TITLE: Viscosupplementation for the Treatment of Osteoarthritis of the Knee: Clinical Effectiveness and Guidelines

DATE: 13 February 2014

RESEARCH QUESTIONS

1. What is the clinical effectiveness of viscosupplementation for the treatment of patients with osteoarthritis of the knee?

2. What are the evidence-based guidelines regarding viscosupplementation for the treatment of patients with osteoarthritis of the knee?

KEY MESSAGE

Nine systematic reviews and eight evidence-based guidelines were identified regarding viscosupplementation for the treatment of patients with osteoarthritis of the knee.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and January 30, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are

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presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Nine systematic reviews and eight evidence-based guidelines were identified regarding viscosupplementation for the treatment of patients with osteoarthritis of the knee. No health technology assessments were identified. Due the large volume of high quality evidence identified, the twenty-five randomized controlled trials were placed in the appendix and non-randomized studies were not included.

**OVERALL SUMMARY OF FINDINGS**

Of the nine systematic reviews (SR) identified, five SRs indicated some benefit regarding the use of intra-articular hyaluronic acid (IAHA) for the treatment of knee osteoarthritis (OA), whereas the other four SRs did not identify any benefit. In the SRs identifying benefits, IAHA was noted to be most efficacious around eight weeks. Prolonged effects of IAHA were observed in studies that compared it to other active treatments, particularly intra-articular corticosteroid injections. In the SRs that observed no benefits of IAHA for knee OA, one highlighted a particularly large placebo effect which appeared to skew the IAHA effectiveness, while another noted that probable industry bias swayed results in favour of IAHA. The other two SRs observed no clinical benefit; however, it was proposed that IAHA could be an alternative to non-steroidal anti-inflammatory drugs in older populations at risk for adverse events, due to its comparable favourable safety profile.

Three of the identified guidelines do not recommend IAHA for the treatment of knee OA and another does not include any conclusive recommendations. Of the four guidelines that recommend IAHA use for knee OA, one conditionally recommends IAHA for patients with inadequate response to initial therapy, another recommends IAHA use for moderate to severe knee OA (noting this was based on consensus only), and the other two guidelines provide algorithms for IAHA use.

Details of study characteristics, conclusions, and limitations (if available) are provided in Table 1.

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<thead>
<tr>
<th>Author, Year</th>
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<td><strong>Systematic Reviews and Meta-Analyses</strong></td>
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| Bannuru et al., 2013 | ● 5 included trials  
● N=712  
● IAHA vs NSAIDs | ● Meta-analysis suggested no significant differences between IAHA and oral NSAIDs at 4 & 12 weeks  
● IAHA had favourable safety profile over NSAIDs & this result might be viable alternative for knee OA; particularly in older patients at risk for AE | Included trials had short follow-up |
| Miller et al., 2013 | ● 29 included studies  
● N=4,866 (n=2,673 IAHA; n=2,193 saline)  
● IAHA vs saline | ● In patients with symptomatic knee OA, US approved IAHA products are safe and efficacious  
● No significant differences in safety outcomes | NR |
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<td>Printz et al., 2013</td>
<td>48 studies: ◦ 30 (60.5%) industry funded ◦ 3 (6.25%) not industry funded ◦ 15 (31.3%) did not identify funding source</td>
<td>• No study with reported financial COI (of at least 1 author) had unfavourable conclusion&lt;br&gt;• 11 (35%) of 31 studies with no confirmed industry-affiliated, author indicated that IAHA was not more effective than PL injection</td>
<td>NA</td>
</tr>
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<td>Trigkilidas and Anand, 2013</td>
<td>14 included studies</td>
<td>• IAHA had modest effect on early to moderate OA&lt;br&gt;• Effect of IAHA peaks around 6-8 weeks; doubtful effects at 6 months</td>
<td>NR</td>
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<td>Cheng et al., 2012</td>
<td>NR</td>
<td>• Strong evidence supported the use of IAHA in the management continuum of OA (between conservative treatment and knee surgery)</td>
<td>NR</td>
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<td>Colen et al., 2012</td>
<td>74 included randomized controlled trials IAHA vs PL (saline) injection&lt;br&gt;• IAHA vs other hyaluronic acid products</td>
<td>• Difference in efficacy between IAHA and PL injection not large and might not have met the MCID&lt;br&gt;• Large PL effect (~30% pain reduction for ≥3 months)&lt;br&gt;• Unable to conclude that one hyaluronic acid product was better than others</td>
<td>• Heterogeneity of studies&lt;br&gt;• Large PL effect</td>
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<td>Rutjes et al., 2012</td>
<td>89 included studies&lt;br&gt;• N=12,667</td>
<td>• IAHA was associated with a small and clinically irrelevant benefit&lt;br&gt;• IAHA also associated with increased risk of SAE</td>
<td>• Important between-trial heterogeneity and an asymmetrical funnel plot (trial size, blinded outcome assessment, and publication status were associated with effect size)&lt;br&gt;• Trial quality generally low&lt;br&gt;• Safety data were often NR</td>
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<td>Bannuru et al., 2009</td>
<td>7 included trials&lt;br&gt;• N=606&lt;br&gt;• IAHA vs IACS</td>
<td>• Between 0-4 weeks, IACS appeared more effective for pain than IAHA&lt;br&gt;• IACS and IAHA were equally effective at week 4&lt;br&gt;• IAHA appeared to have greater efficacy &gt;8 weeks</td>
<td>NR</td>
</tr>
<tr>
<td>Bellamy et al., 2009</td>
<td>IAHA vs IACS&lt;br&gt;• Other comparisons NR</td>
<td>• IAHA found to be comparable in efficacy to systemic forms of</td>
<td>• Safety analysis was not</td>
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### Table 1: Summary of Systematic Reviews, Meta-Analyses, and Guidelines

