EXECUTIVE SUMMARY

(Adapted from the report by AIDATUL AZURA ABDUL RANI and KHAIRIL IDHAM ISMAIL)

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Background

The substantial impact of joint disorders on individuals' daily lives and the significant burden they impose on healthcare systems globally are undeniable. Joints play a vital role in facilitating movement, and chronic pain conditions affecting those present significant challenges in treatment and rehabilitation. The International Classification of Diseases (ICD-11) defines chronic pain as pain persisting beyond three months, with prevalence rates ranging from 11% to 40%. Musculoskeletal conditions, including back pain, musculoskeletal disorders, and neck pain, are major contributors to this burden. According to Global Burden of Disease (GBD) 2019 data, approximately 1.71 billion people globally live with musculoskeletal conditions. Osteoarthritis affected about 528 million people worldwide in 2019, marking an increase of 113% since 1990. This condition commonly affects joints such as the knees, hips, spine and small joints in the hands, impacting the surrounding muscles and tissues.

While conservative management strategies are often recommended, hyaluronic acid (HA) injections have emerged as potential intervention to alleviate symptoms across various joints. Hyaluronic acid has been explored as adjunct therapies, particularly in cases where conservative approaches are indicated. Although evidence suggests potential benefits, cautious interpretation is warranted due to variations in treatment response and the need for skilled administration by healthcare practitioners. This technology review focuses on five joint disorders affecting the spine, shoulder, hip, knee, and ankle. Recognising the widespread use of HA injections and the increase number of private practice clinicians offering this treatment for various joint disorders, the Director of Medical Practice Division, Ministry of Health Malaysia (MOH), requested this technology review to evaluate the effectiveness and safety of hyaluronic acid injections.

Objective

To assess the effectiveness, safety and economic implications of hyaluronic acid injection in the treatment of joint disorders affecting the spine, shoulder, hip, knee, and ankle among the adult population.

Results and conclusion:

A total of 10,284 records were identified through database searches. After screening and full-text assessment, 44 studies were included in the review. These comprised systematic reviews with network/meta-analyses, randomised controlled trials, prospective clinical trials, and other study designs, conducted across Asia, Europe, North and South America.

Effectiveness

The evidence indicates that HA injections offer short-term (less than 6 months) relief in pain and improved joint function for several disorders, particularly when combined with physical therapy or rehabilitation. Key findings include:

(a) Disorders of the spine, shoulder, hip, knee and ankle

i. **Spinal conditions** (lumbar spinal stenosis and radiculopathy): HA-CMC injections showed some early benefit but were not superior to corticosteroids beyond the initial few weeks.

ii. **Shoulder disorders** (rotator cuff tears, rotator cuff tendinopathy, adhesive capsulitis, and supraspinatus tendinitis and tendinosis): HA injections may improve pain and range of

motion in the short-term but these effects were not sustained as long-term functional benefits.

iii. **Knee conditions** related to tendinopathy or chondropathy: Demonstrated consistent short- and long-term benefits in pain reduction and function. However, no benefit was observed for ligament or meniscal injuries.

iv. **Ankle tendinopathies**: Short-term pain relief was observed, especially with high molecular weight HA formulations.

v. **Hip-related conditions:** No retrievable evidence was found to support the effectiveness of HA injections in managing hip-related conditions.

(b) Osteoarthritis of the shoulder, hip, knee and ankle

i. **Glenohumeral (shoulder) osteoarthritis**: IAHA may offer short-term relief, especially when combined with physical therapy. For patients with mild to moderate shoulder OA, these benefits may sustained over the long-term.

ii. **Knee osteoarthritis (OA)**: HA treatments provided good short-term relief but lacked the long-term effectiveness offered by PRP injections. PRP injections when used as comparator demonstrated superiority over IAHA, sustaining pain relief, functional improvement, and reduction in stiffness in both short-term and long-term durations.

iii. **Hip and ankle OA**: Limited or no clinical benefit observed with HA injections.

Safety

Hyaluronic acid injections are generally safe and well-tolerated. Most adverse events were mild and self-limiting (e.g., swelling, injection site pain). However, serious adverse effects such as severe musculoskeletal pain and rare events like abscesses and malignancies were reported in some studies, particularly in glenohumeral OA. The choice of HA formulation and patient characteristics should guide clinical decision-making.

Organisational

Hyaluronic acid (HA) injections are usually performed in outpatient settings by trained practitioners, often utilising image-guided techniques to ensure accuracy and safety. The duration of follow-up varied across studies, with most reporting more favourable outcomes in the short term. Patient satisfaction was generally highest around 12 weeks post-injection. In Malaysia, HA products used are registered with the Medical Device Authority, reflecting adherence to national regulatory standards for safety and quality.

Economic Implications

In the U.S., average reimbursement costs for HA injections ranged from USD 422 to 602, varying by insurance type. While specific local cost data is lacking, these figures highlight the potential financial burden for both payers and patients, especially if multiple injections are required.

Conclusion

There is moderate evidence that HA injections are effective in reducing pain, improving functionality, increasing range of motion, and enhancing quality of life, for conditions such as rotator cuff tears, adhesive shoulder capsulitis, knee tendinopathies and chondral injuries, ankle tendinopathies, and mild to moderate glenohumeral OA, especially when combined with rehabilitation. However, these benefits

are short-term and not sustained beyond six months. Current evidence do not support the superiority of HA injections over other treatments such as corticosteroids or PRP.

For knee OA, HA injections provide short-term symptom relief but lack the long-term effectiveness offered by PRP injections comparatively. There is insufficient evidence to support the use of HA injections for hip and ankle OA, knee ligament or meniscus injuries, and rotator cuff tears. In spinal applications, the role of HA-CMC remains inconclusive due to limited and low-quality data.

Clinical guidelines provide varying recommendations for HA use, with several suggesting limited or no benefit for conditions such as rotator cuff tears, glenohumeral joint OA, and osteoarthritis of the hip and knee. Although HA injections are generally well-tolerated, caution is warranted in specific conditions like glenohumeral OA due to the potential for serious adverse events. It is advisable that these injection to be performed by practitioners with specialised skills and experience.

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® ALL 1946 to October 6, 2023, EBM Reviews - Cochrane Central Register of Controlled Trials September 2023, EBM Reviews - Database of Abstracts of Reviews of Effects - 1st Quarter 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 1, 2023, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in Pubmed, US FDA and INAHTA websites. Google was used to search for additional web-based materials and information. The search was limited to articles on human. There was no language limitation in the search. Additional articles were identified from reviewing the references of retrieved articles. The last search was conducted on 8th November 2023.