



A protocol for developing a clinical practice guideline for intra-articular injection for treating knee osteoarthritis



Dan Xing^a, Bin Wang^a, Yunfei Hou^a, Ziyi Yang^a, Yaolong Chen^{b,c,**}, Jianhao Lin^{a,*}

^a Arthritis Clinic & Research Center, Peking University People's Hospital, Peking University, Beijing 100044, China

^b Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Gansu 73000, China

^c Chinese GRADE Center, Gansu 73000, China

ARTICLE INFO

Article history:

Received 14 September 2017

Accepted 19 September 2017

Available online 15 November 2017

Keywords:

Osteoarthritis

Clinical practice guideline

Intra-articular injection

Protocol

ABSTRACT

Introduction: Osteoarthritis (OA) is the most prevalent disorder of articulating joints in humans. As one of the steps of advanced pharmacological management, intra-articular treatment is applied in knee OA. However, there is no clinical practice guideline (CPG) involving intra-articular injection for knee OA. Here, we will develop a CPG according to a recognized methodology.

Methods and analysis: We will develop the new CPG according to the Institute of Medicine, the Appraisal of Guidelines for Research & Evaluation II (AGREE II), and WHO guideline handbook and make recommendations based on systematic reviews. We will establish a Guideline Working Group (including a Guideline Steering Subgroup, a Guideline Development Subgroup, and a Guideline Secretary Subgroup); formulate clinical questions in the form of Population, Intervention, Comparison, Outcomes (PICO); and complete a literature search. The consensus will be developed through evidence syntheses and the Delphi method. We will also consider patients' values or preferences, peer review results, and declaration of interests in developing CPG. The present CPG was registered on the International Practice Guidelines Registry Platform (<http://www.guidelines-registry.org/>), and the registration number is IPGRP-2016CN004.

Ethics and dissemination: The protocol will provide us a roadmap to systematically develop evidence-based CPG for intra-articular injection for knee OA. The work will be disseminated electronically and in print. The guideline would be the first CPG that is developed primarily by orthopedic specialists in China and strictly based on systematic methodology.

© 2017 The Authors. Published by Elsevier Ltd on behalf of Surgical Associates Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Background

1.1. Description of condition

Osteoarthritis (OA) is the most prevalent disorder of articulating joints in humans and represents a major burden on public health worldwide [1–4]. It results in disability among older people. In epidemiology, half of the world's population aged 65 years or older has OA. Specifically, knee OA involves the largest synovial joints in human, which is prevalent in middle-aged or older people [5]. In estimate, the prevalence of knee OA is more than 250 million patients worldwide [6]. Knee OA involves pathological features

such as cartilage degeneration, bone remodeling, and inflammation. The clinical features of knee OA is mainly characterized by pain, swelling, and joint dysfunction [7]. The symptomatic knee OA affects 24% of the general population [8]. Furthermore, symptomatic knee OA may be associated with an increased risk of all-cause mortality [9–11]. Thus, the purpose of the treatment for knee OA is to alleviate pain and to improve joint function and quality of life.

1.2. Description of interventions

A large number of primary studies were conducted to evaluate knee OA treatments in nonpharmacological, pharmacological, and surgical therapy [12]. However, many limitations such as study design, risk of bias, sample size and individual characteristics hindered the transformation from literature to practice. Therefore, recommendations for the treatment of knee OA have been developed by academic societies including the American Academy of

* Corresponding author at: Arthritis Clinic & Research Center, Peking University People's Hospital, Peking University, Beijing 100044, China.

** Co-corresponding author at: Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Gansu 73000, China.

E-mail addresses: linjianhao@pkuph.edu.cn (J. Lin), yaolongchen21@163.com (Y. Chen).

Orthopaedic Surgeons (AAOS) [13], the UK National Institute for Health and Care Excellence (NICE) [14], the Osteoarthritis Research Society International (OARSI) [12], the American College of Rheumatology (ACR) [15], and the European League Against Rheumatism (EULAR) [16]. However, Feuerstein et al. [17] used the AGREE II instrument to assess the quality of 13 guidelines and concluded that the lowest score was recorded in the domains of comment on conflicts of interest. Thus, optimal clinical practice guidelines (CPGs) are defined as recommendations that are informed by an evaluation of evidence, a development of recommendation strength, and an assessment of the benefits and harms of alternative care options by the Institute of Medicine (IOM) [18]. Unfortunately, the Chinese medical evidence was not evaluated or used in the aforementioned guidelines. Furthermore, no evidence-based guideline for knee OA was currently developed in China.

