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Intra-articular Injections for Management of Knee Osteoarthritis

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Abstract

Knee pain is an increasingly common presentation to general practitioners worldwide which is thought to be related to the obesity epidemic, an ageing population and increasingly sedentary lifestyles in more developed nations. Degenerative osteoarthritis (OA) accounts for the majority of presentations in older age groups and this has traditionally been treated with analgesia, lifestyle modifications and adjuncts such as physiotherapy, braces and insoles. All these therapies aim to delay the need of total knee replacement (TKR), which is often the end-point for severe knee OA. However, TKR is associated with poor levels of patient satisfaction, low functional outcomes and has recently been shown to have low levels of cost-effectiveness except in patients with severe disabling OA. Increasingly doctors are turning to intra-articular injections which can provide temporary pain relief such as corticosteroids, hyaluronic acid and platelet rich plasma. This article aims to review the current options for intra-articular injections, comment on their efficacy and suggest areas for future development.

Keywords: Knee; Osteoarthritis; Injections; Steroid; Actovegin; Viscosupplementation

Introduction

Knee pain is an increasingly common presentation within the United Kingdom with recent estimates showing that almost half of over 50 year olds experience knee pain on an annual basis and a third of those present to their General Practitioners for treatment [1]. Osteoarthritis (OA) is the most common cause of knee pain in the older population [2] and the most common cause of chronic disability in any age within the USA [3]. Recent estimates from Arthritis UK project that we will see an increase in the prevalence of knee OA from 4.7 million in 2010 to 6.5 million in 2020[4].They postulate this is likely to be due to a variety of factors such as population expansion, the ageing population and the rising obesity epidemic.

Often the end point for progressive knee OA is Total Knee Replacement (TKR) and the UK National Joint Registry documents over 100,000 TKRs were performed in 2015 alone. Despite the relative frequency of this operation, recent research shows over a fifth of patients are left dissatisfied with their post-surgical outcomes [5] and this figure is higher in younger patient age groups. Younger patients undergoing primary TKR are also far more likely to require revision surgery in the future due to increased demands and expectations following surgery [6]. Furthermore, a recent analysis performed by Ferket et al. found that current practice on TKR operations leads to minimal changes in quality of life and quality adjusted life years, and is only cost-effective in older patients with severe symptoms [7]. For these reasons TKR should ideally be delayed for as long as reasonably possible and initially managed conservatively.

Physical therapies, bracing and lifestyle management are among many of the physical options available [8]. Oral pharmacological strategies such as simple analgesia, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CS) and dietary supplements such as glucosamine are all routinely used in an attempt to control pain [9]. While these approaches may initially be useful and provide adequate pain relief, they may not work effectively for every patient and therefore, other options should be available for more advanced or symptomatic knee OA pain. Another option for pre-operative treatment is the use of intra-articular injections which has attracted increasing levels of interest from clinicians in recent years. his mini-review aims to highlight the variety of substances available for intra-articular injection, the evidence base and rationale behind their use and the treatment efficacy of these options.

Corticosteroids

Corticosteroids were the first substances to be routinely used as intra-articular injections and have been utilized to reduce pain and in lammation within the knee joint. While OA is predominantly thought of as a degenerative process, recent evidence has demonstrated there is a signi icant in lammatory element presents also [10]. Corticosteroids have a broad range of anti-in lammatory properties; however, it is well documented that oral or intravenous doses have a wide range of systemic side-effects such as osteoporosis, weight gain, an increased susceptibility to infections and the development of hypertension and diabetes mellitus [11]. To alleviate this problem, clinicians irst began delivering intra-articular corticosteroids (IACS) in the 1950s and their use has been increasing in conservative management of knee OA ever since [12].

A recent Cochrane review found that IACS do signi icantly reduce the pain on a visual-analogue scale (VAS) by 3 points a ter 1 month of follow-up (scoring system 0-10) [13]. However, the injection of placebo or no injection also led to a reduction of 2 point on the VAS, indicating that the pain reduction may be relatively marginal. IACS also led to a slight improvement in knee functional status compared to placebo/no injection. Berkoff et al. reviewed current practice and recommend the use of ultrasound-guided injections over plain sight. his improved the accuracy of drug delivery into the synovial space and also led to

improvements in patient reported outcomes and cost-effectiveness [14].

