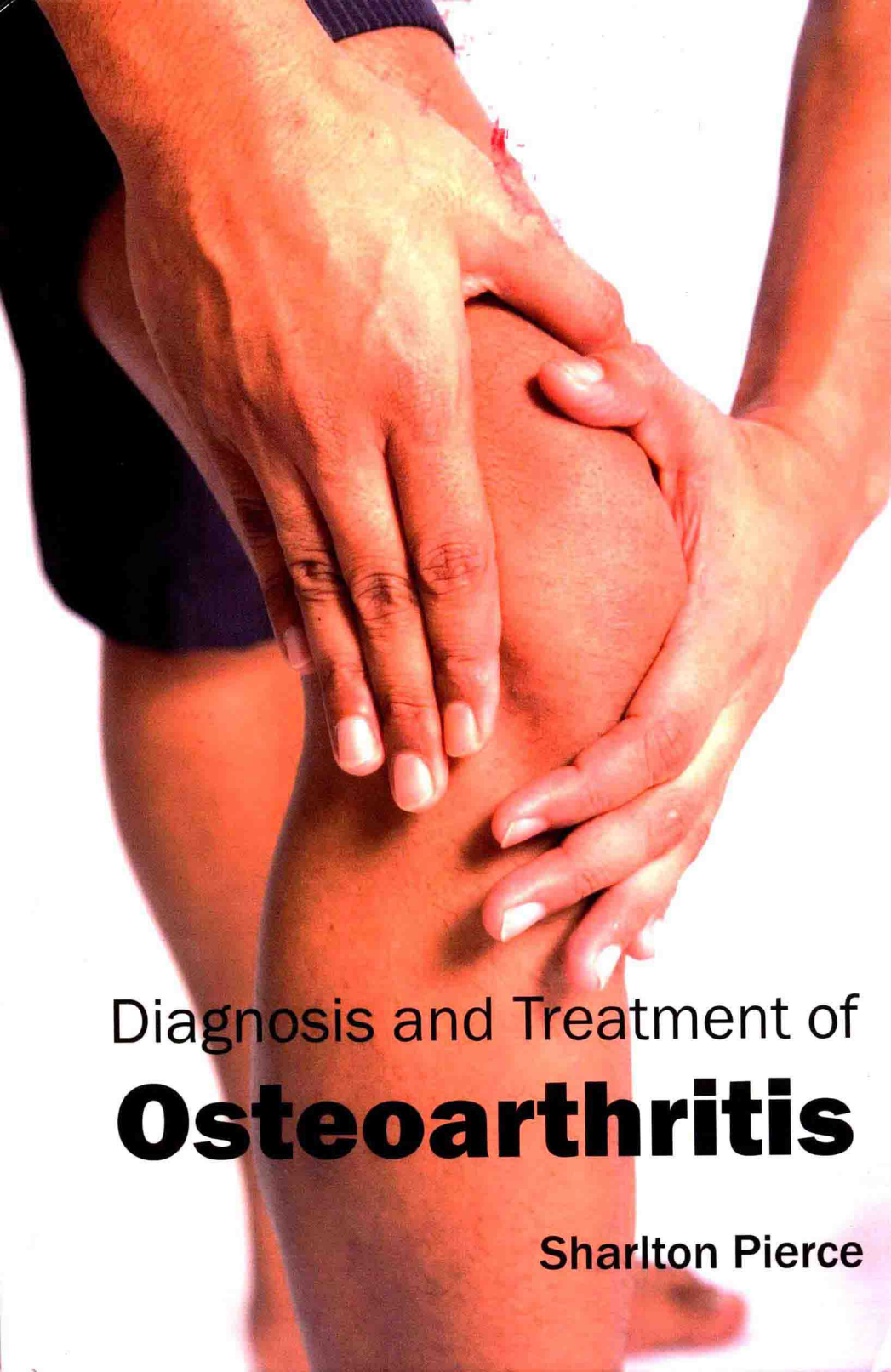

Diagnosis and Treatment of Osteoarthritis

Sharlton Pierce

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Edited by **Sharlton Pierce**