1.3. Description of intra-articular interventions

As one of the steps of advanced pharmacological management in persistent symptomatic OA patients, intra-articular treatment may be applied in a condition that contraindicates the use of NSAIDs or if the patient is still symptomatic despite the use of NSAIDs or was severely symptomatic [19]. Traditionally, hyaluronic acid (HA) and corticosteroids have been the most commonly used intra-articular interventions [20]. Recently, regenerative medicine products including mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), autologous conditioned serum (ACS), and other agents such as intra-articular morphine present promising outcomes in the treatment of knee OA.

1.4. Why is it important to develop this CPG?

However, there was no CPG involving intra-articular injection for knee OA. Therefore, we aimed to develop a practical and applicable CPG for the intra-articular injection for knee OA using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [21] to provide evidence-based recommendations regarding intra-articular injection to clinicians, nurses, and patients.

2. Objectives

The protocol will provide us a roadmap to systematically develop an evidence-based CPG for the intra-articular injection for knee OA. The guideline would be the first CPG developed primarily by orthopedic specialists in China, strictly based on the IOM's new guideline definition, World Health Organization (WHO) guidelines making handbook, GRADE system, AGREE II instrument, and RIGHT statement. The guideline will provide standards for treating knee OA and will help perform intra-articular injection.

3. Methods

3.1. Principle

The CPG will be developed following the new guideline definition from the IOM [18] and AGREE II instrument [22]. We also adhere to the WHO handbook for guideline development [23]. We have registered the guideline on International Practice Guidelines Registry Platform (<http://www.guidelines-registry.org/>), and the registration number is IPGRP-2016CN004.

3.2. Guideline development institutions, target users, and population

The guideline was launched at the 11th COA International Congress in Beijing by the Chinese Orthopedic Society, Chinese Orthopedic Journal, and Arthritis Clinic & Research Center, Peking University People's Hospital in November 2016. Methodological support will be provided by the Chinese GRADE Center. The title of the guideline will be "guideline for the intra-articular injection for knee osteoarthritis." The target end users of the guideline are orthopedists, physical therapists, rheumatologists, and nurses. The target populations are patients with knee OA who could be treated with intra-articular injection. The content of the guideline is about the clinical safety and efficacy of medicine products through intra-articular injection.

3.3. Guideline working group

The Guideline Working Group will be established in December 2016, and it will have three subgroups: the Guideline Development Group, the Guideline Steering Group, and the Guideline Secretary Group. To ensure fair representation by gender and region, the Guideline Working Group will comprise 30 members from multiple fields, as follows: 17 orthopedists (especially who majored knee joint surgery), 2 rheumatologists, 1 physical therapist, 2 evidence-based medical experts, 2 medical laboratory scientists, 2 pharmacologists, 1 statistician, 1 health economist, 1 Chinese medicine practitioner, and 1 nurse. The proportion of females will be not less than 10%. The following items will be the mission of the Guideline Development Group: (1) to define the scope of the guideline, draft the Population, Intervention, Comparison, Outcomes (PICOs); (2) to grade the quality of the evidence; (3) to draft preliminary recommendations; (4) to write the draft guideline; and (5) to publish and promote the guideline.

The Guideline Steering Group comprised 8 members, including 3 orthopedists, 1 evidence-based medical expert, 1 rheumatologist, 2 physical therapists, and 1 health economist physician. The following items will be the mission of the Guideline Steering Group: (1) to approve the PICOs; (2) to supervise the literature search and systematic reviews; (3) to check the grade of the evidence; (4) to draft the final recommendations using the modified Delphi approach; and (5) to approve the publication of the guideline.

The Guideline Secretary Group will comprise 6 members, including 3 evidence-based medical experts, 1 statistician, and 2 orthopedists. The following two items will be the mission of the Guideline Secretary Group: (1) to perform a literature search and complete systematic reviews and (2) to investigate patients' views and preferences.