The clinician has a variety of options available regarding choice of corticosteroids with hydrocortisone, triamcinolone, methylprednisolone and betamethasone being among the most frequently used in practice [12]. There is a lack of conclusive evidence to suggest the efficacy of one corticosteroid over the other, however a systemic review by Hepper et al. did demonstrate a trend suggesting that triamcinolone leads to a greater reduction in pain scores in comparison to other preparations [15].

Despite the apparent benefits of IACS therapy, the treatment method can also lead to side effects after repeated injection such as cartilage and knee bursa damage – ultimately leading to a worsening of the pathological mechanisms of knee OA and subsequently more knee pain. Several case studies have demonstrated these serious adverse effects [16,17] however these involved very high doses of IACS over long time periods and subsequent reviews have not demonstrated signi icant adverse effects. A review article by Habib found that IACS can also induce signi icant systemic side effects as mentioned above, but clearly to a lesser degree than the oral or intravenous routes [18]. Jüni et al. also state that IACS injections do not lead to signi icant improvements in quality of life indicators and do not possess any disease modifying capabilities such as a reduction in joint space narrowing [13]. Both Bellamey et al. and Jüni et al. found the effect of IACS to be relatively short-lived, with a negligible or no effect on pain reduction between 4-24 weeks a ter treatment [13,19]. For these reasons, it is suggested that IACS only be used as a short term solution for acute lares of knee OA

Viscosupplementation

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan found in all synovial joints. It has a variety of functions within joints such as shock absorption, energy dissipation, lubrication [20] and despite primarily being a structural protein it has also been shown to exert an anti-inflammatory effect [21]. Knees with OA have been shown to be deficient in hyaluronic acid (HA) which is a vital component of the synovial fluid and involved in lubricating all synovial joints [22]. McAlindon et al. also note that introduction of exogenous HA also leads to increased endogenous HA production and the effects continue far beyond the duration of the exogenous administration [23].

Huang et al. found 5 weekly doses of HA improved knee pain and functional status of the affected joint for up to 25 weeks after finishing the treatment course [24], while Foti et al. added there are also significant improvements in range of motion and quality of life [25]. Bannuru et al. investigated the time course of HA action and found it reached peak efficacy at 4 weeks post-injection and continued to confer benefit for up to 24 weeks duration [26]. They commented that while IACS were able to exert a measureable effect on the joint more quickly, the duration of their effects were far less when compared to IAHA injections. In their systematic review Trigkilidas & Anard concluded that HA was a useful adjunct in early to moderate knee OA however the current evidence is not conclusive with regards to treatment [27]. Several studies demonstrated beneficial effects of IAHA treatment, however even the placebo knee arthrocentesis groups experienced significant reductions in pain and improvements in knee function between pre- and post-procedure. They also concluded that IACS were superior to HA injections for up to 4 weeks but after this point HA became more effective due to the longer duration of action. As with all therapeutic interventions, there are risks associated. Rutjes et al. found that use of IAHA was associated with an increased but not statistically signi icant risk of lares of OA pain [28]. Despite these warnings a recent review by Nguyen et al. does advocate the use of IAHA based on recent evidence although it acknowledges opinion is still divided on the matter by various international bodies. Their recommendations are that IAHA is conditionally to fully recommended in individuals non-responsive to traditional oral analgesia and NSAIDs when taking into account the latest evidence [29].

Platelet-rich plasma (PRP

The use of platelet-rich plasma (PRP) injections to treat knee OA has also received an increasing level of interest in recent years. PRP is a blood product which contains a higher than normal concentration of platelets than normal donor derived blood, often by a magnitude of 5 to 10 times greater. It is widely accepted that platelets contain a number of growth factors within their alpha-granule and these have a multitude of functions related to tissue repair [30].