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Preface

Degradation of the joints is medically termed as osteoarthritis. Millions of people across the globe are affected by the extremely debilitating disease of osteoarthritis (OA). No disease modifying drug approved by FDA is currently available for this disease in particular. Surgery continues to be an efficient final solution to restore the function of the joints. The increase in the amount of aging populations across the world over the past few years has consequently increased the number of OA patients significantly with estimations of further increase in the near future. This book presents latest developments in diagnosis, treatment and surgery of OA, covering a broad spectrum of topics like alternative medicine and cutting edge gene therapy. Integrative approaches are required for formulation of new and efficient therapies to cure OA in the future. Various surgical methodologies have been elucidated in this book for the restoration of the function of the joints. Also, several treatment options have been discussed, in order to decrease the pain and improve the quality of life of the OA patients.

This book has been the outcome of endless efforts put in by authors and researchers on various issues and topics within the field. The book is a comprehensive collection of significant researches that are addressed in a variety of chapters. It will surely enhance the knowledge of the field among readers across the globe.

It is indeed an immense pleasure to thank our researchers and authors for their efforts to submit their piece of writing before the deadlines. Finally in the end, I would like to thank my family and colleagues who have been a great source of inspiration and support.

Editor

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Topical and Regional Treatment for Osteoarthritis

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1. Introduction

Osteoarthritis (OA) is the most common joint-related disorder. The prevalence rises steeply with age and is a major cause of pain and disability. In the over 65-year-old population, 12% suffer from symptomatic knee OA (1) while 13- 26 % suffer from symptomatic OA in at least one hand joint (2). Hip OA is much less common. The prevalence of radiographic change is much higher; in the elderly population 75% have evidence of hand OA and 30% of knee OA on plain radiographs (3).

The term "osteoarthritis" is used to refer to a number of related conditions that can be broadly classified into two groups. Primary OA, which can be localised or generalised and more commonly affects peri-menopausal woman (especially involving the hand inter-phalangeal joints); or secondary OA which has an underlying cause such as an inflammatory arthritis (e.g. rheumatoid arthritis or crystal arthritis), mechanical damage (e.g. articular fractures), a congenital or developmental disorder or a metabolic or endocrine condition (4). An osteoarthritic joint may show varying degrees of inflammatory change, detectable clinically and histologically. It is uncertain to what degree these (and other) subdivisions of OA are useful in terms of therapy.

This chapter addresses therapies for all forms of OA of limb joints. Much of the evidence that will be considered here does not distinguish between the various types, although where possible, efficacy in knee, hip and hand OA is described separately due to the differing natural history and prognosis of OA at these sites.

Treatments for OA are limited. They consist of a combination of non- pharmacological and pharmacological approaches, which should be tailored to the individual according to their needs and stage of disease. They aim to relieve pain and stiffness and thereby improve function. It is recognised that pain arises from both intra-articular structures (bone or synovial tissue) and from peri-articular structures such as entheses, bursae or tendons. Sensitisation of peripheral nerves and central nervous system changes can also contribute to the persistence of pain over time.

All patients should be offered education, advice and access to information in combination with physical approaches (e.g. strengthening exercises and physiotherapy, including aerobic fitness training) and lifestyle changes (e.g. weight reduction and dietary manipulation) as appropriate. Additional therapies include systemic drugs (e.g. analgesics, anti-inflammatory agents, supplements, and, recently, disease modifying treatment such as hydroxychloroquine) and surgery.

This chapter focuses on treatments that are administered to the joint itself, or in the region of the joint. Pain management techniques such as nerve block and transcutaneous electrical stimulation are beyond the scope of the article.

2. Specific therapies

2.1 Splinting/support

Orthoses (or braces) are external devices mainly prescribed to modulate mechanical stress on a symptomatic joint compartment. They are used in knee and hand OA but not in hip OA. For knee OA, they include rest orthoses, knee sleeves and unloading braces. For hand OA they include thumb and wrist splints. Insoles are used in hip and knee OA: they include cushioned or neutral insoles, which act as shock absorbers; and wedged insoles, which also modulate mechanical stress.

