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Narrative Review

Severe acute localized reactions after intra-articular hyaluronic acid injections: a narrative review and physician's guide to incidence, prevention, and management of these adverse reactions

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ABSTRACT

Introduction: Hyaluronic acids (HAs) are commonly used in osteoarthritis. Whilst adverse events are infrequent, the most common is pain and swelling of the joint.
Objectives and Methods: A narrative review of the incidence and causes of severe acute localized reactions (SALR) with insights into the prevention and management of SALR.
Results: SALR refers to the onset of acute arthralgia, associated swelling, erythema, and motion restriction, after the intra-articular injection of HA. The onset of symptoms is between 4 hours and several days. SALR appears to be immunological responses to the HA and related to poor injection techniques. This literature review identifies that the incidence of SALR following intra-articular injection of HA is relatively low but is not rare. Thus, clinicians using intra-articular HA injections can expect to see patients with SALR and should be prepared to diagnose and treat SALR. The risk of SALR appears to be independent of the source of HA (avian or bacterial fermentation) and the use of crosslinking of the HA product.
Conclusions: Intra-articular HA injections are relatively common treatments for the symptoms of osteoarthritis, where primary interventions have been ineffective. Whilst the risk of complications from such injections is low, both mild and more SALR do occur. The reactions can be mitigated by the careful selection of injection portal and the use of ultrasound guidance. Once the differential diagnosis of septic arthritis is excluded, the management of a SALR will generally consist of reassurance and simple analgesia, with more severe cases requiring nonsteroidal anti-inflammatory medication or intra-articular corticosteroids.
What is known about this topic: Hyaluronic acids have been used in the management of osteoarthritis for over 3 decades. Whilst adverse events are infrequent, the most common is pain and swelling of the joint, which when severe are termed severe acute localized reactions (SALR) or pseudo-sepsis.

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What this study adds: This paper provides the injecting physician with a narrative review of the incidence and causes of SALR, insights into the prevention and a discussion of the management. *How might this affect research practice or policy?:* This information will allow clinicians to mitigate the risks of triggering a SALR and provides a clear pathway for management if such an event occurs. Additionally, it informs the creation of specific policies around the use of HA injections.

Introduction

Hyaluronic acid (HA) also known as hyaluronan, and its associated derivatives have been used as part of the management of osteoarthritis, particularly osteoarthritis of the knee, for over 3 decades.[1] Adverse reactions relating to the injection of HA into joints have been reported as being as low as 3.7% and as high as 8.5%.[2,3] Notably in placebo-controlled trials the rates of adverse events from HA injection are the same as that of the placebo group.[1] Perhaps the most common adverse event a physician is likely to encounter is pain and swelling of the joint, which varies in severity from mild pain requiring little more than expectant recovery to more severe reactions, termed severe acute localized reactions (SALR) or pseudo-sepsis.[4,5]

This paper provides the injecting physician with a review of the incidence and postulated causes of SALR, insights into the prevention of these adverse events and a discussion of the management of these events. Figure shows the flowchart of the prevention and management of the SALR after intra-articular HA injection.

Background

HA is member of the glycosaminoglycan family and the most significant component of normal synovial fluid. It provides mechanical attenuation of shear and compressive forces within the joint. In normal synovial fluid, it has a molecular weight of 5000 to 7000 kDa. It is composed of D-glucuronic acid and d-N-acetylglucosamine molecules which are bound by glycosidic bonds to form a repeating disaccharide polymer chain, thousands of these molecules binding together to form a random coiled structure. This coiled structure can bind to other HA chains, to water and to other molecules. Its physical characteristics, particularly its viscosity, change according to the size of the macromolecule. Although its main role is related to its hydrogel properties, it additionally has molecular