3.4. Declaration of interests and funding support

All members of the Guideline Development Group, the Guideline Steering Group, and the Guideline Secretary Group will be required to complete declaration of conflicts of interest forms before attending the guideline meetings to judge their potential conflicts of interest.

3.5. Formulating questions and choosing outcomes

After the scope of guideline is proposed by the Guideline Development Group and approved by the Guideline Steering Group, we will finalize the PICOs. The Guideline Development Group will choose the clinical outcomes and classify them according to their importance by consensus. The scores of the outcomes range from 1 to 9. According to this scale, 7–9 will be considered critical, 4–6 important, and 1–3 not important [21]. After rating the clinical

outcomes, we will formulate the clinical questions according to the PICO principle.

For example:

Does HA intra-articular injection can be used for symptomatic knee OA patients?

P: all patients with symptomatic knee OA;

I: patients who receive HA intra-articular injection;

C: patients who do not receive HA intra-articular injection;

O: VAS scale, WOMAC, SF-36, and adverse effects.

3.6. Evidence retrieval and synthesis

3.6.1. Databases

We will systematically review the literature (until Dec 31, 2016) in MEDLINE, Embase, Cochrane Library, and three Chinese literature databases (CNKI, CBM, and WanFang).

3.6.2. Search terms

The following MeSH items and free words will be taken to balance the search sensitivity and specificity: osteoarthritis, knee, intra-articular, drugs, hyaluronic acid, corticosteroids, mesenchymal stem cells, platelet-rich plasma, and autologous conditioned serum. Before literature research, a detailed search strategy will be developed and confirmed with the help of an evidence-based medicine expert. The pre-search will be conducted to validate the stability of the search strategy. Gray studies were identified from the reference of included literature through the manual review. No restrictions were made on the publication language.

3.6.3. Pilot search

To ensure the stability and consistency of the literature selection process, the numbers of the systematic reviews will perform a pre-selection test. We will randomly select the number of bibliographical references for the pre-selection test. By summarizing the results of our literature selection and discussing the inconsistencies, we hope that all of the numbers will have a definite understanding of the inclusion and exclusion criteria for each systematic review.

3.6.4. Literature selection

We will identify relevant studies including systematic reviews, meta-analysis, and original studies. After excluding the studies that were not relevant using the titles and abstracts, we will include a number of studies for full-text reading. All members of the Guideline Secretary Group will be divided into three groups and perform literature selection.

3.6.5. Evidence syntheses

The high-quality systematic reviews published in the last 2 years will be used directly. We will update the high-quality systematic reviews when they are published beyond 2 years. If we get low-quality systematic reviews or no systematic review, the Guideline Secretary Group will perform new systematic reviews and synthesize the current evidence.

3.6.6. Evidence assessment

The GRADE instrument will be used to assess the quality of evidence and to develop recommendations. According to the GRADE instrument, the quality of evidence is classified as high, moderate, low, and very low. Randomized controlled trials (RCTs) are regarded as high-quality evidence while observational studies as low-quality evidence. We will conduct the assessment of evidence across studies on an outcome-by-outcome basis. The guideline methodologists will be responsible for quality assessment, drafting the evidence summaries, and presenting these summaries at the Guideline Development Group meeting.

3.7. Patients' values and preferences

Patients' values and preferences about intra-articular injection will be investigated by consulting with the knee OA patients. The results of the feedback from patients will be submitted to the Guideline Steering Group and the Guideline Development Group to consider the formulation of recommendations.

3.8. Developing recommendations

After completion of the GRADE evidence profile, the Guideline Development Group will draft preliminary recommendations based on the quality of evidence, the weighing between the benefits and the harms, patients' values and preferences, and the health economic features. The Guideline Development Group will develop the draft recommendations through 2–4 rounds of the Delphi process [24] and will submit the draft recommendations to the Guideline Steering Group for final approval. GRADE Grid instrument will be used to reach our consensus [25]. Five choices ("strong recommendation," "weak recommendation," "unclear recommendation," "weak not recommendation," and "strong not recommendation") will be used for each recommendation item on the questionnaire. For each item, if more than 50% of the experts vote for any choice except the "unclear" one or if more than 70% of the experts vote for one of the two choices on the same side, this will mean that consensus on the item has been reached. Otherwise, the item will be deemed controversial and will need one more round of the Delphi process.

