCA in knee osteoarthritis, greater improvement in pain scores was found in the TCA group at 3 weeks compared to MPA [56]. Interestingly, there was no difference between the 2 groups at 8 weeks despite TCA being longer acting. There was also no significant difference in functional scores [56].

Several studies have looked into whether intra-articular steroid injections have symptomatic or functional benefit in knee osteoarthritis [58-61]. These have shown short term (lasting between 1-4 weeks) improvement in pain but not function in these patients following injections when compared to placebo. Follow up beyond 4 weeks did not show longer lasting benefits as compared to placebo. These results were further corroborated in a Cochrane systematic review [62]. This suggests that IA steroid injections should be used as a short term bridging treatment to resolve acute painful flares pending further intervention such as surgery or physiotherapy. Trials looking IA injections in the hip echo the results of the studies done in the knee: patients gained rapid and short lived pain relief following injection but that these benefits were not maintained beyond 1 month [63,64].

Other studies, looking at 1st carpo-metacarpal joint (CMC) injections found more mixed results in terms of long term relief. In one study of 40 patients, no benefit was observed between steroid injection when compared to placebo [65]. Patients less likely to have sustained long term benefits were those with worse radiographic appearances (increased number of osteophytes and more advanced joint space narrowing) [66]. In patients with less advanced disease, IA 1st CMC joint injection could provide symptomatic relief up to 18 months following injection and splinting [66].

IA steroid injections work locally via anti-inflammatory effects, inhibiting the inflammatory cascade at multiple points. Local injection avoids the systemic problems associated with steroid use and allows delivery of high doses to the affected tissue. Response to IA injection, however, does not appear to be dependent on inflammation in the affected joint itself [61]. Further studies looking at whether inflammation detected on ultrasound predicted clinical response found that those without inflammatory change fared better in response to IA injection than those with evidence of inflammation. The presence of synovial thickening, synovial fluid volume and white cell count did not predict better response to IA injection [60, 61]. In knee OA, joint aspiration prior to IA injection appears to provide greater symptomatic benefit [60]. This is partly due to confirmation of correct position by prior aspiration and more concentrated drug delivery due to a lower volume [67].

Although IA injections avoid the toxic side effects of systemic steroids, they are not without risks themselves. All patients undergoing IA injection should be consented for the risk of infection, although this is a rare event (incidence reported between 1 in 3,000 to 1 in 50,000) [68] and may be clinically difficult to differentiate from an injection-induced crystal arthritis which can occur in 2-6% of patients [58, 60]. In general, septic arthritis following IA injection occurs 3 to 4 days post procedure. There is a risk of lipoatrophy at the site of injection (estimated 0.6% of patients) [69]. The risk of this is reduced by using shorter-acting preparations and doing imaging-guided injections where possible. Other serious local adverse events include tendon rupture, muscle wasting and local depigmentation. The risk of these can also be minimised by using guided injections where possible.

Systemic adverse events are rare with local corticosteroid injections. The most common is flushing (up to 40%) [69]. There have been reported incidents of unstable diabetic glycaemic control post injection but this tends to be minor and usually settles [70]. There is evidence for systemic absorption of intra-articular steroids [71]. Studies looking at the endocrine axis in patients who had received intra-articular steroid injections found that serum cortisol dipped 24-48 hours after IA injection and took up to 4 weeks to return to baseline [71]. Major complications, such as steroid induced osteoporosis, have not been observed however [72].

Studies in animals have suggested that intra-articular steroids can induce chondrocyte degeneration [73] but prospective clinical trials where patients were receiving regular IA injections have failed to demonstrate increased rate of cartilage loss [74]. There are also limited data to support significant increased risk of osteonecrosis in injected joints. Repeated IA injections offer no long-term benefit [67] and should generally be avoided but short-term use may provide rapid pain relief and can be used as a bridging treatment pending further intervention.