For lower limb OA, the main purpose of orthoses and insoles is to support an unstable joint and to help correct alignment (5). In doing so, they reduce pain, reduce load bearing and improve physical function. They can also improve proprioception (6) and possibly slow disease progression (7). They are particularly recommended in mild or moderate unicompartmental knee OA (8,9,10) where varying degrees of frontal or sagittal instability and varus or valgus mal-alignment occur, and ideally should be used in combination with other therapeutic approaches. The different interventions are described individually below.

1. **Rest orthoses** are made from a stiff composite and are intended for joint immobilization. They are rarely used in practice however, and there are no clinical trial data to suggest effectiveness. Whether they would be helpful in transiently immobilising a swollen knee remains uninvestigated (11).
2. **Knee sleeves** are functional elastic non-adhesive orthoses that can be used alone or in association with various devices and are aimed at patellar alignment or frontal femoro-tibial stabilisation. Simple neoprene knee sleeves used in medial compartment OA have been shown to reduce pain on activity and stiffness but not physical disability in the short term (6 months) when compared with no sleeve (12). This does not appear related to a local thermic effect. They have also been shown to increase static and dynamic balance, which might help prevent falls (13). Heat retaining sleeves (worn for 12 hours per day for 4 weeks) do not offer additional therapeutic benefit over standard devices (14). Medial patellar strapping has also been shown to reduce pain significantly in patello-femoral OA associated with patellar mal-alignment (15).
3. **Unloading knee braces** are functional devices indicated in patients with mal-alignment secondary to medial or lateral unicompartmental OA. They are composed of external stems, hinges and straps and are designed to decrease the compressive load transmitted to the diseased compartment by applying an external valgus or varus force respectively. Analgesic effect is achieved by improved stability, increased joint opening and possibly by reduction in local muscle contractions during gait (7).

   A single randomized controlled trial (RCT) of 110 patients showed that a valgus brace significantly improved pain, functional status and disease-specific quality of life at six months compared with no intervention in patients with medial compartment knee OA, and was more effective than a neoprene sleeve (12). However, a further RCT did not confirm its efficacy in pain reduction (16). A subset of patients in this trial found the varus brace effective for lateral compartment OA; this is the only trial result supporting efficacy of varus bracing. Unloading braces have been shown to improve isokinetic

quadriceps strength and gait symmetry (11) and while they significantly improve joint proprioception, this does not appear to improve postural control (6).

The main drawbacks with unloading braces are a variable response rate (39 to 93% of patients notice improvement) (11), and discomfort due to heaviness, heat and mobility of the device. The latter can also lead to persistent joint instability. In a three-year follow up study of 22 patients, the most common complaint was skin irritation affecting 41% of patients (17). Long-term compliance is therefore a problem: 20% of patients discontinue their brace at 6 months and many discontinue treatment within 1 to 2 years (18). Long term efficacy is therefore unknown. The most serious reported side effect is venous thromboembolism.

4. **Insoles.** There are limited data for the effectiveness of insoles (either laterally wedged or neutral) in reducing the symptoms of OA. In one study there was significant decrease in non-steroidal anti-inflammatory drug (NSAID) consumption and significantly better compliance in the laterally wedged insole group at 6 and 24 months compared to the neutral wedge group but there was no significant difference in pain, stiffness and function (19). Another study has shown that elastic subtalar strapping significantly reduces pain and femoro-tibial angulation at 6 and 24 months compared with traditional laterally wedged insoles (20). Adverse effects include low back, popliteal and foot sole pain (21). However, given their low cost and relatively better compliance, attention to footwear with shock-absorbing properties is worth considering (22).
5. **Thumb Splints.** In patients with hand OA, pain and its anticipation is a major factor in loss of hand function. Pain reduction should therefore be the primary goal of treatment. It appears that 1st carpo-metacarpal (CMC) joint OA contributes more to pain and disability than inter-phalangeal joint OA (23). As heavy stresses are placed on the 1st CMC joint during pinching and grasping, thumb splints are useful especially if the patient has difficulty in performing daily tasks.