3.9. Peer review of guideline

The guideline will be submitted to external experts for peer review. The Guideline Development Group will record the review process and collect the proposals from reviewers. After discussion about the thoughts and opinions from the peer reviewers in the Guideline Development Group, some recommendations or their strengths may be revised if necessary. Moreover, the responses to reviewers are needed to bring back and submit to the Guideline Steering Group.

3.10. Reporting, publishing, and updating of the guideline

The guideline will be drafted and reported according to the format recommended by the Essential Reporting Items for Practice Guidelines in Healthcare (RIGHT) working group [26]. It is estimated that the full text will be published in 1 or 2 years. The guideline will be translated into English and Chinese and published in relevant journals. We also plan to update the guideline every 2 years or when new evidence is published.

3.11. Promotion, implementation, and evaluation of the guideline

After the publication of the guideline, it will be promoted by the Chinese Orthopaedic Association and the Chinese Medical Society in the following ways: (1) The guideline will be presented at conferences relating to OA diseases for 3 years; (2) a learning program for the guideline will be organized for orthopedists, rheumatologists, and nurses in China; (3) the brief and standard edition of the guideline will be published in newspaper, handbooks, pamphlet, and other medical journals; and (4) the Chinese, English, or other language version of the guideline will be placed on popular medical or official health web sites or APP.

Ethical approval

Ethical approval was not required for this study design.

Funding

This study was supported by grants from the National Natural Science Foundation of China (No. 81501919) and Beijing Joint Care Foundation.

Author contribution

Project conceptualization: Dan Xing and Jianhao Lin.
 Study design: Dan Xing, Yaolong Chen and Jianhao Lin.
 Data collection/validation: Dan Xing and Yunfei Hou.
 Result interpretation: Dan Xing, Ziyi Yang and Yunfei Hou.
 Reporting & editing: Yunfei Hou and Bin Wang.
 Final approval of the version to be submitted: Dan Xing, Yaolong Chen and Jianhao Lin.

Potential conflict of interest

There are no conflicts of interest for the authors developing this CPG.

Guarantor

Project guarantor: Jianhao Lin

Research registration UIN

The guideline was registered on International Practice Guidelines Registry Platform (<http://www.guidelines-registry.org/>), and the registration number is IPGRP-2016CN004.