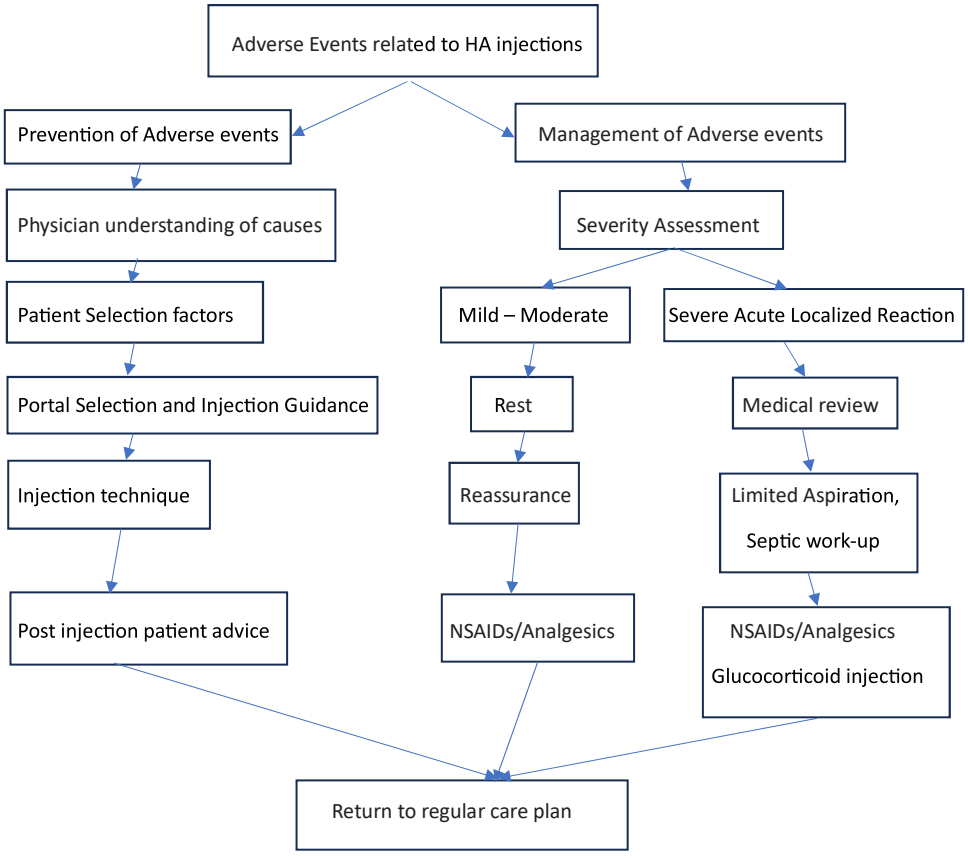

Fig.. Hyaluronic acid injection adverse event flowchart. HA, hyaluronic acid; NSAIDs, nonsteroidal anti-inflammatory drugs.

biological actions which reduce inflammation, provide chondroprotection, and up-regulate repair. These effects appear principally related to the binding of CD 44 and other cell surface receptors to high molecular weight HA.[6–17]

Changes to HA have been described in the synovial fluid of patients with joint disease such as osteoarthritis. In the disease state, the critical change was a drop in the mean concentration of HA, with a modest drop in the mean molecular weight also being noted.[18] The smaller native HA fragments typically seen in the presence of osteoarthritis are proinflammatory.[7] Exogenous HA injection has been used in patients with osteoarthritis, bringing more normalized HA to the local environment. Its structural susceptibility to shear forces means that a relatively viscous gel can still be delivered through a needle.[19] HA injections have been demonstrated to reduce pain, improve function, protect articular cartilage, and delay total arthroplasty surgery.[20–23] It is beyond the scope of this review to discuss the literature concerning the efficacy of HA in more detail.