Their efficacy was shown in a systematic review in 2010, which found high to moderate evidence for thumb CMC joint immobilization in improving pain and function and moderate evidence in improving grip strength (24). A multi-centre trial also showed strong evidence for efficacy at twelve months (but not at one month) in terms of improved pain and disability (25). There are several different designs of thumb CMC splints (from a short opponens splint which supports the 1st CMC and metacarpo-phalangeal (MCP) joint, to a much larger long opponens splint which includes both the MCP and wrist joint) (26). As yet it is unclear which are considered most comfortable for patients and thus will be worn long term, and what degree of support is required at what stage of OA in order to improve pain and function effectively (22).

2.2 Topical non-steroidal anti-inflammatory drugs

Direct application of topical non-steroidal anti-inflammatory drugs (NSAIDs) in the region of a painful joint is a common and recommended treatment in mild to moderate OA (8,9,10,22). This treatment is particularly useful in the management of a single painful osteoarthritic joint (especially the knee), or when a few hand joints are involved. It can provide a safe and effective alternative to systemic anti-inflammatory therapy.

Topical NSAIDs act primarily through inhibition of cyclo-oxygenases responsible for prostaglandin biosynthesis at the site of pain and inflammation, but might also work through peripheral and central desensitisation (27). Unlike other topical treatments, the act

of local rubbing appears less important in achieving a therapeutic effect. Topical NSAIDs can be applied over the affected joint up to 2 to 4 times a day depending on the drug, but currently are not recommended for continuous use beyond one month.

There are several different preparations of topical NSAID available, which differ in the active drug (diclofenac, ibuprofen, ketoprofen, piroxicam and felbinac), formulation (gel, solution, cream, plaster and patch) and the presence of a penetration enhancer to improve drug delivery (45.5% dimethylsulfoxide [DMSO] or menthol). The most commonly studied preparations are diclofenac sodium 1% gel (DSG) and diclofenac sodium 1.5% in 45.5% DMSO solution (Pennsaid).

To be effective, a topical NSAID needs to penetrate the skin and enter the circulation or additionally be absorbed into the underlying tissue. The formulation with respect to its lipid and aqueous solubility (requirements for passing through the stratum corneum and epidermal layer respectively) determines the degree of dermal penetration (28). Formulations of gels and sprays are more effective than creams.

Studies show that penetration of the topical NSAID into the intra- and peri-articular structures via the local bloodstream gives rise to therapeutic concentrations within these tissues without significant systemic absorption (28,29). This accounts for their superior safety profile over oral therapy with respect to systemic renal, cardiovascular and gastrointestinal toxicity.

Peak concentrations in the skin are achieved 2 hours after application, with a second peak 10 hours after application, which is attributed to the systemic circulation. The skin appears to act as a 'reservoir' from which the drug is distributed to deeper tissues (30). Only 3-7% of the applied dose is systemically absorbed (29) and mean plasma concentrations are typically 5% or less of the level reached following oral administration (31,32). Low systemic absorption is evidenced further by the lack of symptom relief in other joints distant to the site of application (33).

With respect to knee osteoarthritis, up until recently there was no research evidence to support the long-term use (greater than a month) of topical NSAIDs; a systematic review in 1998 (34) and two meta-analyses in 2004 (35,36) confirmed that topical NSAIDs were superior to placebo for up to two weeks in the treatment of chronically painful conditions but not longer. Later trials have however shown more long term efficacy, benefit beyond 4 weeks was confirmed in a meta-analysis of trials assessing efficacy between 4 and 12 weeks (37), and two further recent large high quality RCTs have demonstrated a sustained response maintained up to 12 weeks with diclofenac ("DSG" (33) and "Pennsaid" (38)) when compared with placebo. A recent RCT has also found topical ibuprofen to be as effective as oral ibuprofen and other NSAIDs for 12 months (39).

Currently there is insufficient evidence to compare efficacy of topical to oral administration of the same NSAID. The meta-analysis of RCTs in 2004 found that overall topical NSAIDs were less effective than oral NSAIDs (36). Two recent studies comparing topical diclofenac (in DMSO) with oral diclofenac in patients with knee OA have however demonstrated equivalent efficacy (40,41).

Placebo controlled trials and head to head studies with oral NSAIDs also show efficacy of topical NSAIDs in finger joint OA: hence they are preferred to systemic therapy, especially for mild to moderate OA and when few joints are involved (42).