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<td>active intervention</td>
<td></td>
<td>• IAHA had more local reactions but fewer systemic AEs</td>
<td>commented on due to sample size restrictions</td>
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<td>McAlindon et al., 2014</td>
<td>10 countries (US, UK, France, Netherlands, Belgium, Denmark, Sweden, Australia, Japan, Canada) consensus recs  ● Recs graded as: Appropriate, Uncertain, or Not Appropriate</td>
<td>● Rec: Uncertain appropriateness of IAHA for knee OA</td>
<td>NR</td>
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<tr>
<td>AAOS, 2013</td>
<td>Evidence-based recs with grading: Strong, Moderate, Limited, Inconclusive, Consensus</td>
<td>● Rec #9: Strong: the WG cannot recommend the use of hyaluronic acid for patients with symptomatic knee OA</td>
<td>NR</td>
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<td>Hochberg et al., 2012</td>
<td>Update to the 2000 ACR recs for knee OA  ● Grading includes either Strong or Conditional recs  ● Based on consensus judgement/available evidence/balancing benefits and harms</td>
<td>Conditionally recommended IAHA for knee OA in patients with inadequate response to initial therapy (including oral and topical NSAIDs, tramadol, and IACS)</td>
<td>NR</td>
</tr>
<tr>
<td>ACOEM, 2011</td>
<td>Current release of guideline; updated from 2004 guidelines  ● Grading includes: Strong, Moderate, Limited, and Insufficient Evidence</td>
<td>IAHA recommended for moderate to severe knee OA (Recs are consensus-based)</td>
<td>NR</td>
</tr>
<tr>
<td>WLDI, 2011</td>
<td>Updated version of guideline  ● Number of source documents NR</td>
<td>IAHA can decrease symptoms of knee OA  ● ODG Return-To-Work Pathways: IAHA for 7 days</td>
<td>NR</td>
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<tr>
<td>Zhang et al., 2010</td>
<td>OARSI updated version  ● 64 SRs, 266 randomized controlled trials, and 21 economic evaluations published between 2006 and 2009</td>
<td>Effect sizes for pain relief from IAHA diminished  ● No rec provided in abstract</td>
<td>Effect sizes for IAHA diminished and there was greater heterogeneity and publication bias found in evidence</td>
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<tr>
<td>NHMRC, 2009</td>
<td>Includes evidence published from 2005-2007  ● Rec grades: A, B, C, D  ● Algorithms provided</td>
<td>There is some evidence that IAHA may provide some benefit for knee OA  ● Algorithm: IAHA for knee OA for patients with moderate-severe persistent symptoms in whom mild-moderate strategies have</td>
<td>Literature search not designed to identify safety trials; thus this guideline does not provide full safety or usage information on drug</td>
</tr>
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| AHRQ, 2009   | ● Guidelines summarize the effectiveness and safety of IAHA for knee OA  
               ● Graded using a Confidence Scale: High, Medium, Low | ● Any clinical improvement from IAHA is likely small and not clinically meaningful (Medium) | ● Insufficient evidence to demonstrate clinical benefit for higher molecular weight products  
               ● Insufficient evidence to determine whether AEs are associated with repeat injections  
               ● Clinical trials comparing IAHA to PL have yielded inconsistent results |
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses


Viscosupplementation for the Treatment of Osteoarthritis of the Knee

2009 summary based upon a 2006 Cochrane report

Guidelines and Recommendations


See: Recommendation 9


See: Table 2 Summary of Recommendations for Managing Knee Disorders

See: Recommendations Section; Arthritis


See: Hip/knee osteoarthritis management flow chart (algorithm), pg. 15
Recommendation 26 – Viscosupplementation for Knee OA (Grade C), pg. 18, 39-40

See: Clinical Bottom Line and Viscosupplementation

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APPENDIX – FURTHER INFORMATION:

Randomized Controlled Trials


PubMed: PM19304567

PubMed: PM20447955

PubMed: PM20467406

PubMed: PM20151251

PubMed: PM19539353

PubMed: PM20023357

PubMed: PM19337810

PubMed: PM19380288