Despite exogenous HA being derived from a natural source, some patients develop pain and swelling post-intra-articular injection. It has been postulated this may be related to the chemical composition of the exogenous HA used. The most frequent sources of HA for use in osteoarthritis are purified avian HA and microbial fermentation by streptococci bacteria,[24] the majority of products currently on the market being bacterial fermentation-derived products.[11] In some HA products the molecules are cross-linked to create higher molecular weight molecules.[19] There are a variety of methods for achieving cross-linking including the use of formaldehyde, divinyl sulfone, 1,4-butanediol diglycidyl ether, and other agents. Cross-linking is achieved by interactions with the hydroxyl groups on the repeating disaccharide units and remains an area of active research.[11,25] Cross-linked products have the apparent advantage of a longer intra-articular half-life and hence longer duration of action per injection.[26] There is evidence as to the superiority of outcomes with cross-linked products.[27]

SALR is a descriptive term encompassing pain, swelling, erythema, and at times motion restriction in the injected joint, beyond what one would expect from the discomfort caused by the needle trauma of an injection. Generally, it will commence within 4 to 12 hours but has been described up to a few days postinjection. In the author's experience, it appears clinically to be a continuum effect with most affected individuals experiencing mild to moderate symptoms and fewer individuals experiencing severe symptoms that interfere with normal activities of daily living, including difficulty with ambulation. This has variously been described in the literature as SALR, acute aseptic synovitis or pseudo-sepsis.[4,28] SALR does not encompass the rarely reported complications of Nicolau syndrome, livedo racemosa, livedo reticularis, and necrotizing fasciitis, or anaphylaxis.[3,29–31]

SALR may be triggered either by accidental placement of HA into soft tissue (particularly muscle, synovial membrane, and intra-articular fat pad) rather than joint space[28,32] or via an immunological response. Both could trigger the typical synovitic picture of a SALR. Some early reports of reactions to HA injections raised the possibility that the source of HA (avian vs bacterial fermentation) or the use of cross-linking might increase the likelihood of adverse reactions[28,33] and a 2007 meta-analysis[34] found an increased risk of adverse reactions in cross-linked products. Subsequent publications including a well-designed blinded head-to-head trial of avian vs bacterial derived HA,[35] a data set analysis of almost 700,000 HA injections looking at surrogate measures of SALR[5] and a systematic review and network meta-analysis of some 13,000 patients[3] have shown minimal or no difference in the risks of adverse effects within the various HA products, or between HA products and intra-articular placebo.

Management of a SALR

Some general considerations prior to injection of HA should include allergy history, particularly whether the patient has a known allergy to HA products, and in the case of avian-derived HA to avian proteins, eggs, or feathers.[36] A note should be made of the patient's preference for the use of local anesthesia for the procedure. Suitable postinjection advice would include the option of using ice and analgesics as necessary for pain, as well as the need to avoid strenuous activity for 2 days.[36,37] Given that HA is cleared from joints via the synovial membrane into the lymphatics,[38] it is advised to aspirate any effusion immediately prior to injection of HA.[36,37] This same lymphatic clearance mechanism informs the general advice to avoid vigorous activity for 48 hours postinjection.

A key consideration when managing a SALR is what alternative diagnoses could present in this fashion; the main differentials being joint sepsis and acute pseudogout. In terms of likelihood, a SALR is several orders of magnitude more frequent than iatrogenic septic arthritis.[2,39] Acute pseudogout generally presents as a painful swollen joint and pseudogout crystals have been seen in the joint aspirate of some patients with a SALR. It is unclear if this finding means that HA injection is a risk for triggering pseudogout.[28,40,41] The early management of a SALR will to some degree revolve around the severity of the reaction, the confidence of the treating physician regarding the diagnosis and the relative risk profile of the patient (where increasing age and comorbidity indices indicate greater risk of joint sepsis).[42] If the patient has an early onset of relatively modest symptoms and is systemically well then expectant management including rest, and nonsteroidal anti-inflammatories or simple analgesics would be appropriate. In the author's experience, when faced with a tense painful swelling, a limited joint aspiration can relieve pain without significantly compromising the volume of exogenous HA. If the onset of symptoms was delayed by some days, if the reaction was severe, if the patient had systemic symptoms or was in a higher risk profile group then a blood and synovial fluid workup would be appropriate.[42] On occasion, once sepsis has been excluded, intra-articular injection of glucocorticoids may be required.[4,28] The management of septic arthritis, should it be identified, is beyond the scope of this discussion, excellent recent clinical guidelines are available.[43]