The main side effect of topical anti-inflammatory treatment is local application site reactions such as dry skin, rash, pruritis and burning (36,37). They are short-lived and minor

however, and usually resolve when application is discontinued. Studies show that local adverse events are reported with equal frequency for topical NSAIDs and placebo preparations; hence they appear not to be related to the NSAID itself (35). Safety between different topical agents has not been studied. However, three 12-week trials showed a greater incidence (5 to 8 fold higher) of local application site reactions with diclofenac in DMSO solution (26-42%) compared with DSG (5.1%) (33).

Compared to oral NSAIDs, topical therapy is associated with fewer systemic adverse events and gastro-intestinal side effects (33,35,40,41). However, data regarding gastro-intestinal safety and tolerability of topical NSAIDs in older patients (over the age of 50 years) are conflicting. Some studies report minor side effects to be infrequent, including the two-year RCT comparing topical to oral ibuprofen (39,43); but a recent systemic review has demonstrated gastro-intestinal adverse events in 15% and local skin reactions in 39.3% of patients receiving topical NSAIDs including skin sensitivity, contact dermatitis and photodermatitis (44).

While topical NSAIDs should be considered with paracetamol as first line treatment ahead of oral NSAIDs, COX-2 inhibitors or opioids in view of their efficacy and relative safety, further studies are needed to confirm their long-term efficacy and use in bilateral knee OA. Their use in older patients also might still require a degree of caution until further data demonstrating their safety profile in this age group become available.

2.3 Topical counter-irritants

Topical counter-irritants or rubefacients are agents that are frequently applied locally to relieve musculoskeletal pain in the extremities. The most commonly used rubefacient is salicylate, but this class of agent also includes nicotinate esters. Topical capsaicin is commonly considered to be a rubefacient; however its mechanism of action is sufficiently different for this treatment to be described separately.

The principal action of rubefacients is to act as a skin irritant. This results in reddening from vasodilatation and increased blood flow, but also leads to a soothing sensation of warmth i.e. counter-irritation. It is still unclear whether topical salicylates additionally relieve pain via cyclo-oxygenase inhibition, but there is little evidence that there is significant systemic absorption (45). This is consistent with the fact that no benefit is found using a rubefacient applied distal to the site of pain (46). Pain may also be offset or altered in the underlying muscle, joint and tendon by irritation of the sensory nerve endings (47). More recently there is evidence to suggest that salicylates and other rubefacients may act via the transient receptor potential (TRP) ion channels involved in thermal and pain sensation (48,49).

Although topical rubefacients containing salicyclate are widely used in England (almost 1.8 million prescriptions issued in 2006) (50), there is currently no evidence to support their prescription for chronic musculoskeletal pain. A Cochrane analysis in 2009 of six studies of rubefacients in chronic conditions such as osteoarthritis has shown that they produced significant benefit compared with placebo at 14 days, with 1 in 6 individuals achieving 50% pain relief (51). This compares poorly with topical NSAIDs however, where the number needed to treat (NNT) is 3.1 compared to placebo. Additionally their efficacy may be over-estimated as adequate blinding is not possible with any trial involving a rubefacient, the mechanism of action is through local irritation and any sham preparation, which attempts to mimic this, would be a rubefacient itself. However, placebo gels in trials were rubbed on to the skin in the same way as the active treatment overcoming any additional therapeutic effect of rubbing (52).

Based on limited data, rubefacients appear well tolerated and local adverse effects are uncommon in the short term (2% of patients) (51,52). Currently they are usually used as adjuvants to other therapies, such as oral analgesics, support bandages, rest, ice, and compression, and may be useful for patients who cannot tolerate oral analgesics (52). RCTs are needed to support their clinical use with respect to long-term efficacy and safety especially in osteoarthritis, which is a chronically painful condition. Most trials have lasted 14 days only and the longest trial spanned 28 days (52). Consequently rubefacients are not recommended in the UK in osteoarthritis although this recommendation has been based on a small number of limited studies (22).