Several recent systematic reviews have been carried out which all suggest potential beneficial effects of PRP. Lai et al. found that regardless of the outcome measure all studies reviewed demonstrated a significant improvement in pain reduction, knee function and quality of life for all knee OA patients involved [31]. Another study found that the median duration of significant symptomatic relief was at 9 months and after this period indicators of pain and loss of function began to rise slowly [32]. Laudy et al. demonstrated that the efficacy if PRP is superior to control groups in terms of pain reduction, though concluded the evidence base was still limited when comparing PRP to IAHA or placebo [33]. The group were unable to pool data regarding functional capabilities due to the presence of significant heterogeneity but unpooled the studies did not indicate significant improvements. The preparation of PRP also varied significantly between studies, both in terms of laboratory preparation and cellular content. It is still unclear as to the optimum preparation and it is likely there be no clear consensus on this matter for the foreseeable future due to this being a relatively new field of study in both animal models and humans.

Additionally, Sanchez et al. recommend the use of a combination of IA and intra-osseous PRP injections for optimal treatment and pain reduction in knee OA [34]. This approach focuses on the subchondral elements of OA such as subchondral cysts and sclerosis which has previously not been targeted by conventional therapies. From the current research it appears that PRP is a safe, relatively low-cost treatment that may be a useful adjunct to treating knee OA. However far more research is necessary to ascertain the efficacy and long-term safety profile of this methodology. While it is highly likely that IA PRP could be a safe procedure due to the autologous harvest of the substance it is impossible to know without high-quality long term observational studies. Few notable side effects have been described in the literature however Ornetti et al. do state a higher level of injection site pain from PRP compared to other intra-articular injections [35].

Novel substances

While corticosteroids, hyaluronic acid and platelet-rich plasma are the most well researched and established agents to treat intra-articular knee OA, this is a field open to a great deal of research in the future. Given the new insights regarding the inflammatory element in the pathophysiology of OA, this provides the opportunity to explore a wide variety of new treatment options which could potentially be

disease-modifying and not just pain relief. Arthritis Research UK has recently received approval to investigate the potential of oral methotrexate for the treatment of knee OA [36]. This could also be investigated via the intra-articular route to allow more direct delivery of the drug. Actovegin is a protein-free haemodiasylate derived from calf blood which has gained interest for the treatment of a variety of acute musculoskeletal injuries [37] and has previously been shown to be safe and effective in a small scale RCT [38], which is another line for future research. With the high levels of circulating pro-inflammatory cytokines within the knee joint in OA, we recommend the joint be pre-treated with arthroscopic lavage prior to injection of pharmacologically active substances. While a Cochrane review found that washout has no significant effect on knee pain compared to placebo as a standalone treatment [39], in theory a reduction in cytokine levels by washout in combination with an active pharmacological agent should have a synergistic and accumulative effect on reduction in knee pain for OA patients. Further studies are needed to investigate this procedure in greater detail.

Conclusion

Current evidence has demonstrated the efficacy of intra-articular injections for pain management in knee OA. Corticosteroids should be used for acute flares of knee OA pain but not for prolonged periods of time due to the possibility of inducing systemic side effects. Viscosupplementation with hyaluronic acid can be a useful adjunct and while it takes longer to exert a measurable reduction in pain when compared to IACS, it has a much longer duration of pain relief. PRP again can also exert effects for up to 9 months following a course of injections with significant improvements in pain scores when compared to controls. The exact mechanism of action of PRP remains unclear and further work should aim to qualify these effects in vitro and in vivo. Severe side effects of these IA injections are all rare and are minimised by keeping clinical practice in line with current guidelines. While these therapies come with merit and do lead to a short-term reduction in pain, no currently available IA injection has been shown to modify the disease process and prevent the eventual need for TKR. This is problematic due to the poor patient satisfaction, outcomes and lack of cost-effectiveness of TKR operations as mentioned previously.

Clearly a multi-disciplinary approach is beneficial for all patients and doctors should involve the wider range of healthcare professional such as physiotherapists, occupational therapists and orthotists in the care of the patient with knee pain. Ideally, the three principal aims of treatment should entail symptomatic relief, disease modification and the prevention of disease progression, resulting in the need for TKR.

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