Reducing the risk of a SALR

SALR and injection technique

There are a number of things to consider in terms of injection technique and minimizing the risk of a SALR. The first of these is whether the injection is performed via palpation guidance or using ultrasound guidance. Effective ultrasound guidance of joint injection is

predicated on a combination of an excellent knowledge of sonographic anatomy, and good technical skills. There is level 1 evidence that palpation guidance, even in the hands of an experienced clinician, is less accurate than an inexperienced clinician using ultrasound guidance.[44] Using ultrasound guidance may however increase the cost of the procedure. A second practical consideration is which injection portal to use. Use of the supralateral patellar portal in the knee has been shown to be most likely to result in intra-articular placement,[44] but ideally, the clinician will have more than one approach in their skill set. HA is a large molecule that is not easily redistributed, its clearance is via the venous and lymphatic system.[38] If it is placed in one of the highly innervated tissues such as the fat pads or synovium of the knee this is likely to cause acute mechanical discomfort, and possibly movement restriction.[32] It is likely this mechanism will also trigger cytokine release and provoke a SALR. In the author's experience not priming the needle with HA assists with avoiding inadvertent injection of fat pads and synovial tissue. If the patient experiences significant pressure or pain as the injection is commenced this should be considered a relative indication that the needle tip is not intra-articular, repositioning the needle is advisable.[37]

It is probable that the injection of HA intra-articularly cannot be considered in the same way as a less viscous injectate such as local anesthetic. A combined cadaver and randomized controlled trial (RCT) study examined the distribution of HA injected via the medial midpatellar portal and via the anteromedial portal (an infrapatellar approach). Using the medial midpatella portal resulted in HA coverage of 96% of the patellofemoral chondral surface and 71% of the medial tibiofemoral joint, using the anteromedial portal the HA was distributed similarly in the medial tibiofemoral joint but significantly less in the patellofemoral joint.[45] The RCT portion of the study reported that use of the medial mid patella portal resulted in better Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Lequesne total index scores over the entire follow-up period.[45] Use of the infrapatellar portals can also result in inadvertent injection of menisci or cruciate ligaments, a recently described ultrasound guidance approach may mitigate this risk.[32] Minimum effective needle length is a further consideration for avoiding fat pad injection if using the infrapatellar portal.[46] In general, the viscosity of single-dose HA preparations means that a 21- or 22-gauge needle is required, for lower viscosity HA smaller gauge needles may be suitable.[19]

SALR and immunological response

A number of case reports have identified immunological markers related to SALR. These include elevated C-reactive protein, elevated erythrocyte sedimentation rate,[47,48] histiocytic giant cell reactions in the synovium related to HA confirmed on biopsy,[33] and elevated leukocyte counts (predominantly monocytes and neutrophils) in the synovial fluid.[28] Of note a small number of cases have reported elevated eosinophil counts in synovial fluid which would imply previous exposure to the triggering substance.[49] There is significant disagreement as to whether there is a greater risk of SALR with second and subsequent treatment courses.[28] In the experience of 2 of the authors further injections of the same HA product into a patient who has experienced a SALR has not provoked a further SALR suggesting that not all SALRs are immunologically triggered. Other possible risk factors for SALR would include transport or storage of an HA product outside of the manufacturer's recommendations.[36,37]

Conclusion

Intra-articular HA injection is a relatively common treatment for osteoarthritis and the risk of complications related to the procedure and injected product is low. The well-reported complication of SALR may be triggered by extrasynovial placement of the HA or via an immunological mechanism. The risk of a SALR appears to be independent of the HA formulation used. Careful selection of an appropriate injection portal, a good knowledge of sonoanatomy when using ultrasound guidance, and injection technique are likely to influence the risk of SALR. Once other possible diagnoses have been ruled out, a SALR can usually be managed with patient reassurance and simple analgesia, a small proportion of cases will require active intervention including anti-inflammatory medication.

It should be noted that this is a narrative review developed from available research and the authors personal experience.

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Ethics approval

Complete informed consent was obtained from the patient for the publication of this study and accompanying images.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jane Fitzpatrick reports a relationship with Bioventus Coöperatief UA that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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