2.4 Topical capsaicin

Topical capsaicin (0.025%) cream can be used to treat pain from osteoarthritis and rheumatoid arthritis. A higher dose (0.075%) is used in the treatment of neuropathic pain. The preparations contain capsaicin, a lipophilic alkaloid extracted from chilli peppers that has an extremely potent irritant effect. They work by initially selectively activating and sensitising c-nociceptors in the skin by binding the transient receptor vanilloid type 1 (TRPV 1) cation channel (53). Substance P is released which causes local irritation; however with repeated applications, levels are depleted leading to reversible desensitization of pain fibres and eventual degeneration of epidermal nerve fibres resulting in hypoalgesia (54). Although topical capsaicin is better than placebo for treatment of chronic pain, a meta-analysis of topical capsaicin (0.025%) or plaster for chronic musculoskeletal pain calculated the NNT at 4 weeks to be 8.1 for a 50% reduction in pain suggesting that capsaicin is only marginally effective (55).

In general therefore topical capsaicin is best employed as an adjunct to other modes of therapy. It should be used for 3 to 4 weeks (applied 4 times daily) to achieve maximal benefit. A transient local burning sensation (which can be intense), stinging or erythema at the application site are common (40%) (10), and lead to 1 in 10 patients discontinuing the treatment (55) however. Systemic events are rare.

2.5 Thermotherapy

The local application of heat or cold (cryotherapy) to a painful joint has been used for many years in the rehabilitation of patients with OA to relieve pain, stiffness and oedema. Cryotherapy is usually administered by application of cold packs or massage with ice over painful areas or acupoints (56). Cold application helps to reduce pain and swelling by causing temporary vasoconstriction and a reduction in local blood flow. This may in turn help improve range of motion and function (57). Heat therapy is used to reduce pain and stiffness by possibly improving circulation and relaxing muscles. However there are concerns that increased blood flow may worsen inflammation and oedema. 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.

Supporting evidence for the efficacy of this mode of treatment remains very limited. For knee osteoarthritis, ice massage may be a useful adjunct for pain relief and cold packs may be used to lessen knee oedema (Cochrane review of three RCTs in 2003, involving 179 patients) (58). Ice massage for 20 minutes, 5 times a week for 3 weeks had a clinically significant effect on knee strength (29% improvement) with a statistically significant improvement in range of movement (8% relative difference) and function (11% relative

difference) after two weeks of treatment (59) but not at three weeks given three times a week (60). Ice packs did not affect pain significantly compared to controls; however ice massage did have a significant effect. Cold packs also lead to a significant reduction in knee swelling but this has not been seen with hot packs (61). Some studies have shown that heat therapy for knee OA used for 20 minutes every other day for four weeks can significantly improve pain and disability but not stiffness (62). There have been no controlled trials of cryotherapy in hip OA.

There are no experimental studies to examine the role of cryotherapy in hand osteoarthritis. However, a systematic review in 2010 found three studies that had examined the role of heat therapy in 174 patients (63). There is weak evidence for the role of paraffin wax in pain reduction, improved range of movement and function, and moderate level evidence to support the use of low level continuous heat wrap and steam treatments for pain reduction and improved grip strength (64). Local application of heat prior to exercise may be helpful in knee OA; however direct research evidence for the benefit of local application of heat as a pretreatment or in combination with other physical therapies for hand OA is lacking (42).

Although further studies are required to determine their efficacy, heat and cold therapies are easy, non-invasive treatments with very few adverse events, and therefore can be considered as an adjunct to core treatment in hand and knee OA.

2.6 Joint aspiration

Aspiration of synovial fluid from a swollen joint (e.g. aspiration of knee) can provide temporary relief in pain and stiffness, although effusions usually re-accumulate unless steroid is injected. Aspiration of cystic fluid in cystic OA of joints similarly often provides symptomatic relief, but again fluid tends to re-accumulate.

2.7 Intra-articular corticosteroid

Intra-articular (IA) corticosteroid injections have been widely used to treat symptomatic peripheral joint OA for many years. The corticosteroid exerts its anti-inflammatory effect by interrupting the immune and inflammatory cascade at several levels. Local delivery of high doses of corticosteroid minimises systemic toxicity and can result in rapid improvement in symptoms during acute or severe symptom flares, especially in knee and hand OA.