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3.2. Intra-articular hyaluronic acid/hyaluronan

Hyaluronic acid is a large glycosamino-glycan molecule found in synovial and cartilage extra cellular matrix (ECM). It is produced by synoviovytes, chondrocytes and fibroblasts and functions as both lubricant as well as a means to maintain hydration within the joint [75]. Studies have shown that osteoarthritic joints have decreased hyaluronan content in the synovial fluid [76] and therefore IA injection with a synthetic analogue was developed to restore the function in degenerative joints.

Synthetic preparations of hyaluronic acid closely mimic endogenous molecules. Later preparations contain cross linked hyaluronin in order to achieve greater elasticity and viscosity. In theory this confers greater intra-articular durability of the solution. Preparations with a higher molecular weight also seem to be more beneficial than those with a lower weight [78]. This may be related to the difference in volume required for injection as well as the number of injections required and the intra-articular durability of the solution.

Multiple studies have been conducted into the effectiveness of IA injections of hyaluronans in osteoarthritis, mostly of the knee. These have found mixed evidence to recommend their use. In general, hyaluronans appear to be better than placebo in improving pain scores, function and patient global assessment when used in knee osteoarthritis [77]. The greatest clinical benefit is achieved at week 5-13 after a course of treatment of several injections. Part of the problem with interpreting the data is wide variability in trial design, frequency of injections and molecular weight of the synthetic product being used. In hip OA, hyaluronan injections were not superior to placebo nor corticosteroid injections in reducing pain or improving function [79]. These results were echoed in studies looking at its use in hand OA [80].

These injections are relatively safe and tend to provide longer term relief than corticosteroid injections. Its use, however, is restricted by the relatively high cost of the treatment [75]. IA hyaluronan injection is generally reserved for knee osteoarthritis and is offered either as a holding measure until more definitive treatment can be undertaken (e.g. surgery), or in patients for whom such treatment is inappropriate.

3.3. Subcutaneous and soft tissue injections

Trigger points are localised areas of tenderness and thickening in the soft tissues. They are typically found proximal to an inflamed or painful joint such as the rectus femoris in patients with knee OA and paraspinal regions in the cervical and lumbar spine [81]. They have also been described as interstitial fibrositis, myofasciitis and myofascial trigger points [82-84]. The aetiology and pathogenesis of these trigger points is unknown.

Trigger point injection has been used as a way of alleviating pain and discomfort associated with these areas of thickening. This can be direct injection of a substance (e.g. local anaesthetic or corticosteroid) into the point or indirect needling of the soft tissue in that area. The trigger point is identified as the maximal area of tenderness in the muscle and the point is then isolated by the thumb and forefinger to prevent movement in the underlying muscle. A small sterile needle is then introduced into the area and the substance injected directly into it (or alterna-

tively it can be dry needled). If the injection is performed correctly, there is usually an acute worsening of pain associated with muscle spasm [85].

A systematic review of trigger point injection in the management of chronic musculoskeletal pain found an improvement in symptoms when used exclusively [86]. This was irrespective of the injectant used [86]. The addition of a local anaesthetic, however, has been found to reduce the pain and irritation of the caused by the procedure [84].

There are limited data on the efficacy of trigger point injection in the treatment of osteoarthritis. One study found that trigger point injection in conjunction with IA corticosteroid was more effective than IA injection alone in both pain and functional scores [87]. Other studies have looked at trigger point injections as sole treatment and this does not reflect clinical practice. Overall, trigger point injections are safe and can be used as additional therapy in OA.

Drugs used for trigger point injections have included local anaesthetic, corticosteroids, anti-inflammatories such as acetylsalicylate and ketorolac as well as saline and water [84, 88-92]. There have also been several studies looking at the use of subcutaneous salicylate therapy for OA. In one trial 40 patients with OA of the 1st CMC joint [93] were randomised into either sham injection or subcutaneous injection with salicylate into trigger points. Patients were assessed blind at 3, 7 and 13 weeks. Pain scores and tenderness were significantly lower in those treated with salicylate compared to sham injections [93].

The mechanism of action of subcutaneous salicylate injections is unclear, particularly as the site of injection is distant from the affected joint. One theory is that salicylate may alter central sensitisation and this is supported by the immediate relief patients report following injection. An alternative model would be that the local effect of salicylate modifies the neurogenic control of inflammation, which may be abnormal in diseases that affect musculoskeletal structures [94, 95]. Changes in the expression and transport of neurogenic peptides might be induced by the local irritant effect of salicylate [96]. Systemic anti-inflammatory effects are unlikely, since the benefits are not observed in distant sites [93].

There is, however, a degree of overlap with acupuncture in that the injection sites are standard acupuncture locations. Acupuncture involves the insertion of fine filiform needles at or near the painful site, or sometimes at distant acupuncture "points". In a variation of this, the needles are sometimes stimulated electronically or with heat. Patients typically receive six or more sessions for a complete course of treatment. A systematic review of 393 patients with osteoarthritis found that acupuncture significantly improved pain but not function when compared to sham acupuncture [97-104]. In addition, it was not better than standard treatment with physiotherapy or being on a waiting list to receive acupuncture [97,100]. There was also no additional benefit of including acupuncture to standard therapy with exercise and advice [103]. Moreover, there is little evidence for long term benefit following treatment with improvements in symptoms lasting up to 12 weeks only [97,100]. Acupuncture is relatively safe, however, with minimal risks of serious side effects [101-104].

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4. Splinting/support

Osteoarthritic joints may be helped by various forms of external support. Benefit can be obtained by adjusting alignment, modifying stress or load, providing shock absorption, or simply resting the joint. Orthoses (including braces, splints and elasticated sleeves) are frequently used in OA of the hand and knee and hand.. For hand OA they include thumb and wrist splints; for the knee they include rest orthoses, knee sleeves and unloading braces. Medial patellar strapping may be specifically helpful for patellar maltracking [105]. Shoe insoles may be particularly helpful for OA affecting the ankle and knee, and can sometimes alleviate symptoms from OA of the hip: they include cushioned or neutral insoles, which act as a shock absorbers; and wedged insoles, which also modulate mechanical stress.

For OA of the knee and ankle the main purpose of orthoses and insoles is to support joint that is unstable, and to help correct alignment [106]. They can modify load bearing and contribute to pain reduction, and they often improve physical function. There is also evidence that they can improve proprioception [107] and that they may slow disease progression [108]. They are especially useful for mild or moderate uni-compartmental knee OA [109-110, 42] where there may be varying degrees of instability and mal-alignment. Unloading knee braces are designed to reduce the load transmitted to the diseased compartment by applying an external valgus or varus force. Symptomatic relief is achieved by stabilizing the joint, increased joint opening and reduced local muscle contraction [108]. One study [111] demonstrated that patients treated with unloading knee braces had better functional and symptomatic outcomes at 6 months with medial compartment knee OA. These results were not replicated in other studies [112] although there is evidence that they can improve quadriceps strength and gait symmetry [113]. The main disadvantage of these braces is poor tolerability due to the weight and heat of the device. In one study, 41% of patients complained of skin irritation [114] and up to 20% of patients discontinue use within 6 months [115].

Splinting of the thumb carpometacarpal (CMC) joint has also been found to be helpful in improving function and pain [116]. CMC joint OA contributes more to pain and disability than inter-phalangeal joint OA [117] and thus splinting of the CMC joint makes sense. In a systematic review in 2010, CMC splinting was found to improve function and grip strength [116]. Further RCT data has corroborated this finding and showed sustained benefit at 12 months [118]. However, these splints are inevitably somewhat cumbersome to wear, and inhibit many day-today functions of the hand.

In general, splinting might be useful for symptomatic relief and may even improve function with prolonged use in appropriately selected patients.

5. Conclusion

There are a number of different local treatments for osteoarthritis which focus on symptomatic relief. Choice of treatment should, therefore, be guided by patient response and personal

preference. Most local therapies are safe, avoiding any major systemic side effects. In general, these therapies should be used as adjuncts to physiotherapy and systemic analgesia. Although some of these treatments are well established and have been used in clinical practice for many years (e.g. intra-articular injections and orthoses), newer approaches are being developed such as local laser therapy and subcutaneous sodium salicylate injections. There is limited data to show any benefit for long term outcome for any of these local therapies and further studies are required to establish this.

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