References

- [1] J.W. Bijlsma, F. Berenbaum, F.P. Lafeber, Osteoarthritis: an update with relevance for clinical practice, *Lancet* 377 (9783) (2011) 2115–2126.
- [2] J.J. Sacks, Y.H. Luo, C.G. Helmick, Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001–2005, *Arthritis Care Res. (Hoboken)* 62 (4) (2010) 460–464.
- [3] R.C. Lawrence, D.T. Felson, C.G. Helmick, L.M. Arnold, H. Choi, R.A. Deyo, et al., Estimates of the prevalence of arthritis and other rheumatic conditions in the United States, Part II *Arthritis Rheum.* 58 (1) (2008) 26–35.
- [4] C.G. Helmick, D.T. Felson, R.C. Lawrence, S. Gabriel, R. Hirsch, C.K. Kwoh, et al., Estimates of the prevalence of arthritis and other rheumatic conditions in the United States, Part I *Arthritis Rheum.* 58 (1) (2008) 15–25.
- [5] R.J. Douglas, Corticosteroid injection into the osteoarthritic knee: drug selection, dose, and injection frequency, *Int. J. Clin. Pract.* 66 (7) (2012) 699–704.
- [6] R.R. Bannuru, C.H. Schmid, D.M. Kent, E.E. Vaysbrot, J.B. Wong, T.E. McAlindon, Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis, *Ann. Int. Med.* 162 (1) (2015) 46–54.
- [7] E. Smelter, M.C. Hochberg, New treatments for osteoarthritis, *Curr. Opin. Rheumatol.* 25 (3) (2013) 310–316.
- [8] D. Pereira, B. Peleteiro, J. Araújo, J. Branco, R.A. Santos, E. Ramos, The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review, *Osteoarthritis Cartilage* 19 (11) (2011) 1270–1285.
- [9] Q. Liu, J. Niu, J. Huang, Y. Ke, X. Tang, X. Wu, et al., Knee osteoarthritis and all-cause mortality: the Wuchuan Osteoarthritis study, *Osteoarthritis Cartilage* 23 (7) (2015) 1154–1157.
- [10] E. Nüesch, P. Dieppe, S. Reichenbach, S. Williams, S. Iff, P. Jüni, All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study, *BMJ* 342 (2011) d1165.
- [11] D. Xing, Y. Xu, Q. Liu, Y. Ke, B. Wang, Z. Li, et al., Osteoarthritis and all-cause mortality in worldwide populations: grading the evidence from a meta-analysis, *Sci. Rep.* 6 (2016) 24393.
- [12] W. Zhang, G. Nuki, R.W. Moskowitz, S. Abramson, R.D. Altman, N.K. Arden, et al., OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009, *Osteoarthritis Cartilage* 18 (4) (2010) 476–499.
- [13] D.S. Jevsevar, G.A. Brown, D.L. Jones, E.G. Matzkin, P.A. Manner, P. Mooar, et al., The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition, *J. Bone Joint Surg. Am.* 95 (20) (2013) 1885–1886.
- [14] P.G. Conaghan, J. Dickson, R.L. Grant, Care and management of osteoarthritis in adults: summary of NICE guidance, *BMJ* 336 (7642) (2008) 502–503.
- [15] M.C. Hochberg, R.D. Altman, K.T. April, M. Benkhalti, G. Guyatt, J. McGowan, et al., American college of rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee, *Arthritis Care Res. (Hoboken)* 64 (4) (2012) 465–474.
- [16] K.M. Jordan, N.K. Arden, M. Doherty, B. Bannwarth, J.W. Bijlsma, P. Dieppe, et al., EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCSIT), *Ann. Rheum. Dis.* 62 (12) (2003) 1145–1155.
- [17] J.D. Feuerstein, J.R. Pelsis, S. Lloyd, A.S. Cheifetz, K.R. Stone, Systematic analysis of the quality of the scientific evidence and conflicts of interest in osteoarthritis of the hip and knee practice guidelines, *Semin. Arthritis Rheum.* 45 (4) (2016) 379–385.
- [18] J. Kung, R.R. Miller, P.A. Mackowiak, Failure of clinical practice guidelines to meet institute of medicine standards: two more decades of little, if any, progress, *Arch. Int. Med.* 172 (21) (2012) 1628–1633.
- [19] O. Bruyère, C. Cooper, J.P. Pelletier, J. Branco, B.M. Luisa, F. Guillemin, et al., An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO), *Semin. Arthritis Rheum.* 44 (3) (2014) 253–263.
- [20] M.K. Demange, M. Sisto, S. Rodeo, Future trends for unicompartmental arthritis of the knee: injectables & stem cells, *Clin. Sports Med.* 33 (1) (2014) 161–174.
- [21] G.H. Guyatt, A.D. Oxman, G.E. Vist, R. Kunz, Y. Falck-Ytter, P. Alonso-Coello, et al., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, *BMJ* 336 (7650) (2008) 924–926.
- [22] The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines, *BMJ*, 354 (2016) i4852.
- [23] D. Sinclair, R. Isba, T. Kredon, B. Zani, H. Smith, P. Garner, World health organization guideline development: an evaluation, *PLoS One* 8 (5) (2013) e63715.
- [24] J. Jones, D. Hunter, Consensus methods for medical and health services research, *BMJ* 311 (7001) (1995) 376–380.
- [25] R. Jaeschke, G.H. Guyatt, P. Dellinger, H. Schünemann, M.M. Levy, R. Kunz, et al., Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive, *BMJ* 337 (2008) a744.
- [26] Y. Chen, K. Yang, A. Marušić, A. Qaseem, J.J. Meerpohl, S. Flottorp, et al., A reporting tool for practice guidelines in health care: the right statement, *Ann. Intern. Med.* (2016).