Corticosteroid preparations differ in solubility and potency: more soluble preparations have a shorter duration of action, e.g. hydrocortisone acetate, compared to longer acting emulsion based preparations, which are only slightly soluble, e.g. methlyprednisolone acetate (MPA) or relatively insoluble, e.g.triamcinolone acetonide (TCA). Longer acting preparations are more effective for intra-articular injections as they remain in the joint longer, but there are few randomised, controlled trials comparing different IA corticosteroids. In a double blind RCT of 57 patients with symptomatic knee OA comparing TCA 20mg with MPA 40mg, there was a greater reduction in pain compared with baseline at 3 weeks with TCA compared to MPA, but this was only maintained at 8 weeks in the MPA group despite TCA being less soluble (65). In practice the choice of agent is usually based on local availability and cost. The dose-response relationship has not been systematically studied.

Most manufacturers advise against corticosteroid dilution with local anaesthetic (e.g. lignocaine) because of the risk of clumping and precipitation of steroid crystals. However this remains common practice and provides additional benefits: there is early

temporary relief of symptoms; it verifies delivery of steroid to site of pain (66); and it dilutes the suspension, enabling even distribution within the joint, (especially in shoulder joint injections), and hence avoids placement of highly concentrated fluid into a single area.

Several randomised controlled trials (67-70) and one Cochrane systematic review (71) have shown significant short-term efficacy (between 1 to 4 weeks) in terms of pain reduction for a single IA corticosteroid (TCA, MPA and cortivazol) over placebo in knee OA although effects on function appear less marked. There was no significant benefit at 4 to 24 weeks post injection. Hence IA corticosteroids work rapidly, but the effects are mostly short-lived. The lack of a sustained response over placebo in these studies might relate to lower than recommended steroid doses used, and a strong beneficial effect seen in patients receiving IA placebo injection. In clinical practice, IA steroid injections provide rapid short-term pain relief to settle flares of pain and permit patients to begin other interventions such as quadriceps strengthening exercises.

The benefit of IA corticosteroid injections to the hip remains inconclusive. One small RCT of 35 patients examining the role of TCA in patients awaiting hip replacement showed good pain relief at one month, but this was not maintained, and in 8.5% symptoms deteriorated (72). Another RCT showed significant improvement by IA MPA 40mg at 2 weeks compared with placebo 0.9% saline injection, but efficacy was lost at 3 months (73).

The efficacy of IA 1st CMC joint injection was evaluated in a trial of 40 patients with primary moderate to severe OA, randomized to either 0.25mls TCA (5mg) or an equivalent volume of 0.9% saline. No clinical benefit was gained compared to placebo injection (74). A further prospective study of 30 patients with radiographically staged hand OA has shown long-term benefit (18 months) with a single IA 1st CMC joint injection and subsequent splinting for 3 weeks, in 80% of patients with early radiographic disease i.e preserved joint space and minimal other changes. In patients with more radiographically advanced OA with osteophytes and joint space narrowing, sustained pain relief was less reliably achieved (75).

While IA corticosteroids have marked anti-inflammatory effects and reduce the volume of synovitis in OA (73), disease factors which might relate to the presence of inflammation have not been found to determine clinical response including local heat and synovial thickening (70), and synovial fluid (SF) volume and leucocyte count (69). Furthermore the presence of a knee effusion does not appear to predict response either (67,70). In one study prior synovial fluid aspiration did lead to a greater reduction in pain (69); however this may have been related to less steroid dilution by synovial fluid and more accurate placement of the IA injection confirmed by prior synovial fluid aspiration (76). Hence the presence of a knee effusion is not necessarily an indication for corticosteroid injection unless it causes significant restriction in movement. (22)

Additionally a steroid response is not confined to joints with clinical evidence of inflammation (70). This appears not to be related to inaccuracy in detecting inflammation on clinical examination; a recent ultrasound scanning study showed that patients with non-inflammatory features on ultrasound derived more prolonged benefit compared to patients with inflammatory features (77).

The risks in IA steroid injection are generally small but the following potential side effects can occur: