Gaceta Sanitaria

Embolización de la arteria genicular para el tratamiento de la artrosis de rodilla: una revisión sistemática con metanálisis y análisis de costes

Special Issue on Health Economics
--Borrador del manuscrito--

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Resumen:	Objetivo: Evaluar la efectividad, seguridad y coste-efectividad de la embolización de la arteria genicular (EAG) para el tratamiento de la artrosis de rodilla (AR) leve o moderada, refractaria al tratamiento habitual, o grave en personas no candidatas a cirugía. Diseño: Se llevó a cabo una revisión sistemática con metanálisis y un análisis de costes, para comparar la EAG y el tratamiento habitual, desde la perspectiva del Sistema Nacional de Salud (SNS) español, con un horizonte temporal de un año. Se estimó la mejora en salud necesaria para que la EAG se considere coste-efectiva, con un umbral de 25.000 €/año de vida ajustado por calidad (AVAC). Resultados: Se incluyeron dos ensayos controlados aleatorizados (ECA). Los resultados en dolor fueron inconsistentes y no se observaron efectos significativos en la función general, calidad de vida o necesidad de medicación para el dolor. No se observaron complicaciones graves ni eventos adversos mayores. La calidad de la evidencia fue de moderada a baja. No se identificaron evaluaciones económicas previas. El coste incremental de la EAG sería de 3.432,37 €/paciente, requiriendo una mejora de 0,137 AVAC/paciente para ser coste-efectiva. Conclusiones: La evidencia de certeza moderada a baja no permite concluir si hay diferencias entre la EAG y el tratamiento habitual para la AR. Sin embargo, el uso de la EAG incrementaría los costes. Se necesitan ECA de mayor tamaño para determinar los efectos de la EAG en el dolor crónico secundario a la AR y establecer si podría ser coste-efectiva desde la perspectiva del SNS.

October 17, 2024

PhD. María Errea and PhD. Pilar Pinilla
Editors of the Special Issue on Health Economics
Gaceta Sanitaria

Dear Editors,

Please find enclosed for your consideration a paper entitled ***"Genicular Artery Embolization for the Treatment of Knee Osteoarthritis: A Systematic Review with Meta-Analysis and Economic Evaluation"***. Please accept it as a candidate for publication in the ***Special Issue on Health Economics*** of ***Gaceta Sanitaria*** with the classification of Review. Authors of this manuscript are: Aránzazu Hernández-Yumar, Yadira González-Hernández, Tasmania del Pino-Sedeño, Cristina Valcárcel Nazco, Aythami de Armas Castellano, Estefanía Herrera-Ramos, Julián Portero Navarro, Montserrat Carmona-Rodríguez, María Ximena Rojas-Reyes, and María M. Trujillo-Martín.

Genicular artery embolization (GAE) has been proposed as an alternative or complementary treatment to the standard non-surgical treatment for knee osteoarthritis (KO), particularly for patients resistant to conventional therapies, including those who cannot or prefer not to undergo surgery. However, there is still uncertainty about its effectiveness and safety, as well as its cost-effectiveness. This article thoroughly reviews the current scientific evidence regarding the safety, effectiveness, and cost-effectiveness of GAE for the treatment of mild to moderate KO refractory to conservative treatment, and/or severe KO in individuals not eligible for surgery. A cost-analysis was also conducted from the perspective of the Spanish National Health System.

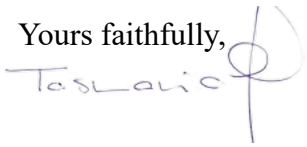
We have followed the PRISMA statement for reporting systematic reviews and meta-analyses in the preparation of this manuscript. The manuscript has been professionally edited by a native English speaker.

All authors of this research paper meet the journal's criteria. None of the authors have declared financial interests that could create a potential conflict of interest concerning the subject matter or materials discussed in the manuscript. In addition, the main text of the manuscript contains 2999 words (not including the abstract, bibliography, tables or figures), according with the journal's requirements.

This study was commissioned and funded by the Spanish Ministry of Health in the framework of activities carried out by the Spanish Network of Agencies for Health Technology Assessment and Services for the National Health System (RedETS). Additionally, this work received support from the Living Evidence to Inform Health Decisions (LE-IHD) program's project entitled "Strengthening decision-making capacity in the Spanish Health System through living evidence: An innovative framework", which has been funded by Instituto de Salud Carlos III (ISC-III) Grant PI21/01564. The study was conducted independently of study sponsors.

Finally, this paper is an original unpublished work. No portion of the data has been published in proceedings or transactions of meetings or symposium volumes. It is not being considered for publication elsewhere and will not be submitted elsewhere unless rejected by *Gaceta Sanitaria*.

Yours faithfully,



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TÍTULO: Embolización de la arteria genicular para el tratamiento de la artrosis de rodilla: una revisión sistemática con metanálisis y evaluación económica

Special Issue on Health Economics

COMENTARIOS PARA EL AUTOR:

Dear authors

Thanks for submitting this manuscript for consideration at the Special Issue in Health Economics in Gaceta Sanitaria

We believe this article is methodologically robust and contributes, with an updated analysis to an area that had been identified as relevant for further research previously.

The reviewers have made some suggestions that I believe will contribute to enhance the manuscript further, so I encourage you to consider their comments and address them accordingly, where appropriate.

Looking forward to receiving a revised version of your manuscript in due course.

Response: *We sincerely appreciate your valuable feedback on our manuscript, as well as all your comments and suggestions. We strongly believe that, after the revision, the manuscript has significantly improved its overall value. Below, we provide detailed responses to each comment and outline the specific changes made to the manuscript. Editorial and structural changes in the marked-up copy of the revised manuscript are highlighted in bold.*

Comments from reviewers:

REVIEWER #1

Congratulations to the authors for this very thorough and methodologically rigorous work. It is also very important to publish articles whose results do not benefit the introduction of a new health technology, since the drive for the new is often stronger than the perspective of the public health system, and this work invites reflection in that sense.

Response: *We deeply appreciate your positive assessment of our work.*

I would just like to make a few brief comments:

Comment 1. In the introduction, the standard treatment for early-stage KO (mild to moderate) includes exercise, postural measures, weight control, and pharmacotherapy. There is no specific mention of the use of hyaluronic acid (very present in the literature in recent years) although it is considered in the costs, so it would be appropriate to mention it.

Response: *We thank you for your observation. In response to your suggestion, in the introduction section, we have incorporated the use of hyaluronic acid.*

Comment 2. Another very 'fashionable' treatment for KO is the application of Platelet Rich Plasma, which according to some reviews is more effective than hyaluronic acid. But the only thing I want to point out is that the standard treatment is taken for granted and there are nuances, especially as none of them meet patients' expectations.

Response: *We have also incorporated the use of platelet-rich plasma.*

Comment 3. In the summary, methodology and discussion, it is mentioned that considering this incremental cost, GAE should improve patient health by 0.137 QALYs to be considered cost-effective compared to the standard treatment. However, despite presenting the formula in the methodology, the results do not clearly express its calculation, and the reader may be misled into thinking that the improvement provided by GAE is 0.137 QALYs/patient.

Response: *Thank you for your comment. In response, we have revised the text to clarify that we estimated the health improvement required for GAE to be considered cost-effective compared to the standard treatment, rather than the actual benefit of the technology in terms of QALY (Lines 17-18, 260-261, and 306-308).*

Comment 4. Among the limitations cited in the discussion are the following, Another limitation arises from the methodology, potentially excluding unpublished studies, published in languages other than English or Spanish, or in unindexed journals, this would go against the methodology used, it is intrinsic to its robustness.

Response: *Thank you for your valuable comment. We understand and agree that the exclusion of unpublished studies, studies in languages other than English or Spanish, or those published in non-indexed journals is a standard methodological practice in systematic reviews. We have*

revised the relevant section of the discussion to clarify that this aspect is intrinsic to the robustness of the methodology and not a methodological flaw.

REVIEWER #2

It is a pleasure to read manuscripts based on health technology assessment reports submitted for potential publication in Gaceta Sanitaria. This study presents a valuable evaluation of genicular artery embolisation (GAE) for knee osteoarthritis. Below, I provide recommendations that I believe could enhance the clarity and impact of your manuscript.

Response: *We would like to sincerely thank you for your valuable comments and suggestions.*

Comment 1. Time horizon of the economic evaluation:

The decision to use a one-year time horizon for the cost analysis is understandable given the limitations in available evidence. However, extending the horizon would allow for a more comprehensive evaluation of the long-term cost-effectiveness of GAE. If this is not feasible due to data constraints, providing a more detailed justification for the use of a short horizon, such as the expected duration of the benefits, would strengthen the analysis. Additionally, incorporating different time horizons as an additional parameter in the univariate sensitivity analysis could further enrich the study.

Response: *Thank you for your observation. In response, we have added a justification for using this short time horizon to the text. Although a longer time horizon would be preferable, there is no evidence on effectiveness and safety beyond one year, so the impact on resource use is unknown. In addition, a previous study suggests that the benefits of GAE are particularly noticeable in the short and medium term [Bathia & Bathia, 2023] (Lines 348-349).*

Reference

14. Bhatia A, Bhatia S. The short-to-midterm outcomes of geniculate artery embolization for mild-to-moderate osteoarthritis of the knee: a systematic review. J Orthop. 2023;39:30-41. doi:10.1016/j.jor.2023.03.009

Comment 2. Justification for the lack of a QALY-based ICER:

While the manuscript does not calculate an ICER due to data limitations, it would be helpful to provide a more detailed explanation of this decision and explicitly discuss its implications for the study's conclusions.

Response: *Thank you for your insightful comment. As mentioned in the discussion, we could not perform a cost-effectiveness analysis because the identified evidence is insufficient to establish significant differences between the GAE technique and the comparator or to conclude that both treatments have equivalent effectiveness. However, given the usefulness of ICER, as an efficiency measure, in the decision-making process, we estimated the improvement in health required for GAE to be deemed cost-effective compared to the standard treatment.*

In response to your suggestion, we have emphasised this justification in the discussion, adding the types of economic evaluation that could not be performed based on the results of effectiveness data (Line 298). Furthermore, we have also emphasised the usefulness of the ICER in the decision-making process, for which reason we estimated the needed health improvement for GAE to achieve cost-effectiveness (Lines 299-300).

Comment 3. Consideration of an alternative/additional ICER based on clinical outcomes:

Given the uncertainty surrounding quality-of-life data and the inability to calculate a QALY-based ICER, I suggest including an alternative ICER based on clinical outcomes. For instance, you could calculate the incremental cost per point of improvement on the Visual Analogue Scale (VAS) for pain or per unit of improvement on the WOMAC index, which measures functional capacity. Although there is no established threshold for these clinical outcomes, such an analysis could still provide useful insights to support decision-making, particularly given the uncertainty observed in the study's results and conclusions. This approach would allow decision-makers to better understand the economic value of GAE in terms of tangible clinical benefits and provide a practical framework for evaluating its cost-effectiveness compared to other interventions.

Response: *Thank you for your thoughtful suggestion. As mentioned in the previous response, we are aware of the usefulness of an ICER in the decision-making from an economic perspective. However, the identified evidence is insufficient to establish significant differences between the GAE technique and the comparator (necessary to perform a cost-effectiveness analysis) or to conclude that both treatments have the same effectiveness (necessary to perform a cost-minimization analysis). For this reason, we only compared the costs conducting a cost-analysis. However, trying to provide useful insights for decision-making, we estimated the improvement in health required for GAE to be deemed cost-effective compared to the standard treatment.*

Comment 4. Discussion of sensitivity analysis results:

The sensitivity analysis in the manuscript is comprehensive, exploring the variability of key parameters such as the cost per session, the number of sessions, and the duration of the procedure. However, the results highlight significant uncertainties that warrant further discussion to provide decision-makers with clearer insights into the robustness of the findings. For instance, the sensitivity analysis reveals that changes in cost-related parameters (e.g., cost of materials, operating room costs, and procedure duration) can substantially alter the incremental cost per patient. This variability indicates that the results are sensitive to assumptions about clinical practice and resource utilisation. Explicitly addressing how these variations impact the study's conclusions would strengthen the discussion.

Response: *We agree with your suggestion. We have discussed the results of the sensitivity analysis, relating them to the possible variation in clinical practice existing among Spanish regions. Although we assumed consistency in the clinical practice across Spain, there could be some differences (Lines 338-339).*

REVIEWER #3

Apreciados/as autores/as y coautores/as,

Enhorabuena por el trabajo realizado. Tras la revisión, a continuación, se detallan algunos comentarios y observaciones orientadas a mejorar la calidad del artículo presentado. Estos comentarios y observaciones se presentan ordenadamente según cada una de las secciones (ver nota al final de mi comentario) que conforman el manuscrito.

Respuesta: *Le agradecemos sinceramente su valoración, sus comentarios y sugerencias.*

INTRODUCCIÓN:

Comment 1. Se recomienda que los objetivos sigan siempre la misma estructura para mayor coherencia y facilidad de lectura. En este sentido, en el resumen aparece "To assess the safety, effectiveness, and cost-effectiveness of genicular artery embolization (GAE) [...]" En la introducción, el objetivo aparece ligeramente modificado al detallarse la efectividad antes de la seguridad: "This study evaluates the effectiveness, safety, and cost-effectivenes of GAE [...]".

Respuesta: *Gracias por su sugerencia. Se ha realizado el cambio en el resumen para facilitar la coherencia a lo largo de todo el texto (the effectiveness, safety, and cost-effectiveness).*

Comment 2. En el título 2.1, de nuevo el orden "effectiveness, safety and cost-effectiveness" aparece distinto al orden del objetivo detallado en el resumen. Sería recomendable unificar el orden de aparición de las dimensiones evaluadas para mayor coherencia y facilidad en la lectura.

Respuesta: *Se ha realizado el cambio en el resumen dado que en el resto del documento había coherencia en la aparición de las dimensiones "effectiveness, safety and cost-effectiveness" o "effectiveness and safety".*

MÉTODOS:

Comment 3. La versión del PRISMA Statement citado en el artículo, fue actualizada en 2020 (https://doi.org/10.1136/bmj.n71). Se recomienda citar la nueva versión, revisar que se hayan cumplido las directrices que se detallan en ella y si procede, aplicar los cambios para que así sea en la mayor medida posible. En caso contrario, y menos deseable, se recomienda que se indique que se trata de la versión de 2009.

Respuesta: *Se ha incorporado la referencia actualizada.*

Comment 4. Se sugiere que se indique si se ha utilizado algún filtro temporal (ej. restricción de los últimos 10 años) en la ejecución de las búsquedas realizadas en MEDLINE, Embase, CENTRAL, y CINAHL para la identificación de ECAs u otros estudios comparativos y en MEDLINE, Embase y WOS para la identificación de evaluaciones económicas. Asimismo, se recomienda citar las bases de datos de la misma forma a lo largo del documento ya que "Embase" se escribe también "EMBASE" en la misma sección (según la misma base de datos,

Embase es la denominación correcta). Por otro lado, se sugiere indicar si se ha ejecutado la búsqueda en MEDLINE mediante Ovid o PubMed.

Respuesta: *Gracias por su sugerencia. En apartado 2.1.1 hemos aclarado que "All search strategies were limited to studies published in English or Spanish within the last 10 years, as the earliest study on joint embolization for pain management in inflammatory musculoskeletal diseases was published in 2013". Además, hemos homogeneizado la nomenclatura de la base de datos Embase en todo el documento para garantizar la coherencia, y hemos especificado que la búsqueda en MEDLINE se realizó a través de la plataforma Ovid, junto con las demás plataformas utilizadas para acceder a las distintas bases de datos.*

Comment 5. De manera adicional, y con relación a la fecha des del lanzamiento de las distintas búsquedas (superior al año respecto a la fecha de publicación tal como recomienda el Cochrane Handbook for Systematic Reviews), se recomienda indicar si se ha efectuado alguna actualización antes de la publicación de este artículo con el objetivo de verificar que no haya información más reciente que pueda ser relevante. En caso contrario, se sugiere que se detalle este aspecto (período desde la ejecución de las búsquedas hasta la fecha de publicación del artículo) como una limitación de la revisión.

Respuesta: *Hemos aclarado que la búsqueda de ECA y otros estudios comparativos en Epistemonikos se mantuvo activa hasta finales de mayo de este año (líneas 92-93), sin que se identificara nueva evidencia susceptible de ser incorporada a la RS de efectividad y seguridad (líneas 188-189). Reconocemos, no obstante, que existe un período no cubierto hasta la fecha actual, y este aspecto se ha señalado como una limitación en la sección de discusión para garantizar la transparencia del estudio (líneas 320-323).*

Comment 6. Con relación a la estrategia de búsqueda, se recomienda que se añadan los hits para cada una de las líneas de la sintaxis. En caso que no sea posible debido al tiempo transcurrido desde el lanzamiento de las búsquedas, se sugiere que se tenga en cuenta en futuras revisiones.

Respuesta: *Se han añadido los hits para cada una de las líneas de la sintaxis de las bases de datos: MEDLINE, Embase, CENTRAL, CINAHL y Web of Science. Sin embargo, Epistemonikos no nos proveyó de esta información.*

Comment 7. Respecto a los criterios de selección detallados en la tabla 1, se sugiere modificar el orden de las categorías de manera que "type of study" esté debajo de "outcome measure" para seguir la estructura PICO-D. Es decir: Population, Intervention, Comparator, Outcome measure, Type of study, etc.

Respuesta: *Se ha realizado el cambio en el orden de las categorías para seguir la estructura PICO-D.*

Comment 8. Se sugiere citar RevMan 5 tal como se ha hecho con Zotero.

Respuesta: *Se ha incluido la referencia para el programa estadístico RevMan 5.*

Comment 9. Por otro lado, sería recomendable que se detallara mejor el procedimiento seguido para identificar los costes e indicar a partir de qué fuentes de información proceden.

Respuesta: *Gracias por su sugerencia. En el apéndice B se describe el procedimiento de obtención del uso de recursos y de los costes unitarios (cálculos realizados y fuentes de información), así como los valores utilizados para cada parámetro (Tabla S1), tanto para el caso base como para el análisis de sensibilidad probabilístico, para el que también se especifica las distribuciones de probabilidad utilizadas. Se ha añadido en dicho material suplementario que "los costes unitarios fueron extraídos todos ellos de fuentes de datos españolas". Esta es una información importante dado que las evaluaciones económicas (completas o parciales) son contexto-dependientes.*

RESULTADOS

Comment 10. Podría ser que haya un error en la citación de las RS del párrafo inicial del apartado 3.1 y la citación de las RS en el Apéndice C. En primer lugar, se describen 13 RS, pero únicamente se citan 9. En segundo lugar, en el Apéndice C se ha incorporado 2 veces la citación 13, se ha incorporado la citación 34 que no aparece en el párrafo inicial del apartado 3.1 y falta la cita 31.

Respuesta: *Gracias por su indicación. Ha sido un error al trasladar en el texto el proceso de selección de las RS, de forma que son nueve las referencias seleccionadas a título y abstract, tal y como aparecen ahora citadas en el documento.*

Por otro lado, se han actualizado y corregido las referencias incluidas en el Apéndice C.

Comment 11. En el título del punto 3.1.4.1 se ha escrito COE en lugar de CoE. Creo que debería ser CoE.

Respuesta: *Sentimos la errata. Se ha corregido el término.*

Comment 12. Figure 1: Se recomienda que se utilice el diagrama de la última versión del PRISMA Statement (2020) que incorpora el flujo de identificación de estudios mediante otras vías (búsqueda manual).

Respuesta: *Gracias por su sugerencia. En respuesta, se ha empleado el diagrama de flujo de identificación de estudios mediante otras vías (Figure 1).*

Comment 13. Appendix G: Sería adecuado reportar el riesgo de sesgo mediante el gráfico de semáforos típico del RoB 2.0.

Respuesta: *Gracias por su sugerencia. En respuesta, se ha incluido la figura del riesgo de sesgo de los estudios incluidos, ahora Figure 2 del manuscrito.*

DISCUSIÓN

Comment 14. Al principio de la discusión se indica que el comparador es "gestión/ tratamiento conservador" o "terapia farmacológica". En cambio, en otras secciones del documento, el

comparador se denomina "conservative treatment", "conservative or pharmacological treatment", "standard treatment", "standard-of-care treatment alone (comparator)". Para mayor coherencia, se recomendaría utilizar siempre la misma denominación a lo largo del documento para que quede claro cuál es el comparador.

Respuesta: *Se ha unificado el término del comparador ("standard treatment") para facilitar la coherencia en la lectura.*

Comment 15. Sería recomendable indicar como limitación la fecha transcurrida entre el lanzamiento de la búsqueda y la publicación del presente estudio.

Respuesta: *Tal y como comentamos en una respuesta anterior, reconocemos que existe un período no cubierto en las búsquedas que se ha señalado como una limitación en la sección de discusión para garantizar la transparencia del estudio (líneas 320-323).*

Comment 16. Sería adecuado que se indicaran los motivos por los que no se ha realizado una evaluación económica completa.

Respuesta: *Gracias por su sugerencia. Se ha añadido en la discusión: 1) que una evaluación económica completa no se pudo realizar "debido a los resultados de efectividad" (líneas 325-326), y 2) los tipos de evaluación económica completa (esto es, análisis coste-efectividad o análisis coste-minimización) que no se han podido llevar a cabo debido a que la evidencia sobre efectividad identificada es insuficiente para establecer diferencias significativas entre la técnica evaluada y el comparador o para concluir que la efectividad de ambas alternativas es la misma (líneas 297-300).*

CONCLUSIONES

Comment 17. Al tratarse de una revisión, según la normativa de la revista, debería constar una apartado específico con título propio relativo a las conclusiones.

Respuesta: *Gracias por su observación. Hemos añadido un apartado específico al final del manuscrito.*

APÉNDICES

Comment 18. Los apéndices H y G están en orden invertido en el apartado de apéndices a pesar que en el texto salen correctamente. En orden alfabético, debería aparecer primero el apéndice G y después el H.

Respuesta: *Gracias por señalar esta inconsistencia. Hemos corregido el orden de los apéndices, de modo que ahora aparecen en orden alfabético.*

Nota: en el cuerpo del artículo no existe numeración alguna de las líneas y/o de los párrafos (tampoco de las páginas) tal como sí existe en los materiales suplementarios. Por este motivo, no se detalla el número de línea/párrafo en cada comentario.

Respuesta: *Lamentamos la omisión inicial de la numeración en el cuerpo del artículo. Hemos incluido la numeración de las páginas y de las líneas para facilitar su revisión. Agradecemos su observación al respecto.*

Nº. DE REFERENCIA: GACETA-D-24-00319R1

TÍTULO: Embolización de la arteria genicular para el tratamiento de la artrosis de rodilla: una revisión sistemática con metanálisis y evaluación económica

Special Issue on Health Economics

Comment for the authors:

Dear authors

Thanks very much for sending an updated version of the manuscript addressing the reviewers' suggestions. This has enhanced the quality and clarity of the manuscript. I understand the differences in HRQL are not big enough to conduct an economic evaluation or to provide an ICER.

However, in line with the reviewers' suggestion, I wonder whether it would be possible to provide, at least, the EQ-5D total score for the technology and comparator at 1 year, and estimate their associated QALYs, even if the difference isn't statistically significant, for completeness and to support decision-making, with the caveat that the results are based on low-moderate quality evidence as stated in the manuscript.

Furthermore, given that an economic evaluation isn't conducted, I would suggest a slight modification to the title to say 'economic analysis' or 'cost-analysis' as described in the main body of the manuscript.

Thanks in advance and looking forward to your response

Response: *We sincerely appreciate your comments and suggestions. Below, we have provided a detailed response to each one.*

Although it would have been desirable to estimate QALYs, we were unable to do so due to the lack of evidence on the impact on health-related quality of life (HRQoL) of the two alternatives evaluated in the cost-analysis. The only study identified in the systematic review evaluating the HRQoL is that of Landers et al. (2023). We have reviewed it to determine the possibility of estimating QALYs. In this paper, the alternatives compared were an embolization procedure and a sham embolization procedure, not corresponding to those considered in our cost-analysis (embolization procedure plus the standard treatment in Spain vs. the standard treatment alone). In addition, the information on the EQ-5D-5L provided in this study does not allow us to estimate utility values and, consequently, QALYs. The authors showed the percentages of patients reporting "no/slight problem" or "moderate-extreme problem" for each dimension of the EQ-5D-5L. This aggregation of the levels of problem severity does not allow us to apply the established Spanish value set for estimating the utilities. Therefore, we are not able to perform the suggested analysis. However, we would like

to highlight that we have calculated the health improvement (measured in QALYs) required for GAE to be considered cost-effective compared to the standard treatment.

Regarding the comment on the title of the manuscript, we have modified the title according to your suggestion. We have substituted "economic evaluation" by "cost-analysis".

Genicular Artery Embolization for the Treatment of Knee Osteoarthritis: A Systematic Review with Meta-Analysis and Cost-analysis

Special Issue on Health Economics

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Authors' contributions

Aránzazu Hernández-Yumar and Yadira González-Hernández participated in the design, acquisition, analysis, and interpretation of data, as well as drafting the work. These authors share first authorship. Tasmania del Pino-Sedeño, Cristina Valcárce-Nazco, Aythami de Armas-Castellano, and Estefanía Herrera-Ramos participated in the design, acquisition, analysis, and interpretation of data, and reviewed the work. Julián Portero Navarro, Montserrat Carmona Rodríguez, María Ximena Rojas-Reyes, and María M. Trujillo-Martín participated in the design, and critically reviewed the work. Tasmania del Pino-Sedeño and María M. Trujillo-Martín also contributed to project administration. All authors read and approved the final manuscript.

Transparency statement

The corresponding author, on behalf of the other signatories, guarantees the accuracy, transparency and honesty of the data and information contained in the study; that no relevant information has been omitted; and that all discrepancies between authors have been adequately resolved and described.

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The study was conducted independently of study sponsors. There was no sponsor involvement in the study design; collection, analysis and interpretation of the data; in writing of the manuscript; or in the decision to submit the manuscript for publication.

Conflict of interest

The authors have no conflict of interest with the subject matter or materials discussed in the manuscript.

Registry

The protocol of the Systematic Review was registered in OSF [https://osf.io/ytxvu].

Para los autores:

Falta explicar asterisco en pie de tabla 2

Special Issue on Health Economics

Genicular artery embolization for knee osteoarthritis: a systematic review with meta-analysis and cost-analysis

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ABSTRACT

Objective: To assess the effectiveness, safety, and cost-effectiveness of genicular artery embolization (GAE) for the treatment of mild or moderate knee osteoarthritis (KO) refractory to standard treatment, and/or severe KO in individuals not eligible for surgery.

Method: We conducted a systematic review with meta-analysis, supplemented by a cost-analysis, comparing GAE and standard treatment, from the perspective of the Spanish National Health System (NHS) over a one-year time horizon. The health improvement required for GAE to be deemed cost-effective was quantified, considering a willingness-to-pay threshold of 25 000 €/quality-adjusted life year (QALY).

Results: We included two randomized controlled trials in our analysis. Pain estimates showed inconsistent results, and no significant effects were observed for overall function, health-related quality of life, or changes in the need for pain management medication. No serious complications or major adverse events were observed. GRADE quality of evidence ranged from moderate to low. No economic evaluations were identified. Our cost-analysis revealed that GAE would result in an incremental cost of € 3432.37 per patient, requiring a health improvement of 0.137 QALY per patient to be deemed a cost-effective technology.

Conclusions: In summary, based on moderate to low-certainty evidence, it remains inconclusive whether there is any difference between GAE and standard treatment for KO. However, the use of GAE would increase the costs. Larger randomized controlled trials are needed to determine the effects of using GAE for chronic pain secondary to KO and, consequently, to ascertain whether this technology could potentially become cost-effective from the NHS perspective.

Key words:

Genicular artery

Embolization

Knee osteoarthritis

Pain

Systematic review

Economic evaluation

Embolización de la arteria genicular en la artrosis de rodilla: revisión sistemática, metaanálisis y análisis de costes

RESUMEN

Objetivo: Evaluar la efectividad, la seguridad y el coste-efectividad de la embolización de la arteria genicular (EAG) para el tratamiento de la artrosis de rodilla (AR) leve o moderada, refractaria al tratamiento habitual, o grave en personas no candidatas a cirugía.

Método: Se llevó a cabo una revisión sistemática con metaanálisis y un análisis de costes para comparar la EAG y el tratamiento habitual, desde la perspectiva del Sistema Nacional de Salud (SNS) español, con un horizonte temporal de 1 año. Se estimó la mejora en salud necesaria para que la EAG se considere coste-efectiva, con un umbral de 25.000 €/año de vida ajustado por calidad (AVAC).

Resultados: Se incluyeron dos ensayos controlados aleatorizados. Los resultados en dolor fueron inconsistentes y no se observaron efectos significativos en la función general, la calidad de vida ni la necesidad de medicación para el dolor. No se observaron complicaciones graves ni eventos adversos mayores. La calidad de la evidencia fue de moderada a baja. No se identificaron evaluaciones económicas previas. El coste incremental de la EAG sería de 3.432,37 €/paciente, requiriendo una mejora de 0,137 AVAC/paciente para ser coste-efectiva.

Conclusiones: La evidencia de certeza moderada a baja no permite concluir si hay diferencias entre la EAG y el tratamiento habitual para la AR. Sin embargo,

el uso de la EAG incrementaría los costes. Se necesitan ensayos controlados aleatorizados de mayor tamaño para determinar los efectos de la EAG en el dolor crónico secundario a la AR y establecer si podría ser coste-efectiva desde la perspectiva del SNS.

Palabras clave:

Arteria genicular

Embolización

Osteoartritis de rodilla

Dolor

Revisión sistemática

Evaluación económica

Introduction

Knee osteoarthritis (KO) is a leading cause of chronic pain and disability worldwide, particularly among women, individuals over 50, and individuals who are overweight or obese,[1,2] with an estimated prevalence of 29.3% in the general population.[3]

Standard treatment for early-stage KO (mild to moderate) includes exercise, postural measures, weight control,[1,4] and pharmacotherapy.[4–6] Intra-articular injections of hyaluronic acid or platelet-rich plasma have emerged as newer non-surgical treatment options for managing KO.[1,7] Joint replacement surgery is reserved for severe cases with intense pain and functional disability.[8] However, many patients experience refractory chronic pain or are not surgical candidates. Additionally, some patients may experience complications associated with long-term pharmacotherapy, such as kidney or liver failure, opioid addiction, or local issues arising from injections.[9]

Recently, genicular artery embolization (GAE) has emerged as a promising minimally invasive procedure for managing secondary pain to locomotor inflammatory diseases.[10] GAE selectively embolizes genicular branches to painful or abnormal vascularized areas,[11] typically using microspheres or polyvinyl alcohol particles.[12]

GAE has been proposed as an alternative or complementary treatment to the standard non-surgical treatment for KO,[4-7,13-16] particularly for patients resistant to conventional therapies, including those who cannot or prefer not to undergo surgery. While some studies suggest that GAE may benefit patients across the spectrum of KO severity,[13] others suggest its potential for early and low-grade KO, especially in the short and medium term.[14] Additionally, this procedure is considered safe, without major complications,[4,6,13] although minor complications are not infrequent.[13]

This study evaluates the effectiveness, safety and cost-effectiveness of GAE in treating mild to moderate KO refractory to standard treatment or severe KO in non-surgical candidates, due to the still existing uncertainty.

Method

Systematic review on effectiveness, safety and cost-effectiveness

A systematic review on the clinical effectiveness and safety of GAE for treating mild to moderate KO refractory to standard treatment or severe KO in non-surgical candidates was conducted according to the Cochrane Collaboration methodology,[17] with reporting in accordance with the PRISMA statement.[18] The protocol was registered in OSF [OSF osf.io/ytxvu]. Complementary, a systematic review of cost-effectiveness were performed following the Campbell-Cochrane Economic Methods.[19]

1) Information sources and search strategy

The systematic review searches and subsequent identification of their included randomized controlled trials or non-randomized comparative studies was conducted using technological enablers from the Epistemonikos database, in April 2023. The results were automatically incorporated into the Epistemonikos L·OVE platform,[20] where subsequent selection was conducted. An alert service for randomized controlled trials and non-randomized comparative studies was also created, which remained active until May 31, 2024.

Additionally, to identify randomized controlled trials or other comparative studies not included in available systematic reviews, searches were conducted in MEDLINE (Ovid), Embase (Elsevier), CENTRAL (Wiley), and CINAHL (EBSCOhost), in October 2023.

Economic evaluations were identified through searches in MEDLINE, Embase, and Web of Science, in June 2023. The terms from this strategy were combined with a strategy specifically designed by the University of York[21] to identify economic evaluations.

All search strategies were limited to studies published in English or Spanish within the last 10 years, as the earliest study on joint embolization for pain management in inflammatory musculoskeletal diseases was published in 2013.[10]

Retrieved references were managed using Zotero 6.0.23[22] and deduplicated using Deduklick,[23] followed by manual removal of duplicates and study selection in Microsoft Excel.

Furthermore, the bibliography of included articles was manually examined, and studies citing the selected studies were verified through Google Scholar.

Full search strategies for all database searches are provided in Appendix A in Supplementary data.

2) Selection criteria

Studies were eligible for inclusion if they fulfilled the criteria summarized in Table 1.

3) Study selection, data extraction process and assessment of risk of bias

Two reviewers independently and in parallel performed the selection process, data extraction, and assessment of risk of bias. Titles and abstracts were initially assessed, followed by a full-text review for studies meeting the criteria. A standardized data extraction form was created in Microsoft Excel, including information on article identification, study design, participant characteristics, eligibility criteria, intervention and comparator details; assessed effectiveness and safety outcomes along with measurement timing; cost-effectiveness methodology and outcomes; study funding source, and disclosed conflicts of interest by the researchers.

To assess the methodological quality of the identified systematic reviews, the AMSTAR-2 tool was selected.[24] The risk of bias of the included primary studies was assessed using the Cochrane RoB 2 tool for parallel and crossover randomized controlled trials.[25] The appraisal of methodological quality of economic evaluations was planned based on Drummond et al.'s criteria list.[26]

Discrepancies between reviewers were resolved through discussion.

4) Publication bias assessment

The assessment of publication bias was planned by creating a funnel plot and computing the Egger's regression test;[27] however, the minimum number of studies necessary was not reached.

5) Synthesis of the evidence

Study characteristics were summarized narratively and presented in summary tables. Meta-analyses were conducted for quantitative synthesis. Heterogeneity was assessed using forest plots, the χ^2 statistical ($p < 0.01$) and the Higgins I^2 test. Initially, a fixed-effect model was used to evaluate the statistical

heterogeneity among included studies (I^2 statistics). In cases of high unexplained heterogeneity (I^2 >70%), meta-analyses was not performed, and results were reported narratively. All analyses were conducted using RevMan 5.4.[28]

Potential confounders considered were baseline pain level, osteoarthritis severity, and type of embolic agents used. However, subgroup analyses were limited due to the small number of studies evaluated.

6) Certainty of evidence

The certainty of the evidence for all outcomes was judged using the GRADE methodology, considering risk of bias, consistency, directness, precision and reporting bias.[29] Certainty was assessed as high, moderate, low or very low. A summary of findings table was prepared to present the certainty of the evidence and the magnitude of the effects for the main comparison.[30,31]

Economic evaluation

A cost-analysis was conducted to compare the costs (in Euros of 2023) of two treatments for chronic pain secondary to KO: the use of GAE of the affected knee followed by standard treatment (evaluated strategy), and the standard treatment alone (comparator), which involves annual hyaluronic acid injections and prescription of physical exercise, in addition to radiofrequency sessions if the patient does not improve.

The target patients were those with chronic pain secondary to mild to moderate KO refractory to standard treatment or non-surgical candidates with severe KO. The analysis was performed from the perspective of the Spanish National Health System (NHS) with a one-year time horizon covering the entire treatment period in the evaluated strategy. No discount rate was applied due to the short-term horizon.

The incremental cost per patient and the annual cost for a hospital with a target population size of 40 patients (value reported by experts) were calculated.

Additionally, we estimated the health improvement, in quality-adjusted life years (QALY), that GAE should generate per patient to be considered a cost-effective technology. This was estimated by solving the incremental effectiveness $(E_A - E_B)$ from the incremental cost-effectiveness ratio equation ($ICER = (C_A - C_B)/(E_A - E_B)$, where $(C_A - C_B)$ is the estimated incremental cost, and *A* and *B* represent the evaluated strategy and the comparator, respectively). The cost-effectiveness threshold estimated for Spain (€ 25 000 per QALY)[32] was applied. The analysis was conducted using Microsoft Excel 2013.

We performed one-way deterministic and probabilistic (1000 second-order Monte-Carlo simulations) sensitivity analyses.

1) Parameters

Since both alternatives include the standard treatment, only the resource use and the corresponding costs of the GAE were considered, as the inclusion of shared costs would not affect the incremental cost.[26]

The analysis included those associated with the intervention (drugs, instruments, wound closure, healthcare personnel, operating room use, and post-intervention observation period) and the follow-up (Appendix B in Supplementary data).

Results

Systematic review on effectiveness and safety

The search in Epistemonikos yielded a total of 13 systematic reviews. Nine were initially considered potentially eligible after title and abstract screening according to the selection criteria; however, none were finally included because they did not attain a high-quality rating.[4,6,13-16,33-35] The full quality assessment can be found in Appendix C in Supplementary data.

The search for primary studies retrieved 126 references after removing duplicates (Fig. 1). After the title and abstract screening, 12 publications were selected for

full-text analysis. According to pre-established criteria, nine of these were excluded. Appendix D in Supplementary data shows the list of excluded references and the main reason for exclusion.

Examination of the bibliographic listing of included studies and the Google Scholar search did not lead to any additional studies. No additional studies were identified through the alert service created using the Epistemonikos database. Therefore, the final selection consisted of two randomized controlled trials,[36,37] reported in three publications.[36–38]

1) Characteristics of included studies

The main characteristics of the included studies are summarized in Tables 2 and 3. For a detailed description of the characteristics and further details of the included studies, please refer to Appendix E and F in Supplementary data.

2) Risk of bias in included studies

The overall risk of bias in the included randomized controlled trials was considered low. The summary of the assessment can be found in Figure 2 and Appendix G in Supplementary data.

3) Certainty of evidence

The overall quality of evidence was considered low. The evidence profile for GAE vs. standard treatment outcomes indicated moderate to low certainty of the evidence (Appendix H in Supplementary data).

4) Summary of results

Results of all meta-analysis conducted are available in Appendix I in Supplementary data.

- Pain (certainty of the evidence: low ⨁⨁◯◯/moderate ⨁⨁⨁◯)

The included randomized controlled trials examined the effect of GAE on pain at 1 month,[36,37] 6 months[36], and 12 months.[36] However, due to very high heterogeneity rates (I^2 = 91%) in the 1-month pain analysis, pooled data are not presented.

Preliminary findings reveal significant discrepancies in pain levels 1 month after GAE. There is low-quality evidence suggesting that GAE may have little to no effect according to the KOOS Pain subscale (1 study; 59 patients)[36] or may result in a slight decrease in pain levels assessed with the visual analogue scale (VAS) (mean difference [MD] = 50.1 mm; 95% confidence interval [95%CI]: 29.0-72.3; 1 study; 21 patients).[37] At 6 and 12 months of follow-up, moderate quality evidence suggests GAE probably results in little to no effect.

In the Bagla et al.[37] study, the response rates at 1 month were 79% (11/14) and 0% (0/7) for the GAE and sham arms, respectively. However, in the Landers et al.[36] study, overall change in knee pain at 12 months indicated that 17 participants (58.6%) in the GAE group reported being moderately or much better, compared to 11 participants (37.9%) in the control group, though this difference was also not statistically significant.

- Overall function (certainty of the evidence: moderate ⨁⨁⨁◯)

The included studies examined the impact of interventions (GAE vs. sham) on overall functional improvement at 1 month,[36,37] 6 months,[36] and 12 months,[36] using the WOMAC,[37] KOOS Daily Living subscale, and KOOS Function in Sport and Recreation subscale.[36] The effects in all these scales were pooled.

Moderate-quality evidence suggests GAE likely has little to no effect on functional capacity at 1 month (SMD = −0.18; 95%CI: −0.62-0.27; I^2 = 0%, 2 studies, 80 patients), 6 months (SMD = −0.17; 95%CI: −0.68-0.34, 1 study, 59 patients) and 12 months (SMD = 0.07; 95%CI: −0.44- 0.58, 1 study, 59 patients) compared to standard or pharmacological treatment.

- Health related quality of life (HRQoL) (certainty of the evidence: low ⨁⨁⨀⨀/moderate ⨁⨁⨁⨀)

Only Landers et al.[36] reported on the effect of interventions on HRQoL. Low-quality evidence suggests that GAE may have little to no effect on HRQoL assessed with the KOOS Quality of Life subscale at 1 month compared to standard treatment (1 study, 59 patients). GAE probably results in little to no difference in HRQoL at 6 and 12 months.

However, low-quality evidence suggests that GAE may result in a slight improvement of HRQoL levels using the EQ-5D VAS at 6-month follow-up (MD = −10.00; 95%CI: −19.45 to −0.55; 1 study, 59 patients). Moderate-quality evidence suggests that GAE likely has little to no effect on HRQoL at 1 month and 12 months compared to standard treatment (1 study, 59 patients).

No differences were observed in the rates of patients who did not present or presented slight problems with anxiety, discomfort, mobility, usual activities, or self-care assessed with EQ-5D.

- Need for pain medication (certainty of the evidence: moderate ⨁⨁⨁⨀)

Only Landers et al.[36] reported changes in the need for pain medication. At 12 months, the GAE group had a lower proportion of participants taking analgesics (control 48%, intervention 24%). However, moderate-quality evidence suggests that GAE likely does not reduce or increase the need for pain medication (risk ratio: 0.52; 95%CI: 0.24-1.10; 1 study, 59 patients).

- Adverse events and complications

No major adverse events were reported in either of the two studies.[36,37] Specifically, in the study by Landers et al.,[36] it was reported that no evidence of osteonecrosis or ischemic complications were found on magnetic resonance

imaging up to two years following the procedure. No differences were observed in minor adverse events.[36,37]

Systematic review on cost-effectiveness

The electronic databases retrieved nine references, but after reading titles and abstracts, all of them were excluded (Appendix J in Supplementary data). Therefore, no economic evaluations focused on GAE and that meet the established inclusion criteria were identified.

Economic evaluation

Over a one-year horizon, the inclusion of GAE in the standard treatment generates an increment in costs of € 3432.37 per patient, from the NHS perspective (Table 4). Considering this incremental cost, a health improvement of 0.137 QALY per patient is required for GAE to be deemed cost-effective compared to the standard treatment. In addition, the estimated annual cost of implementing this technology would be € 137 294.86 for a general hospital treating a target population of 40 patients per year.

The one-way sensitivity analysis shows that the incremental cost can vary from € 2884.14, if the intervention duration is reduced from 1.5 hours to 1 hour, to € 9722.02, if GAE is administered three times to the same patient within the time horizon. Meanwhile, the probabilistic analysis estimates an incremental cost of € 6741.84 per patient (95%CI: 2992.10-11,726.68), associated with the application of the GAE technique (Table 4).

Discussion

The present systematic review on the effectiveness and safety of GAE for chronic pain secondary to KO refractory to standard treatment identified two randomized controlled trials (n = 80) evaluating GAE compared to standard treatment.

The results show that evidence is insufficient to draw definitive conclusions regarding the beneficial effects of GAE compared to standard treatment for KO in terms of knee pain, overall functional improvement, HRQoL, changes in the need for pain medication, adverse events or complications. Evidence for these outcomes is affected by inconsistency and imprecision, with wide confidence intervals and/or a very small sample size.

Recent research has shown promising results for GAE as an alternative treatment for chronic joint pain in patients with KO.[4,13-16] Some studies suggest that GAE can offer benefits across varying degrees of osteoarthritis severity,[13] while others consider that this technique has potential mainly for early and low-grade osteoarthritis, particularly in the short and medium term.[14] Additionally, this procedure is considered safe, with no serious complications reported,[4,6,13] but minor complications are not uncommon.[13]

However, these findings are predominantly based on observational studies, highlighting the need to confirm them with high-quality randomized controlled trials. Further research is needed to evaluate GAE long-term outcomes, its comparative efficacy with other modalities, and its role in the therapeutic approach.[4,6,16,35]

The present systematic review findings suggest that GAE appears to be a safe alternative, as previous studies have indicated, but without evidence of its effectiveness within a one-year timeframe. The above-mentioned limitations, and considering the low certainty evidence supporting our conclusions, justify keeping this question in “living mode” as proposed in our original protocol.[39]

The systematic review did not identify any economic evaluation on GAE that met the established inclusion criteria. The identified evidence is insufficient to establish significant differences between the GAE technique and the comparator (necessary to perform a cost-effectiveness analysis) or to conclude that both treatments have the same effectiveness (necessary to perform a cost-

minimization analysis). Therefore, we only compared the costs conducting a cost-analysis.

The cost-analysis results showed that the incorporation of GAE into the standard treatment (application of hyaluronic acid once a year plus a prescribed physical exercise regimen) would lead to an increase in cost of € 3432.37 per patient compared to the standard treatment alone in a year. This translates to an additional annual cost of € 137,294.86 for a general hospital with a target population of 40 patients per year. This technology could only be considered cost-effective if an improvement in health of at least 0.137 QALY per patient within a year is achieved.

This systematic review has several strengths. It was developed using a robust predefined methodology outlined in a registered protocol. All steps were performed in duplicate to minimize errors throughout the review process. Additionally, the evidence was synthesized using the GRADE methodology, known for its transparency in evidence development and presentation.

However, the main limitation of this review is the scarcity of evidence, stemming from a low number of studies with small sample sizes, leading to inconsistent results in measured outcomes. Others, mainly due to the low number of studies, include the absence of sensitivity, subgroup and meta-regression analyses. Additionally, as is standard in systematic reviews, the methodology may have excluded unpublished studies, published in languages other than English or Spanish, or in unindexed journals, which could potentially limit the comprehensiveness of the evidence. Furthermore, although an alert service for identifying randomized controlled trials and non-randomized comparative studies remained active until May 31, 2024, a gap exists between this date and the present, which may have excluded more recent evidence potentially influencing the findings.

To the best of the authors' knowledge, this is the first analysis assessing the costs of the GAE technique in Spain. A complete economic evaluation comparing costs and effects could not be performed due to effectiveness results. However, given the usefulness of ICER, as an efficiency measure, in the decision-making process, we estimated the health improvement per patient necessary for GAE to

be considered cost-effective, compared to the standard treatment, for a willing-to-pay threshold of € 25,000 per QALY.

The main limitations of the cost analysis arise from data scarcity. First, evidence on the proportion of target patients requiring vascular closure or those allergic to antibiotics could not be identified, thus assumptions and a value for a general patient[40] were used, respectively. Second, the cost of wound closure with manual compression was obtained from a single study without specifying the year in which the Euros were measured.[41] Therefore, 2020 (the publication year) was assumed as the reference year. Third, instrument costs were extracted from tender documents of some Spanish public hospitals,[42-44] reflecting their reality but may vary contextually. Fourth, resource use information was provided by an expert. Although clinical practice was assumed to be at least similar across Spain, there could be regional differences. Sensitivity analyses show that the incremental cost per patient can range from € 2884.14 to € 11 726.68, a wide variation especially influenced by the number of sessions conducted during the time horizon. Bearing in mind this, regional differences in terms of incremental costs related to the use of resources derived from the clinical practice and the unit costs in each region could be observed. Nonetheless, experts validated the assumptions (face validity) and sensitivity analyses variations of these parameters did not significantly alter the results. Finally, the time horizon was restricted to one year because there is no evidence on effectiveness and safety beyond this period, so the impact on resource use is unknown. In addition, a previous study suggests that the benefits of GAE are particularly noticeable in the short and medium term.[14]

Conclusion

The present study suggests that there is no difference between GAE and control groups in terms of effectiveness and safety, but it is more costly than the standard treatment in Spain. Larger randomized controlled trials are necessary to elucidate the effects of GAE for chronic pain secondary to KO and, consequently, to determine whether it could potentially become cost-effective.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at htt://dx.doi.org/10.1016.....

What is known about the topic?

Genicular artery embolization has emerged as a promising minimally invasive procedure for refractory knee osteoarthritis, but evidence on its safety, effectiveness and cost-effectiveness compared to standard care is still uncertainty.

What does the study add to the literature?

Genicular artery embolization appears safe, but its effectiveness over standard treatment for knee osteoarthritis is unclear, and its use generates and additional € 3432.37 per patient, requiring 0.137 quality-adjusted life years improvement to be cost-effective.

What are the implications of the results?

Genicular artery embolization is more costly than standard care in Spain and requires specific health improvements to be cost-effective; larger studies are needed to confirm its viability as a cost-effective treatment for knee osteoarthritis.

Authorship contributions

A. Hernández-Yumar and Y. González-Hernández participated in the design, acquisition, analysis, and interpretation of data, as well as drafting the work. These authors share first authorship. T. del Pino-Sedeño, C. Valcárce-Nazco, A. de Armas-Castellano and E. Herrera-Ramos participated in the design,

acquisition, analysis, and interpretation of data, and reviewed the work. J. Portero Navarro, M. Carmona Rodríguez, M.X. Rojas-Reyes and M.M. Trujillo-Martín participated in the design, and critically reviewed the work. T. del Pino-Sedeño and M.M. Trujillo-Martín also contributed to project administration. All authors read and approved the final manuscript.

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Conflicts of interest

None.

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Table 1

Selection criteria for studies assessing effectiveness and safety.

Criteria category	Inclusion criteria
Population	Individuals with chronic pain secondary to mild or moderate KO refractory to standard treatment and/or severe KO who are not candidates for surgery
Intervention	GAE
Comparator	Standard treatment, usual treatment, conservative management, drug therapy (without GAE) or non-intervention
Outcome measure	Outcomes of interest included KO pain, overall function, HRQoL, need for pain medication, complications, and adverse events. For economic evaluations, the outcomes were: ICER, costs expressed in monetary units, and benefits expressed in QALY, LYG, monetary units, or any of the outcome measures included in the safety or effectiveness section
Type of study	High-quality systematic reviews were included, as well as randomized controlled trials. In their absence, non-randomized clinical trials and observational comparative studies were considered Full economic evaluations (either alongside primary studies or modelling based) were included: cost-benefit analysis, cost-utility analysis, cost-effectiveness analysis, cost-consequence analysis, and cost-minimization analysis
Language	Studies published in Spanish or English
Publication type	Only full original publications

GAE: genicular artery embolization; HRQoL: health related quality of life; ICER: incremental cost-effectiveness ratio; KO: knee osteoarthritis; LYG: life years gained; QALY: quality-adjusted life years.

Table 2

Selection criteria and baseline characteristics of participants in the included studies.

First author, year	n	n woman (%)	KO grade	Inclusion criteria	Exclusion criteria	GAE group				Control Group			
						n	Age Mean ± SD (range)	BMI Mean ± SD (range) / Median (IQR)*	Other characteristics Mean ± SD (range) / Median (IQR)*	n	Age mean ± SD (range)	BMI Mean ± SD (range) / Median (IQR)*	Other characteristics Mean ± SD (range) / Median (IQR)*
Bagla, 2022[37]	21	18 (85.7)	1-3 KL	1. >40 years 2. KL grade 1-3 findings on knee radiography 3. ≥50/100 on the VAS for pain 4. Pain refractory to 3 m of conservative therapies	1. Local infection 2. Life expectancy of <6 m 3. Severe atherosclerosis seen on prior imaging 4. RA 5. Infectious arthritis 6. Prior knee replacement surgery 7. INR of >2.5 8. Platelets less than 30,000/μL 9. Iodinated contrast medium allergy resulting in anaphylaxis	14	63.9 ± 8.37 (49-78)	30.8 ± 8.14 (16.9-43.8)	KL: 2.3 ± 0.51 (2-3) WOMAC: 64.9 ± 17 (33-87) VAS: 81.3 ± 12 (55-99)	7	62.9 ± 7.13 (49–71)	33.4 ± 10.5 (21.5-52.9)	KL: 2.3 ± 0.76 (1-3) WOMAC: 70.9 ± 13 (56-94) VAS: 78.9 ± 10 (69-92)

				10. eGFR of <60 mL/min/1.73 m^2									
Landers, 2023[36]	59	37 (62.7)	2 KL	1. 18-75 years 2. KL grade 2 3. Knee pain ≥6 m 4. Moderate to severe unilateral knee pain (≥3/10 knee pain on at least half the days in the preceding month according to an 11-point numeric scale) 5. Resistant to conservative treatment for at least 6 m 6. Willing, able and mentally competent to provide informed consent	1. Local infection 2. Active malignancy 3. RA or seronegative arthropathies 4. Prior ipsilateral knee surgery, excluding arthroscopic surgery >6 m ago 5. Ipsilateral knee intra-articular injection in past 6 m 6. KL grade 3-4 7. Pregnant or attempting pregnancy during the study period 8. Allergy to contrast media 9. Reduced kidney function or failure 10. Body weight >200 kg	29	61.1± 8.0 (NR)	30.3 (27.8 -37.8)*	Knee pain (years): 1.5 (1-5)*	30	60.1 ± 7.7 (NR)	33.6 (29.4-36.2)*	Knee pain (years): 1.0 (1-3)*

	11. Platelets <100 × 10^9/L 12. INR >1.5 13. Approved for knee joint replacement surgery 14. Moderate to severe pain in other lower limb joints 15. History of allergy to carbapenem, or immediate/severe reaction to penicillin/cephalosporin antibiotic 16. History of seizures or valproate use	

BMI: body mass index; eGFR: estimated glomerular filtration rate; GAE: genicular artery embolization; IQR: interquartile range; INR: International Normalized Ratio; KO: knee osteoarthritis; KL: Kellgren-Lawrence; NR: not reported; RA: rheumatoid arthritis; SD: standard deviation; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

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Table 3

Characteristics of genicular artery embolization and control procedures in the included studies.

First author, year	GAE group							Control group		
	Type of embolizer	Doses	Time (min) Mean ± SD (range)	Anesthesia type (details)	Sedation level (drugs)	Fluoroscopy time (min) Mean ± SD (range)	Radiation dose (mGy) Mean ± SD (range)	Type of control	Anesthesia type (details)	Sedation level (drugs)
Bagla, 2022[37]	Absorbable particles (Opti Sphere; Teleflex, Minneapolis, Minnesota)	100-300 micron	29.9 ± 15.8 (13-55)	NR	Moderate (midazolam + fentanyl)	6.70 ± 4.96 (4.05-17.8)	17.9 ± 5.52 (8.8-23.8)	Sham procedure	NR	Moderate (midazolam + fentanyl)
Landers, 2023[36]	Imipenem and cilastatin sodium (IPM-CS, Primaxin; Merck & Co, USA)	0.5 g	NR (30-60)	Local (into the groin immediately superficial to the femoral artery)	Light (NR)	NR	NR	Sham procedure	Local (into the groin immediately superficial to the femoral artery)	Light (NR)

GAE: genicular artery embolization; NR: not reported; SD: standard deviation.

Table 4

Results of the cost analysis: base case and sensitivity analysis. Costs per patient

Base case			
Cost		**Euros**	
Embolizers		38.59	
Anesthesia		0.37	
Instruments		765.25	
Digital subtraction angiography		792.06	
Wound closure		68.22	
Operating room use		1239.25	
Observation period		100.14	
Healthcare personnel		140.94	
Follow-up		287.55	
GAE total cost (= incremental cost per patient)		3432.37	
Probabilistic sensitivity analysis			
Incremental total cost (95%CI)]		€ 6741.84 (2992.10-11,726.68)	
One-way deterministic sensitivity analysis			
Parameter	**Value in base case**	**New value**	**Cost of GAE (= incremental cost per patient)**
Patients with allergy to antibiotics (%)	15	12 [Asm, −20%]	3426.67
		18 [Asm, +20%]	3438.07

Patients needed a vascular closure of the wound (%)	1	5 [Asm]	3433.86
		10 [Asm]	3435.71
GAE sessions (per year)	1	2 [Experts]	6577.20
		3 [Experts]	9722.02
GAE duration (hours)	1.5	1 [Experts]	2884.14
		2 [Experts]	3866.60
Observation period (hours)	4	3.2 [Asm, −20%]	3412.34
		4.8 [Asm, +20%]	3452.40
Follow-up visits	3	2 [Asm]	3336.52
		4 [Asm]	3528.22
Cost of usual embolizer (€ per vial)	10.10	8.08 [Asm, −20%]	3430.65
		12.12 [Asm, +20%]	3434.09
Cost of embolizer used in case of antibiotic allergy (€ per vial)	200	160 [Asm, −20%]	3426.37
		240 [Asm, +20%]	3438.37
Cost of anesthesia (€ per ampoule)	0.37	0.22 [Min[45]]	3432.22
		0.67 [Min[45]]	3432.67
Cost of wound closure by manual compression	67.85	54.28 [Asm, −20%]	3418.94
		81.42 [Asm, +20%]	3445.81
Cost of vascular closure of the wound	105	84 [Asm, −20%]	3432.16
		126 [Asm, +20%]	3432.58

Cost of digital subtraction angiography	792.06	428.85 [Min[46]]	3069.16
		1054 [Max[46]]	3694.31
Cost of 5 Fr introducer	97.01	13.33 [Min[42-44]]	3348.69
		193.88 [Max[42-44]]	3529.24
Cost of 5 Fr catheter (cobra)	38.17	19.27 [Min[42,44]]	3413.47
		111.63 [Max[42,44]]	3505.83
Cost of microcatheter	368.82	311.38 [Min[42,44]]	3374.92
		456.40 [Max[42,44]]	3519.95
Cost of 0.35 microguide	261.25	209 [Asm, −20%]	3380.12
		313.51 [Asm, +20%]	3484.62
Cost of the observation period (€ per hour)	25.04	4.67 [Min[46]]	3350.90
		51.46 [Max[46]]	3538.06
Labor cost (€ per hour)	31.32	25.06 [Asm, −20%]	3404.18
		37.58 [Asm, +20%]	3460.56
Cost of follow-up visit	95.85	40.02 [Min[46]]	3264.89
		153.04 [Max[46]]	3603.95
Cost of operating room (€ per session of 1.5 hours)	1239.25	991.4 [Asm, −20%]	3184.52
		1487.1 [Asm, +20%]	3680.22

Asm: assumption; 95%CI: 95% confidence interval; GAE: genicular artery embolization.

Figure Legends

Figure 1. Flow diagram of the selection process of effectiveness and safety studies.

Figure 2. Risk of bias in included studies.

Genicular Artery Embolization for the Treatment of Knee Osteoarthritis: A Systematic Review with Meta-Analysis and Cost-analysis

Embolización de la Arteria Genicular para el Tratamiento de la Osteoartritis de Rodilla: Una Revisión Sistemática con Metanálisis y Análisis de Costes

Abstract

Objective: To assess the effectiveness, **safety**, and cost-effectiveness of genicular artery embolization (GAE) for the treatment of mild or moderate knee osteoarthritis (KO) refractory to **standard treatment**, and/or severe KO in individuals not eligible for surgery.

Design: We conducted a systematic review with meta-analysis, supplemented by a cost-analysis, comparing GAE and standard treatment, from the perspective of the Spanish National Health System (NHS) over a one-year time horizon. The health improvement required for GAE to be deemed cost-effective was quantified, considering a willingness-to-pay threshold of 25 000 €/quality-adjusted life year (QALY).

Results: We included two randomized controlled trials (RCTs) in our analysis. Pain estimates showed inconsistent results, and no significant effects were observed for overall function, health-related quality of life, or changes in the need for pain management medication. No serious complications or major adverse events were observed. GRADE quality of evidence ranged from moderate to low. No economic evaluations were identified. Our cost-analysis revealed that GAE would result in an incremental cost of EUR 3432.37 per patient**, requiring a health improvement of 0.137 QALY per patient** to be deemed **a** cost-effective **technology**.

Conclusions: In summary, based on moderate to low-certainty evidence, it remains inconclusive whether there is any difference between GAE and standard treatment for KO. However, the use of GAE would increase the costs. Larger RCTs are needed to determine the effects of using GAE for chronic pain secondary to KO and,

consequently, to ascertain whether this technology could potentially become cost-effective from the NHS perspective.

Keywords

Genicular artery, embolization, knee osteoarthritis, pain, systematic review, economic evaluation

Resumen

Objetivo: Evaluar la efectividad, seguridad y coste-efectividad de la embolización de la arteria genicular (EAG) para el tratamiento de la artrosis de rodilla (AR) leve o moderada, refractaria al tratamiento habitual, o grave en personas no candidatas a cirugía.

Diseño: Se llevó a cabo una revisión sistemática con metanálisis y un análisis de costes, para comparar la EAG y el tratamiento habitual, desde la perspectiva del Sistema Nacional de Salud (SNS) español, con un horizonte temporal de un año. Se estimó la mejora en salud necesaria para que la EAG se considere coste-efectiva, con un umbral de 25.000 €/año de vida ajustado por calidad (AVAC).

Resultados: Se incluyeron dos ensayos controlados aleatorizados (ECA). Los resultados en dolor fueron inconsistentes y no se observaron efectos significativos en la función general, calidad de vida o necesidad de medicación para el dolor. No se observaron complicaciones graves ni eventos adversos mayores. La calidad de la evidencia fue de moderada a baja. No se identificaron evaluaciones económicas previas. El coste incremental de la EAG sería de 3.432,37 €/paciente, requiriendo una mejora de 0,137 AVAC/paciente para ser coste-efectiva.

Conclusiones: La evidencia de certeza moderada a baja no permite concluir si hay diferencias entre la EAG y el tratamiento habitual para la AR. Sin embargo, el uso de la EAG incrementaría los costes. Se necesitan ECA de mayor tamaño para determinar los efectos de la EAG en el dolor crónico secundario a la AR y establecer si podría ser coste-efectiva desde la perspectiva del SNS.

Palabras clave: Arteria genicular, embolización, osteoartritis de rodilla, dolor, revisión sistemática, evaluación económica.

1. Introduction

Knee osteoarthritis (KO) is a leading cause of chronic pain and disability worldwide, particularly among women, individuals over 50, and individuals who are overweight or obese,[1,2] with an estimated prevalence of 29.3% in the general population.[3]

Standard treatment for early-stage KO (mild to moderate) includes exercise, postural measures, weight control,[1,4] and pharmacotherapy.[4–6] **Intra-articular injections of hyaluronic acid or platelet-rich plasma have emerged as newer non-surgical treatment options for managing KO[1,7].** Joint replacement surgery is reserved for severe cases with intense pain and functional disability.[8] However, many patients experience refractory chronic pain or are not surgical candidates. Additionally, some patients may experience complications associated with long-term pharmacotherapy, such as kidney or liver failure, opioid addiction, or local issues arising from injections.[9]

Recently, genicular artery embolization (GAE) has emerged as a promising minimally invasive procedure for managing secondary pain to locomotor inflammatory diseases.[10] GAE selectively embolizes genicular branches to painful or abnormal vascularized areas,[11] typically using microspheres or polyvinyl alcohol particles.[12]

GAE has been proposed as an alternative or complementary treatment to the standard non-surgical treatment for KO,(5–7)[4,13–16] particularly for patients resistant to conventional therapies, including those who cannot or prefer not to undergo surgery. While some studies suggest that GAE may benefit patients across the spectrum of KO severity,[13] others suggest its potential for early and low-grade KO, especially in the short and medium term.[14] Additionally, this procedure is considered safe, without major complications,[4,6,13] although minor complications are not infrequent.[13]

This study evaluates the effectiveness, safety and cost-effectiveness of GAE in treating mild to moderate KO refractory to **standard treatment** or severe KO in non-surgical candidates, due to the still existing uncertainty.

2. Methods

2.1. Systematic review on effectiveness, safety and cost-effectiveness

A systematic review (SR) on the clinical effectiveness and safety of GAE for treating mild to moderate KO refractory to **standard treatment** or severe KO in non-surgical candidates was conducted according to the Cochrane Collaboration methodology,[17] with reporting in accordance with the PRISMA statement.[18] The protocol was registered in OSF [OSF osf.io/ytxvu]. Complementary, a SR of cost-effectiveness were performed following the Campbell-Cochrane Economic Methods.[19]

2.1.1. Information sources and search strategy

The SR searches and subsequent identification of their included randomized controlled trials (RCTs) or non-randomized comparative studies was conducted using technological enablers from the Epistemonikos database, in April 2023. The results were automatically incorporated into the Epistemonikos L·OVE platform,[20] where subsequent selection was conducted. **An alert service for RCTs and non-randomized comparative studies was also created, which remained active until May 31, 2024.**

Additionally, to identify RCTs or other comparative studies not included in available SRs, searches were conducted in MEDLINE **(Ovid)**, Embase **(Elsevier)**, CENTRAL **(Wiley)**, and CINAHL **(EBSCOhost)**, in October 2023.

Economic evaluations (EEs) were identified through searches in MEDLINE, **Embase**, and Web of Science, in June 2023. The terms from this strategy were combined with a strategy specifically designed by the University of York[21] to identify EEs.

All search strategies were limited to studies published in English or Spanish within the last 10 years, as the earliest study on joint embolization for pain management in inflammatory musculoskeletal diseases was published in 2013.[10]

Retrieved references were managed using Zotero 6.0.23[22] and deduplicated using Deduklick,[23] followed by manual removal of duplicates and study selection in Microsoft Excel.

Furthermore, the bibliography of included articles was manually examined, and studies citing the selected studies were verified through Google Scholar.

Full search strategies for all database searches are provided in Appendix A.

2.1.2. Selection criteria

Studies were eligible for inclusion if they fulfilled the criteria summarized in Table 1.

2.1.3. Study selection, data extraction process and assessment of risk of bias

Two reviewers independently and in parallel performed the selection process, data extraction, and assessment of risk of bias.

Titles and abstracts were initially assessed, followed by a full-text review for studies meeting the criteria.

A standardized data extraction form was created in Microsoft Excel, including information on article identification, study design, participant characteristics, eligibility criteria, intervention and comparator details; assessed effectiveness and safety outcomes along with measurement timing; cost-effectiveness methodology and outcomes; study funding source, and disclosed conflicts of interest by the researchers.

To assess the methodological quality of the identified SRs, the AMSTAR-2 tool was selected.[24] The risk of bias of the included primary studies was assessed using the Cochrane RoB 2 tool for parallel and crossover RCTs.[25] The appraisal of methodological quality of EEs was planned based on Drummond et al.'s criteria list.[26]

Discrepancies between reviewers were resolved through discussion.

2.1.4. Publication bias assessment

The assessment of publication bias was planned by creating a funnel plot and computing the Egger's regression test;[27] however, the minimum number of studies necessary was not reached.

2.1.5. Synthesis of the evidence

Study characteristics were summarized narratively and presented in summary tables. Meta-analyses (MA) were conducted for quantitative synthesis. Heterogeneity was assessed using forest plots, the χ^2 statistical ($P < 0.01$) and the Higgins I^2 test. Initially, a fixed-effect model was used to evaluate the statistical heterogeneity among included studies (I^2 statistics). In cases of high unexplained heterogeneity ($I^2 > 70\%$), MA was not performed, and results were reported narratively. All analyses were conducted using RevMan 5.4.[28]

Potential confounders considered were baseline pain level, osteoarthritis (OA) severity, and type of embolic agents used. However, subgroup analyses were limited due to the small number of studies evaluated.

2.1.6. Certainty of evidence

The certainty of the evidence (CoE) for all outcomes was judged using the GRADE methodology, considering risk of bias, consistency, directness, precision and reporting bias.[29] Certainty was assessed as high, moderate, low or very low. A Summary

of Findings table was prepared to present the CoE and the magnitude of the effects for the main comparison.[30,31]

2.2. Economic evaluation

A cost-analysis was conducted to compare the costs (in Euros of 2023) of two treatments for chronic pain secondary to KO: the use of GAE of the affected knee followed by **standard** treatment (evaluated strategy), and the standard treatment alone (comparator), which involves annual hyaluronic acid injections and prescription of physical exercise, in addition to radiofrequency sessions if the patient does not improve.

The target patients were those with chronic pain secondary to mild to moderate KO refractory to **standard treatment** or non-surgical candidates with severe KO. The analysis was performed from the perspective of the Spanish National Health System (NHS) with a one-year time horizon covering the entire treatment period in the evaluated strategy. No discount rate was applied due to the short-term horizon.

The incremental cost per patient and the annual cost for a hospital with a target population size of 40 patients (value reported by experts) were calculated. Additionally, we estimated the health improvement, in quality-adjusted life years (QALYs), that GAE should generate per patient to be considered a cost-effective technology. This was estimated by solving the incremental effectiveness $(E_A - E_B)$ from the incremental cost-effectiveness ratio equation ($ICER = (C_A - C_B)/(E_A - E_B)$, where $(C_A - C_B)$ is the estimated incremental cost, and A and B represent the evaluated strategy and the comparator, respectively). The cost-effectiveness threshold estimated for Spain (€25 000 per QALY)[32] was applied. The analysis was conducted using Microsoft Excel 2013.

We performed one-way deterministic and probabilistic (1000 second-order Monte-Carlo simulations) sensitivity analyses.

2.2.1. Parameters

Since both alternatives include the standard treatment, only the resource use and the corresponding costs of the GAE were considered, as the inclusion of shared costs would not affect the incremental cost.[26]

The analysis included those associated with the intervention (drugs, instruments, wound closure, healthcare personnel, operating room use, and post-intervention observation period) and the follow-up (Appendix B).

3. Results

3.1. Systematic review on effectiveness and safety

The search in Epistemonikos yielded a total of 13 SRs. **Nine** were initially considered potentially eligible **after title and abstract screening** according to the selection criteria; however, none were finally included because they did not attain a high-quality rating.[4,6,13–16,33–35] The full quality assessment can be found in Appendix C.

The search for primary studies retrieved 126 references after removing duplicates (Figure 1). After the title and abstract screening, 12 publications were selected for full-text analysis. According to pre-established criteria, nine of these were excluded. Appendix D shows the list of excluded references and the main reason for exclusion.

Examination of the bibliographic listing of included studies and the Google Scholar search did not lead to any additional studies. **No additional studies were identified through the alert service created using the Epistemonikos database.** Therefore, the final selection consisted of two RCTs,[36,37] reported in three publications.[36–38]

3.1.1. Characteristics of included studies

The main characteristics of the included studies are summarized in Table 2 and Table 3. For a detailed description of the characteristics and further details of the included studies, please refer to Appendix E and Appendix F.

3.1.2. Risk of bias in included studies

The overall risk of bias in the included RCTs was considered low. The summary of the assessment can be found in **Figure 2** and Appendix G.

3.1.3. Certainty of evidence

The overall quality of evidence was considered low. The evidence profile for GAE vs. **standard treatment** outcomes indicated moderate to low CoE (Appendix H).

3.1.4. Summary of results

Results of all meta-analysis conducted are available in Appendix I.

3.1.4.1. Pain (**CoE**: low ⨁⨁⨀⨀/moderate ⨁⨁⨁⨀)

The included RCTs examined the effect of GAE on pain at 1 month,[36,37] 6 months[36], and 12 months.[36] However, due to very high heterogeneity rates (I^2= 91%) in the 1-month pain analysis, pooled data are not presented.

Preliminary findings reveal significant discrepancies in pain levels 1 month after GAE. There is low-quality evidence suggesting that GAE may have little to no effect according to the KOOS Pain subscale (1 study; 59 patients)[36] or may result in a slight decrease in pain levels assessed with the VAS (Mean difference [MD]= 50.1 millimeter; 95% CI [29.0, 72.3]; 1 study; 21 patients).[37] At 6 and 12 months of follow-up, moderate quality evidence suggests GAE probably results in little to no effect.

In the Bagla et al. study,[37] the response rates at 1 month were 79% (11/14) and 0% (0/7) for the GAE and sham arms, respectively. However, in the Landers et al. study,[36] overall change in knee pain at 12 months indicated that 17 participants (58.6%) in the GAE group reported being moderately or much better, compared to 11 participants (37.9%) in the control group, though this difference was also not statistically significant.

3.1.4.2. Overall function (CoE: moderate ⨁⨁⨁⨀)

The included studies examined the impact of interventions (GAE vs. sham) on overall functional improvement at 1 month,[36,37] 6 months,[36] and 12 months,[36] using the WOMAC,[37] KOOS Daily Living subscale, and KOOS Function in Sport and Recreation subscale.[36] The effects in all these scales were pooled.

Moderate-quality evidence suggests GAE likely has little to no effect on functional capacity at 1 **month (SMD= -0.18; 95% CI [-0.62, 0.27], I^2= 0%, 2 studies; 80 patients)**, 6 **months (SMD= -0.17; 95% CI [-0.68, 0.34], 1 study; 59 patients)** and 12 months **(SMD= 0.07; 95% CI [-0.44, 0.58], 1 study; 59 patients)** compared to **standard** or pharmacological treatment.

3.1.4.3. Health related quality of life (HRQoL) (CoE: low ⨁⨁⨀⨀/moderate ⨁⨁⨁⨀)

Only Landers et al.[36] reported on the effect of interventions on HRQoL. Low-quality evidence suggests that GAE may have little to no effect on HRQoL assessed with the KOOS Quality of Life subscale at 1 month compared to **standard** treatment (1 study, 59 patients). GAE probably results in little to no difference in HRQoL at 6 and 12 months.

However, low-quality evidence suggests that GAE may result in a slight improvement of HRQoL levels using the EQ-5D VAS at 6-month follow-up (MD= -10.00; 95% CI [-19.45, -0.55], 59 patients). Moderate-quality evidence suggests that GAE likely has little to no effect on HRQoL at 1 month and 12 months compared to **standard** treatment (1 study, 59 patients).

No differences were observed in the rates of patients who did not present or presented slight problems with anxiety, discomfort, mobility, usual activities, or self-care assessed with EQ-5D.

3.1.4.4. Need for pain medication (CoE: moderate ⨁⨁⨁⨀)

Only Landers et al.[36] reported changes in the need for pain medication. At 12 months, the GAE group had a lower proportion of participants taking analgesics (control 48%, intervention 24%). However, moderate-quality evidence suggests that GAE likely

does not reduce or increase the need for pain medication (Risk ratio [RR]= 0.52; 95% CI [0.24, 1.10]; 1 study; 59 patients).

3.1.4.5. Adverse events and complications

No major adverse events were reported in either of the two studies.[36,37] Specifically, in the study by Landers et al.,[36] it was reported that no evidence of osteonecrosis or ischemic complications were found on magnetic resonance imaging up to two years following the procedure. No differences were observed in minor adverse events.[36,37]

3.2. Systematic review on cost-effectiveness

The electronic databases retrieved nine references, but after reading titles and abstracts, all of them were excluded (Appendix J). Therefore, no economic evaluations focused on GAE and that meet the established inclusion criteria were identified.

3.3. Economic evaluation

Over a one-year horizon, the inclusion of GAE in the **standard treatment** generates an increment in costs of €3432.37 per patient, from the NHS perspective (Table 4). Considering this incremental cost, **a health improvement of** 0.137 QALYs **per patient is required for GAE** to be **deemed** cost-effective compared to the **standard** treatment. In addition, the estimated annual cost of implementing this technology would be €137 294.86 for a general hospital treating a target population of 40 patients per year.

The one-way sensitivity analysis shows that the incremental cost can vary from €2884.14, if the intervention duration is reduced from 1.5 hours to 1 hour, to €9722.02, if GAE is administered three times to the same patient within the time horizon. Meanwhile, the probabilistic analysis estimates an incremental cost of €6741.84 per

277 patient (95% CI [€2992.10, €11 726.68]), associated with the application of the GAE
278 technique (Table 4).
279

4. Discussion

The present SR on the effectiveness and safety of GAE for chronic pain secondary to KO refractory to **standard** treatment identified two RCTs (n=80) evaluating GAE compared to **standard treatment**.

The results show that evidence is insufficient to draw definitive conclusions regarding the beneficial effects of GAE compared to standard treatment for KO in terms of knee pain, overall functional improvement, HRQoL, changes in the need for pain medication, adverse event or complications. Evidence for these outcomes is affected by inconsistency and imprecision, with wide confidence intervals and/or a very small sample size.

Recent research has shown promising results for GAE as an alternative treatment for chronic joint pain in patients with KO.[4,13–16] Some studies suggest that GAE can offer benefits across varying degrees of OA severity,[13] while others consider that this technique has potential mainly for early and low-grade OA, particularly in the short and medium term.[14] Additionally, this procedure is considered safe, with no serious complications reported,[4,6,13] but minor complications are not uncommon.[13]

However, these findings are predominantly based on observational studies, highlighting the need to confirm them with high-quality RCTs. Further research is needed to evaluate GAE long-term outcomes, its comparative efficacy with other modalities, and its role in the therapeutic approach.[4,6,16,35]

The present SR findings suggest that GAE appears to be a safe alternative, as previous studies have indicated, but without evidence of its effectiveness within a one-year timeframe. The above-mentioned limitations, and considering the low certainty

evidence supporting our conclusions, justify keeping this question in "living mode" as proposed in our original protocol.[39]

The SR did not identify any EE on GAE that met the established inclusion criteria. The identified evidence is insufficient to establish significant differences between the GAE technique and the comparator **(necessary to perform a cost-effectiveness analysis)** or to conclude that both treatments have the same effectiveness **(necessary to perform a cost-minimization analysis)**. Therefore, we **only compared the costs** conducting a cost-analysis.

The cost-analysis results showed that the incorporation of GAE into the **standard treatment** (application of hyaluronic acid once a year plus a prescribed physical exercise regimen) would lead to an increase in cost of €3432.37 per patient compared to the **standard treatment** alone in a year. This translates to an additional annual cost of €137 294.86 for a general hospital with a target population of 40 patients per year. This technology could **only** be considered cost-effective if an improvement in health of at least 0.137 QALYs per patient within a year **is achieved**.

This SR has several strengths. It was developed using a robust predefined methodology outlined in a registered protocol. All steps were performed in duplicate to minimize errors throughout the review process. Additionally, the evidence was synthesized using the GRADE methodology, known for its transparency in evidence development and presentation.

However, the main limitation of this review is the scarcity of evidence, stemming from a low number of studies with small sample sizes, leading to inconsistent results in measured outcomes. Others, mainly due to the low number of studies, include the absence of sensitivity, subgroup and meta-regression analyses. **Additionally, as is standard in**

SRs, the methodology **may have** exclud**ed** unpublished studies, published in languages other than English or Spanish, or in unindexed journals**, which could potentially limit the comprehensiveness of the evidence. Furthermore, although an alert service for identifying RCTs and non-randomized comparative studies remained active until May 31, 2024, a gap exists between this date and the present, which may have excluded more recent evidence potentially influencing the findings.**

To the best of the authors' knowledge, this is the first analysis assessing the costs of the GAE technique in Spain. **A** complete EE comparing costs and effects could not be performed **due to effectiveness results. However, given the usefulness of ICER, as an efficiency measure, in the decision-making process,** we estimated the health improvement per patient necessary for GAE to be considered cost-effective**, compared to the standard treatment, for a willing-to-pay threshold of €25,000 per QALY.**

The main limitations of the cost analysis arise from data scarcity. First, evidence on the proportion of target patients requiring vascular closure or those allergic to antibiotics could not be identified, thus assumptions and a value for a general patient[40] were used, respectively. Second, the cost of wound closure with manual compression was obtained from a single study without specifying the year in which the Euros were measured.[41] Therefore, 2020 (the publication year) was assumed as the reference year. Third, instrument costs were extracted from tender documents of some Spanish public hospitals,[42–44] reflecting their reality but may vary contextually. Fourth, resource use information was provided by an expert. **Although** clinical practice **was assumed to be at least similar** across Spain**, there could be regional differences**. Sensitivity analyses show that the incremental cost per patient can range from €2884.14 to €11 726.68, a wide variation especially influenced by the number of sessions conducted during the time horizon. **Bearing in mind this, regional differences in terms of incremental costs**

related to the use of resources derived from the clinical practice and the unit costs in each region could be observed. Nonetheless, experts validated the assumptions (face validity) and sensitivity analyses variations of these parameters did not significantly alter the results. **Finally, the time horizon was restricted to one year because there is no evidence on effectiveness and safety beyond this period, so the impact on resource use is unknown. In addition, a previous study suggests that the benefits of GAE are particularly noticeable in the short and medium term.**[14]

5. Conclusion

The present study suggests that there is no difference between GAE and control groups in terms of effectiveness and safety, but it is more costly than the **standard treatment** in Spain. Larger RCTs are necessary to elucidate the effects of GAE for chronic pain secondary to KO and, consequently, to determine whether it could potentially become cost-effective.

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Table 1. Selection Criteria for Studies Assessing Effectiveness and Safety

Criteria Category	Inclusion criteria
Population	Individuals with chronic pain secondary to mild or moderate KO refractory to **standard treatment** and/or severe KO who are not candidates for surgery.
Intervention	GAE.
Comparator	**Standard treatment**, usual treatment, conservative management, drug therapy (without GAE) or non-intervention.
Outcome measure	Outcomes of interest included KO pain, overall function, HRQoL, need for pain medication, complications, and adverse events. For EEs, the outcomes were: ICER, costs expressed in monetary units, and benefits expressed in QALYs, LYG, monetary units, or any of the outcome measures included in the safety or effectiveness section.
Type of study	**High-quality SRs were included, as well as RCTs. In their absence, non-randomized clinical trials and observational comparative studies were considered.** **Full EEs (either alongside primary studies or modelling based) were included: cost-benefit analysis, cost-utility analysis, cost-effectiveness analysis, cost-consequence analysis, and cost-minimization analysis.**
Language	Studies published in Spanish or English.
Publication type	Only full original publications.

Note. GAE: Genicular artery embolization; HRQoL: health related quality of life; ICER: incremental cost-effectiveness ratio; KO: Knee Osteoarthritis; LYG: life years gained; QALYs: quality-adjusted life years.

Table 2. Selection criteria and baseline characteristics of participants in the included studies.

First author, year	N	N woman (%)	KO Grade	Inclusion criteria	Exclusion criteria	GAE group				Control Group			
						N	Age Mean ± SD (range)	BMI Mean ± SD (range) / Median (IQR)*	Other characteristics Mean ± SD (range) / Median (IQR)*	N	Age Mean ± SD (range)	BMI Mean ± SD (range) / Median (IQR)*	Other characteristics Mean ± SD (range) / Median (IQR)*
Bagla, 2022[37]	21	18 (85.7)	1–3 KL	1. >40 years 2. KL grade 1–3 findings on knee radiography 3. ≥ 50/100 on the VAS for pain 4. Pain refractory to 3 m of conservative therapies	1. Local infection 2. Life expectancy of <6 m 3. Severe atherosclerosis seen on prior imaging 4. RA 5. Infectious arthritis 6. Prior knee replacement surgery 7. INR of >2.5 8. Platelets less than 30,000/μL 9. Iodinated contrast medium allergy resulting in anaphylaxis 10. eGFR of <60 mL/min/1.73 m2	14	63.9 ± 8.37 (49-78)	30.8 ± 8.14 (16.9-43.8)	KL: 2.3 ± 0.51 (2-3) WOMAC: 64.9 ± 17 (33-87) VAS: 81.3 ± 12 (55-99)	7	62.9 ± 7.13 (49–71)	33.4 ± 10.5 (21.5–52.9)	KL: 2.3 ± 0.76 (1–3) WOMAC: 70.9 ± 13 (56–94) VAS: 78.9 ± 10 (69–92)
Landers, 2023[36]	59	37 (62.7)	2 KL	1. 18–75 years 2. KL grade 2 3. Knee pain ≥ 6 m 4. Moderate to severe unilateral knee pain (≥3/10 knee pain on at least half the days in the preceding month according to an 11-point numeric scale) 5. Resistant to	1. Local infection 2. Active malignancy 3. RA or seronegative arthropathies 4. Prior ipsilateral knee surgery, excluding arthroscopic surgery >6 m ago 5. Ipsilateral knee intra-articular injection in past 6 m 6. KL grade 3-4 7. Pregnant or	29	61.1± 8.0 (NR)	30.3 (27.8 -37.8)*	Knee pain(yrs): 1.5 (1-5)*	30	60.1 ± 7.7 (NR)	33.6 (29.4-36.2)*	Knee pain(yrs): 1.0 (1-3)*

	conservative treatment for at least 6 m 6. Willing, able and mentally competent to provide informed consent	attempting pregnancy during the study period 8. Allergy to contrast media 9. Reduced kidney function or failure 10. Body weight over 200 kg 11. Platelets <100×109/L 12. INR >1.5 13. Approved for KJR surgery 14. Moderate to severe pain in other lower limb joints 15. History of allergy to carbapenem, or immediate/severe reaction to penicillin/cephalosporin antibiotic 16. History of seizures or valproate use	

Note: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; GAE: Genicular artery embolization; IQR: Interquartile Range; INR: International normalized ratio; KJR: Knee joint replacement; KO: Knee osteoarthritis; KL: Kellgren–Lawrence; m: months; N: number of patients; RA: Rheumatoid arthritis; SD: standard deviation; NR: Not reported; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; yrs: years

Table 3. Characteristics of GAE and control procedures in the included studies.

First author, year	GAE group							Control Group		
	Type of embolizer	**Doses**	**Time (min)** Mean ± SD (range)	**Anesthesia** Type (details)	**Sedation** Level (drugs)	**Fluoroscopy time (min)** Mean ± SD (range)	**Radiation dose (mGy)** Mean ± SD (range)	**Type of control**	**Anesthesia** Type (details)	**Sedation** Level (drugs)
Bagla, 2022[37]	Absorbable particles (Opti Sphere; Teleflex, Minneapolis, Minnesota)	100–300 micron	29.9 ± 15.8 (13–55)	NR	Moderate (midazolam + fentanyl)	6.70 ± 4.96 (4.05–17.8)	17.9 ± 5.52 (8.8 –23.8)	Sham procedure	NR	Moderate (midazolam + fentanyl)
Landers, 2023[36]	Imipenem and cilastatin sodium (IPM-CS, Primaxin; Merck & Co, USA)	0.5 g	NR (30-60)	Local (into the groin immediately superficial to the femoral artery)	Light (NR)	NR	NR	Sham procedure	Local (into the groin immediately superficial to the femoral artery)	Light (NR)

Note: g: gram; GAE: genicular artery embolization; mGy: milligray; min: minutes; NR: Not reported; SD: standard deviation

Table 4. Results of the cost analysis: base case and sensitivity analysis. Costs per patient

Base case			
Cost		**Euros**	
Embolizers		38.59	
Anesthesia		0.37	
Instruments		765.25	
Digital subtraction angiography		792.06	
Wound closure		68.22	
Operating room use		1239.25	
Observation period		100.14	
Healthcare personnel		140.94	
Follow-up		287.55	
GAE total cost (= incremental cost per patient)		**3432.37**	
Probabilistic sensitivity analysis			
Incremental total cost [95% CI]		€ 6741.84 [2992.10, 11 726.68]	
One-way deterministic sensitivity analysis			
Parameter	**Value in base case**	**New value**	**Cost of GAE (= incremental cost per patient). Euros**
Patients with allergy to antibiotics (%)	15	12 [Asm, -20%]	3426.67
		18 [Asm, +20%]	3438.07
Patients needed a vascular closure of the wound (%)	1	5 [Asm]	3433.86
		10 [Asm]	3435.71
GAE sessions (per year)	1	2 [Experts]	6577.20
		3 [Experts]	9722.02
GAE duration (hours)	1.5	1 [Experts]	2884.14
		2 [Experts]	3866.60
Observation period (hours)	4	3.2 [Asm, -20%]	3412.34
		4.8 [Asm, +20%]	3452.40
Follow-up visits	3	2 [Asm]	3336.52
		4 [Asm]	3528.22
Cost of usual embolizer (€ per vial)	10.10	8.08 [Asm, -20%]	3430.65
		12.12 [Asm, +20%]	3434.09
	200	160 [Asm, -20%]	3426.37

Cost of embolizer used in case of antibiotic allergy (€ per vial)		240 [Asm, +20%]	3438.37
Cost of anesthesia (€ per ampoule)	0.37	0.22 [Min[45]]	3432.22
		0.67 [Min[45]]	3432.67
Cost of wound closure by manual compression	67.85	54.28 [Asm, -20%]	3418.94
		81.42 [Asm, +20%]	3445.81
Cost of vascular closure of the wound	105	84 [Asm, -20%]	3432.16
		126 [Asm, +20%]	3432.58
Cost of digital subtraction angiography	792.06	428.85 [Min[46]]	3069.16
		1054 [Max[46]]	3694.31
Cost of 5Fr introducer	97.01	13.33 [Min[42–44]]	3348.69
		193.88 [Max[42–44]]	3529.24
Cost of 5Fr catheter (cobra)	38.17	19.27 [Min[42,44]]	3413.47
		111.63 [Max[42,44]]	3505.83
Cost of microcatheter	368.82	311.38 [Min[42,44]]	3374.92
		456.40 [Max[42,44]]	3519.95
Cost of 0.35 microguide	261.25	209 [Asm, -20%]	3380.12
		313.51 [Asm, +20%]	3484.62
Cost of the observation period (€ per hour)	25.04	4.67 [Min[46]]	3350.90
		51.46 [Max[46]]	3538.06
Labor cost (€ per hour)	31.32	25.06 [Asm, -20%]	3404.18
		37.58 [Asm, +20%]	3460.56
Cost of follow-up visit	95.85	40.02 [Min[46]]	3264.89
		153.04 [Max[46]]	3603.95
Cost of operating room (€ per session of 1.5 hours)	1239.25	991.4 [Asm, -20%]	3184.52
		1487.1 [Asm, +20%]	3680.22

Asm: Assumption; CI: Confidence interval; GAE: Genicular artery embolization; min: minimum; max: maximum

Figure Legends

Figure 1. Flow diagram of the selection process of effectiveness and safety studies

Figure 2. Risk of Bias in Included Studies

Genicular Artery Embolization for the Treatment of Knee Osteoarthritis: A Systematic Review with Meta-Analysis and Cost-analysis

Embolización de la Arteria Genicular para el Tratamiento de la Osteoartritis de Rodilla: Una Revisión Sistemática con Metanálisis y Análisis de Costes

Abstract

Objective: To assess the effectiveness, safety, and cost-effectiveness of genicular artery embolization (GAE) for the treatment of mild or moderate knee osteoarthritis (KO) refractory to standard treatment, and/or severe KO in individuals not eligible for surgery.

Design: We conducted a systematic review with meta-analysis, supplemented by a cost-analysis, comparing GAE and standard treatment, from the perspective of the Spanish National Health System (NHS) over a one-year time horizon. The health improvement required for GAE to be deemed cost-effective was quantified, considering a willingness-to-pay threshold of 25 000 €/quality-adjusted life year (QALY).

Results: We included two randomized controlled trials (RCTs) in our analysis. Pain estimates showed inconsistent results, and no significant effects were observed for overall function, health-related quality of life, or changes in the need for pain management medication. No serious complications or major adverse events were observed. GRADE quality of evidence ranged from moderate to low. No economic evaluations were identified. Our cost-analysis revealed that GAE would result in an incremental cost of EUR 3432.37 per patient, requiring a health improvement of 0.137 QALY per patient to be deemed a cost-effective technology.

Conclusions: In summary, based on moderate to low-certainty evidence, it remains inconclusive whether there is any difference between GAE and standard treatment for KO. However, the use of GAE would increase the costs. Larger RCTs are needed to determine the effects of using GAE for chronic pain secondary to KO and, consequently, to ascertain whether this technology could potentially become cost-effective from the NHS perspective.

Keywords

Genicular artery, embolization, knee osteoarthritis, pain, systematic review, economic evaluation

Resumen

Objetivo: Evaluar la efectividad, seguridad y coste-efectividad de la embolización de la arteria genicular (EAG) para el tratamiento de la artrosis de rodilla (AR) leve o moderada, refractaria al tratamiento habitual, o grave en personas no candidatas a cirugía.

Diseño: Se llevó a cabo una revisión sistemática con metanálisis y un análisis de costes, para comparar la EAG y el tratamiento habitual, desde la perspectiva del Sistema Nacional de Salud (SNS) español, con un horizonte temporal de un año. Se estimó la mejora en salud necesaria para que la EAG se considere coste-efectiva, con un umbral de 25.000 €/año de vida ajustado por calidad (AVAC).

Resultados: Se incluyeron dos ensayos controlados aleatorizados (ECA). Los resultados en dolor fueron inconsistentes y no se observaron efectos significativos en la función general, calidad de vida o necesidad de medicación para el dolor. No se observaron complicaciones graves ni eventos adversos mayores. La calidad de la evidencia fue de moderada a baja. No se identificaron evaluaciones económicas previas. El coste incremental de la EAG sería de 3.432,37 €/paciente, requiriendo una mejora de 0,137 AVAC/paciente para ser coste-efectiva.

Conclusiones: La evidencia de certeza moderada a baja no permite concluir si hay diferencias entre la EAG y el tratamiento habitual para la AR. Sin embargo, el uso de la EAG incrementaría los costes. Se necesitan ECA de mayor tamaño para determinar los efectos de la EAG en el dolor crónico secundario a la AR y establecer si podría ser coste-efectiva desde la perspectiva del SNS.

Palabras clave

Arteria genicular, embolización, osteoartritis de rodilla, dolor, revisión sistemática, evaluación económica.

1. Introduction

Knee osteoarthritis (KO) is a leading cause of chronic pain and disability worldwide, particularly among women, individuals over 50, and individuals who are overweight or obese,[1,2] with an estimated prevalence of 29.3% in the general population.[3]

Standard treatment for early-stage KO (mild to moderate) includes exercise, postural measures, weight control,[1,4] and pharmacotherapy.[4–6] Intra-articular injections of hyaluronic acid or platelet-rich plasma have emerged as newer non-surgical treatment options for managing KO[1,7]. Joint replacement surgery is reserved for severe cases with intense pain and functional disability.[8] However, many patients experience refractory chronic pain or are not surgical candidates. Additionally, some patients may experience complications associated with long-term pharmacotherapy, such as kidney or liver failure, opioid addiction, or local issues arising from injections.[9]

Recently, genicular artery embolization (GAE) has emerged as a promising minimally invasive procedure for managing secondary pain to locomotor inflammatory diseases.[10] GAE selectively embolizes genicular branches to painful or abnormal vascularized areas,[11] typically using microspheres or polyvinyl alcohol particles.[12]

GAE has been proposed as an alternative or complementary treatment to the standard non-surgical treatment for KO,(5–7)[4,13–16] particularly for patients resistant to conventional therapies, including those who cannot or prefer not to undergo surgery. While some studies suggest that GAE may benefit patients across the spectrum of KO severity,[13] others suggest its potential for early and low-grade KO, especially in the short and medium term.[14] Additionally, this procedure is considered safe, without major complications,[4,6,13] although minor complications are not infrequent.[13]

This study evaluates the effectiveness, safety and cost-effectiveness of GAE in treating mild to moderate KO refractory to standard treatment or severe KO in non-surgical candidates, due to the still existing uncertainty.

2. Methods

2.1. Systematic review on effectiveness, safety and cost-effectiveness

A systematic review (SR) on the clinical effectiveness and safety of GAE for treating mild to moderate KO refractory to standard treatment or severe KO in non-surgical candidates was conducted according to the Cochrane Collaboration methodology,[17] with reporting in accordance with the PRISMA statement.[18] The protocol was registered in OSF [OSF osf.io/ytxvu]. Complementary, a SR of cost-effectiveness were performed following the Campbell-Cochrane Economic Methods.[19]

2.1.1. Information sources and search strategy

The SR searches and subsequent identification of their included randomized controlled trials (RCTs) or non-randomized comparative studies was conducted using technological enablers from the Epistemonikos database, in April 2023. The results were automatically incorporated into the Epistemonikos L·OVE platform,[20] where subsequent selection was conducted. An alert service for RCTs and non-randomized comparative studies was also created, which remained active until May 31, 2024.

Additionally, to identify RCTs or other comparative studies not included in available SRs, searches were conducted in MEDLINE (Ovid), Embase (Elsevier), CENTRAL (Wiley), and CINAHL (EBSCOhost), in October 2023.

Economic evaluations (EEs) were identified through searches in MEDLINE, Embase, and WOS, in June 2023. The terms from this strategy were combined with a strategy specifically designed by the University of York[21] to identify EEs.

All search strategies were limited to studies published in English or Spanish within the last 10 years, as the earliest study on joint embolization for pain management in inflammatory musculoskeletal diseases was published in 2013.[10]

Retrieved references were managed using Zotero 6.0.23[22] and deduplicated using Deduklick,[23] followed by manual removal of duplicates and study selection in Microsoft Excel.

Furthermore, the bibliography of included articles was manually examined, and studies citing the selected studies were verified through Google Scholar.

Full search strategies for all database searches are provided in Appendix A.

2.1.2. Selection criteria

Studies were eligible for inclusion if they fulfilled the criteria summarized in Table 1.

2.1.3. Study selection, data extraction process and assessment of risk of bias

Two reviewers independently and in parallel performed the selection process, data extraction, and assessment of risk of bias.

Titles and abstracts were initially assessed, followed by a full-text review for studies meeting the criteria.

A standardized data extraction form was created in Microsoft Excel, including information on article identification, study design, participant characteristics, eligibility criteria, intervention and comparator details; assessed effectiveness and safety outcomes along with measurement timing; cost-effectiveness methodology and outcomes; study funding source, and disclosed conflicts of interest by the researchers.

To assess the methodological quality of the identified SRs, the AMSTAR-2 tool was selected.[24] The risk of bias of the included primary studies was assessed using the Cochrane RoB 2 tool for parallel and crossover RCTs.[25] The appraisal of methodological quality of EEs was planned based on Drummond et al.'s criteria list.[26]

Discrepancies between reviewers were resolved through discussion.

2.1.4. Publication bias assessment

The assessment of publication bias was planned by creating a funnel plot and computing the Egger's regression test;[27] however, the minimum number of studies necessary was not reached.

2.1.5. Synthesis of the evidence

Study characteristics were summarized narratively and presented in summary tables. Meta-analyses (MA) were conducted for quantitative synthesis. Heterogeneity was assessed using forest plots, the χ^2 statistical ($P < 0.01$) and the Higgins I^2 test. Initially, a fixed-effect model was used to evaluate the statistical heterogeneity among included studies (I^2 statistics). In cases of high unexplained heterogeneity ($I^2 > 70\%$), MA was not performed, and results were reported narratively. All analyses were conducted using RevMan 5.4.[28]

Potential confounders considered were baseline pain level, osteoarthritis (OA) severity, and type of embolic agents used. However, subgroup analyses were limited due to the small number of studies evaluated.

2.1.6. Certainty of evidence

The certainty of the evidence (CoE) for all outcomes was judged using the GRADE methodology, considering risk of bias, consistency, directness, precision and reporting bias.[29] Certainty was assessed as high, moderate, low or very low. A Summary

of Findings table was prepared to present the CoE and the magnitude of the effects for the main comparison.[30,31]

2.2. Economic evaluation

A cost-analysis was conducted to compare the costs (in Euros of 2023) of two treatments for chronic pain secondary to KO: the use of GAE of the affected knee followed by standard treatment (evaluated strategy), and the standard treatment alone (comparator), which involves annual hyaluronic acid injections and prescription of physical exercise, in addition to radiofrequency sessions if the patient does not improve.

The target patients were those with chronic pain secondary to mild to moderate KO refractory to standard treatment or non-surgical candidates with severe KO. The analysis was performed from the perspective of the Spanish National Health System (NHS) with a one-year time horizon covering the entire treatment period in the evaluated strategy. No discount rate was applied due to the short-term horizon.

The incremental cost per patient and the annual cost for a hospital with a target population size of 40 patients (value reported by experts) were calculated. Additionally, we estimated the health improvement, in quality-adjusted life years (QALYs), that GAE should generate per patient to be considered a cost-effective technology. This was estimated by solving the incremental effectiveness $(E_A - E_B)$ from the incremental cost-effectiveness ratio equation ($ICER = (C_A - C_B)/(E_A - E_B)$, where $(C_A - C_B)$ is the estimated incremental cost, and A and B represent the evaluated strategy and the comparator, respectively). The cost-effectiveness threshold estimated for Spain (€25 000 per QALY)[32] was applied. The analysis was conducted using Microsoft Excel 2013.

We performed one-way deterministic and probabilistic (1000 second-order Monte-Carlo simulations) sensitivity analyses.

2.2.1. Parameters

Since both alternatives include the standard treatment, only the resource use and the corresponding costs of the GAE were considered, as the inclusion of shared costs would not affect the incremental cost.[26]

The analysis included those associated with the intervention (drugs, instruments, wound closure, healthcare personnel, operating room use, and post-intervention observation period) and the follow-up (Appendix B).

3. Results

3.1. Systematic review on effectiveness and safety

The search in Epistemonikos yielded a total of 13 SRs. Nine were initially considered potentially eligible after title and abstract screening according to the selection criteria; however, none were finally included because they did not attain a high-quality rating.[4,6,13–16,33–35] The full quality assessment can be found in Appendix C.

The search for primary studies retrieved 126 references after removing duplicates (Figure 1). After the title and abstract screening, 12 publications were selected for full-text analysis. According to pre-established criteria, nine of these were excluded. Appendix D shows the list of excluded references and the main reason for exclusion.

Examination of the bibliographic listing of included studies and the Google Scholar search did not lead to any additional studies. No additional studies were identified through the alert service created using the Epistemonikos database. Therefore, the final selection consisted of two RCTs,[36,37] reported in three publications.[36–38]

3.1.1. Characteristics of included studies

The main characteristics of the included studies are summarized in Table 2 and Table 3. For a detailed description of the characteristics and further details of the included studies, please refer to Appendix E and Appendix F.

3.1.2. Risk of bias in included studies

The overall risk of bias in the included RCTs was considered low. The summary of the assessment can be found in Figure 2 and Appendix G.

3.1.3. Certainty of evidence

The overall quality of evidence was considered low. The evidence profile for GAE vs. standard treatment outcomes indicated moderate to low CoE (Appendix H).

3.1.4. Summary of results

Results of all meta-analysis conducted are available in Appendix I.

3.1.4.1. Pain (CoE: low ⨁⨁⨀⨀/moderate ⨁⨁⨁⨀)

The included RCTs examined the effect of GAE on pain at 1 month,[36,37] 6 months[36], and 12 months.[36] However, due to very high heterogeneity rates (I^2= 91%) in the 1-month pain analysis, pooled data are not presented.

Preliminary findings reveal significant discrepancies in pain levels 1 month after GAE. There is low-quality evidence suggesting that GAE may have little to no effect according to the KOOS Pain subscale (1 study; 59 patients)[36] or may result in a slight decrease in pain levels assessed with the VAS (Mean difference [MD]= 50.1 millimeter; 95% CI [29.0, 72.3]; 1 study; 21 patients).[37] At 6 and 12 months of follow-up, moderate quality evidence suggests GAE probably results in little to no effect.

In the Bagla et al. study,[37] the response rates at 1 month were 79% (11/14) and 0% (0/7) for the GAE and sham arms, respectively. However, in the Landers et al. study,[36] overall change in knee pain at 12 months indicated that 17 participants (58.6%) in the GAE group reported being moderately or much better, compared to 11 participants (37.9%) in the control group, though this difference was also not statistically significant.

3.1.4.2. Overall function (CoE: moderate ⨁⨁⨁⨀)

The included studies examined the impact of interventions (GAE vs. sham) on overall functional improvement at 1 month,[36,37] 6 months,[36] and 12 months,[36] using the WOMAC,[37] KOOS Daily Living subscale, and KOOS Function in Sport and Recreation subscale.[36] The effects in all these scales were pooled.

Moderate-quality evidence suggests GAE likely has little to no effect on functional capacity at 1 month (SMD= -0.18; 95% CI [-0.62, 0.27], I^2= 0%, 2 studies; 80

patients), 6 months (SMD= -0.17; 95% CI [-0.68, 0.34], 1 study; 59 patients) and 12 months (SMD= 0.07; 95% CI [-0.44, 0.58], 1 study; 59 patients) compared to standard or pharmacological treatment.

3.1.4.3. Health related quality of life (HRQoL) (CoE: low ⨁⨁⨀⨀/moderate ⨁⨁⨁⨀)

Only Landers et al.[36] reported on the effect of interventions on HRQoL. Low-quality evidence suggests that GAE may have little to no effect on HRQoL assessed with the KOOS Quality of Life subscale at 1 month compared to standard treatment (1 study, 59 patients). GAE probably results in little to no difference in HRQoL at 6 and 12 months.

However, low-quality evidence suggests that GAE may result in a slight improvement of HRQoL levels using the EQ-5D VAS at 6-month follow-up (MD= -10.00; 95% CI [-19.45, -0.55], 1 study, 59 patients). Moderate-quality evidence suggests that GAE likely has little to no effect on HRQoL at 1 month and 12 months compared to standard treatment (1 study, 59 patients).

No differences were observed in the rates of patients who did not present or presented slight problems with anxiety, discomfort, mobility, usual activities, or self-care assessed with EQ-5D.

3.1.4.4. Need for pain medication (CoE: moderate ⨁⨁⨁⨀)

Only Landers et al.[36] reported changes in the need for pain medication. At 12 months, the GAE group had a lower proportion of participants taking analgesics (control 48%, intervention 24%). However, moderate-quality evidence suggests that GAE likely does not reduce or increase the need for pain medication (Risk ratio [RR]= 0.52; 95% CI [0.24, 1.10]; 1 study; 59 patients).

3.1.4.5. Adverse events and complications

No major adverse events were reported in either of the two studies.[36,37] Specifically, in the study by Landers et al.,[36] it was reported that no evidence of osteonecrosis or ischemic complications were found on magnetic resonance imaging up to two years following the procedure. No differences were observed in minor adverse events.[36,37]

3.2. Systematic review on cost-effectiveness

The electronic databases retrieved nine references, but after reading titles and abstracts, all of them were excluded (Appendix J). Therefore, no economic evaluations focused on GAE and that meet the established inclusion criteria were identified.

3.3. Economic evaluation

Over a one-year horizon, the inclusion of GAE in the standard treatment generates an increment in costs of €3432.37 per patient, from the NHS perspective (Table 4). Considering this incremental cost, a health improvement of 0.137 QALYs per patient is required for GAE to be deemed cost-effective compared to the standard treatment. In addition, the estimated annual cost of implementing this technology would be €137 294.86 for a general hospital treating a target population of 40 patients per year.

The one-way sensitivity analysis shows that the incremental cost can vary from €2884.14, if the intervention duration is reduced from 1.5 hours to 1 hour, to €9722.02, if GAE is administered three times to the same patient within the time horizon. Meanwhile, the probabilistic analysis estimates an incremental cost of €6741.84 per patient (95% CI [€2992.10, €11 726.68]), associated with the application of the GAE technique (Table 4).

4. Discussion

The present SR on the effectiveness and safety of GAE for chronic pain secondary to KO refractory to standard treatment identified two RCTs (n=80) evaluating GAE compared to standard treatment.

The results show that evidence is insufficient to draw definitive conclusions regarding the beneficial effects of GAE compared to standard treatment for KO in terms of knee pain, overall functional improvement, HRQoL, changes in the need for pain medication, adverse event or complications. Evidence for these outcomes is affected by inconsistency and imprecision, with wide confidence intervals and/or a very small sample size.

Recent research has shown promising results for GAE as an alternative treatment for chronic joint pain in patients with KO.[4,13–16] Some studies suggest that GAE can offer benefits across varying degrees of OA severity,[13] while others consider that this technique has potential mainly for early and low-grade OA, particularly in the short and medium term.[14] Additionally, this procedure is considered safe, with no serious complications reported,[4,6,13] but minor complications are not uncommon.[13]

However, these findings are predominantly based on observational studies, highlighting the need to confirm them with high-quality RCTs. Further research is needed to evaluate GAE long-term outcomes, its comparative efficacy with other modalities, and its role in the therapeutic approach.[4,6,16,35]

The present SR findings suggest that GAE appears to be a safe alternative, as previous studies have indicated, but without evidence of its effectiveness within a one-year timeframe. The above-mentioned limitations, and considering the low certainty

evidence supporting our conclusions, justify keeping this question in "living mode" as proposed in our original protocol.[39]

The SR did not identify any EE on GAE that met the established inclusion criteria. The identified evidence is insufficient to establish significant differences between the GAE technique and the comparator (necessary to perform a cost-effectiveness analysis) or to conclude that both treatments have the same effectiveness (necessary to perform a cost-minimization analysis). Therefore, we only compared the costs conducting a cost-analysis.

The cost-analysis results showed that the incorporation of GAE into the standard treatment (application of hyaluronic acid once a year plus a prescribed physical exercise regimen) would lead to an increase in cost of €3432.37 per patient compared to the standard treatment alone in a year. This translates to an additional annual cost of €137 294.86 for a general hospital with a target population of 40 patients per year. This technology could only be considered cost-effective if an improvement in health of at least 0.137 QALYs per patient within a year is achieved.

This SR has several strengths. It was developed using a robust predefined methodology outlined in a registered protocol. All steps were performed in duplicate to minimize errors throughout the review process. Additionally, the evidence was synthesized using the GRADE methodology, known for its transparency in evidence development and presentation.

However, the main limitation of this review is the scarcity of evidence, stemming from a low number of studies with small sample sizes, leading to inconsistent results in measured outcomes. Others, mainly due to the low number of studies, include the absence of sensitivity, subgroup and meta-regression analyses. Additionally, as is standard in SRs,

the methodology may have excluded unpublished studies, published in languages other than English or Spanish, or in unindexed journals, which could potentially limit the comprehensiveness of the evidence. Furthermore, although an alert service for identifying RCTs and non-randomized comparative studies remained active until May 31, 2024, a gap exists between this date and the present, which may have excluded more recent evidence potentially influencing the findings.

To the best of the authors' knowledge, this is the first analysis assessing the costs of the GAE technique in Spain. A complete EE comparing costs and effects could not be performed due to effectiveness results. However, given the usefulness of ICER, as an efficiency measure, in the decision-making process, we estimated the health improvement per patient necessary for GAE to be considered cost-effective, compared to the standard treatment, for a willing-to-pay threshold of €25,000 per QALY.

The main limitations of the cost analysis arise from data scarcity. First, evidence on the proportion of target patients requiring vascular closure or those allergic to antibiotics could not be identified, thus assumptions and a value for a general patient[40] were used, respectively. Second, the cost of wound closure with manual compression was obtained from a single study without specifying the year in which the Euros were measured.[41] Therefore, 2020 (the publication year) was assumed as the reference year. Third, instrument costs were extracted from tender documents of some Spanish public hospitals,[42–44] reflecting their reality but may vary contextually. Fourth, resource use information was provided by an expert. Although clinical practice was assumed to be at least similar across Spain, there could be regional differences. Sensitivity analyses show that the incremental cost per patient can range from €2884.14 to €11 726.68, a wide variation especially influenced by the number of sessions conducted during the time horizon. Bearing in mind this, regional differences in terms of incremental costs related

to the use of resources derived from the clinical practice and the unit costs in each region could be observed. Nonetheless, experts validated the assumptions (face validity) and sensitivity analyses variations of these parameters did not significantly alter the results. Finally, the time horizon was restricted to one year because there is no evidence on effectiveness and safety beyond this period, so the impact on resource use is unknown. In addition, a previous study suggests that the benefits of GAE are particularly noticeable in the short and medium term.[14]

5. Conclusion

The present study suggests that there is no difference between GAE and control groups in terms of effectiveness and safety, but it is more costly than the standard treatment in Spain. Larger RCTs are necessary to elucidate the effects of GAE for chronic pain secondary to KO and, consequently, to determine whether it could potentially become cost-effective.

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513 **Table 1**. Selection Criteria for Studies Assessing Effectiveness and Safety

Criteria Category	Inclusion criteria
Population	Individuals with chronic pain secondary to mild or moderate KO refractory to standard treatment and/or severe KO who are not candidates for surgery.
Intervention	GAE.
Comparator	Standard treatment, usual treatment, conservative management, drug therapy (without GAE) or non-intervention.
Outcome measure	Outcomes of interest included KO pain, overall function, HRQoL, need for pain medication, complications, and adverse events. For EEs, the outcomes were: ICER, costs expressed in monetary units, and benefits expressed in QALYs, LYG, monetary units, or any of the outcome measures included in the safety or effectiveness section.
Type of study	High-quality SRs were included, as well as RCTs. In their absence, non-randomized clinical trials and observational comparative studies were considered. Full EEs (either alongside primary studies or modelling based) were included: cost-benefit analysis, cost-utility analysis, cost-effectiveness analysis, cost-consequence analysis, and cost-minimization analysis.
Language	Studies published in Spanish or English.
Publication type	Only full original publications.

514 Note. GAE: Genicular artery embolization; HRQoL: health related quality of life; ICER: incremental cost-effectiveness
515 ratio; KO: Knee Osteoarthritis; LYG: life years gained; QALYs: quality-adjusted life years.

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Table 2. Selection criteria and baseline characteristics of participants in the included studies.

First author, year	N	N woman (%)	KO Grade	Inclusion criteria	Exclusion criteria	GAE group				Control Group			
						N	Age Mean ± SD (range)	BMI Mean ± SD (range) / Median (IQR)*	Other characteristics Mean ± SD (range) / Median (IQR)*	N	Age Mean ± SD (range)	BMI Mean ± SD (range) / Median (IQR)*	Other characteristics Mean ± SD (range) / Median (IQR)*
Bagla, 2022[37]	21	18 (85.7)	1–3 KL	1. >40 years 2. KL grade 1–3 findings on knee radiography 3. ≥ 50/100 on the VAS for pain 4. Pain refractory to 3 m of conservative therapies	1. Local infection 2. Life expectancy of <6 m 3. Severe atherosclerosis seen on prior imaging 4. RA 5. Infectious arthritis 6. Prior knee replacement surgery 7. INR of >2.5 8. Platelets less than 30,000/μL 9. Iodinated contrast medium allergy resulting in anaphylaxis 10. eGFR of <60 mL/min/1.73 m2	14	63.9 ± 8.37 (49-78)	30.8 ± 8.14 (16.9-43.8)	KL: 2.3 ± 0.51 (2-3) WOMAC: 64.9 ± 17 (33-87) VAS: 81.3 ± 12 (55-99)	7	62.9 ± 7.13 (49–71)	33.4 ± 10.5 (21.5–52.9)	KL: 2.3 ± 0.76 (1–3) WOMAC: 70.9 ± 13 (56–94) VAS: 78.9 ± 10 (69–92)
Landers, 2023[36]	59	37 (62.7)	2 KL	1. 18–75 years 2. KL grade 2 3. Knee pain ≥ 6 m 4. Moderate to severe unilateral knee pain (≥3/10 knee pain on at least half the days in the preceding month according to an 11-point numeric scale) 5. Resistant to	1. Local infection 2. Active malignancy 3. RA or seronegative arthropathies 4. Prior ipsilateral knee surgery, excluding arthroscopic surgery >6 m ago 5. Ipsilateral knee intra-articular injection in past 6 m 6. KL grade 3-4 7. Pregnant or	29	61.1± 8.0 (NR)	30.3 (27.8 -37.8)*	Knee pain(yrs): 1.5 (1-5)*	30	60.1 ± 7.7 (NR)	33.6 (29.4-36.2)*	Knee pain(yrs): 1.0 (1-3)*

	conservative treatment for at least 6 m 6. Willing, able and mentally competent to provide informed consent	attempting pregnancy during the study period 8. Allergy to contrast media 9. Reduced kidney function or failure 10. Body weight over 200 kg 11. Platelets <100×109/L 12. INR >1.5 13. Approved for KJR surgery 14. Moderate to severe pain in other lower limb joints 15. History of allergy to carbapenem, or immediate/severe reaction to penicillin/cephalosporin antibiotic 16. History of seizures or valproate use	

Note: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; GAE: Genicular artery embolization; IQR: Interquartile Range; INR: International normalized ratio; KJR: Knee joint replacement; KO: Knee osteoarthritis; KL: Kellgren–Lawrence; m: months; N: number of patients; RA: Rheumatoid arthritis; SD: standard deviation; NR: Not reported; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; yrs: years

Table 3. Characteristics of GAE and control procedures in the included studies.

First author, year	GAE group							Control Group		
	Type of embolizer	**Doses**	**Time (min)** Mean ± SD (range)	**Anesthesia** Type (details)	**Sedation** Level (drugs)	**Fluoroscopy time (min)** Mean ± SD (range)	**Radiation dose (mGy)** Mean ± SD (range)	**Type of control**	**Anesthesia** Type (details)	**Sedation** Level (drugs)
Bagla, 2022[37]	Absorbable particles (Opti Sphere; Teleflex, Minneapolis, Minnesota)	100–300 micron	29.9 ± 15.8 (13–55)	NR	Moderate (midazolam + fentanyl)	6.70 ± 4.96 (4.05–17.8)	17.9 ± 5.52 (8.8 –23.8)	Sham procedure	NR	Moderate (midazolam + fentanyl)
Landers, 2023[36]	Imipenem and cilastatin sodium (IPM-CS, Primaxin; Merck & Co, USA)	0.5 g	NR (30-60)	Local (into the groin immediately superficial to the femoral artery)	Light (NR)	NR	NR	Sham procedure	Local (into the groin immediately superficial to the femoral artery)	Light (NR)

Note: g: gram; GAE: genicular artery embolization; mGy: milligray; min: minutes; NR: Not reported; SD: standard deviation

Table 4. Results of the cost analysis: base case and sensitivity analysis. Costs per patient

Base case			
Cost		**Euros**	
Embolizers		38.59	
Anesthesia		0.37	
Instruments		765.25	
Digital subtraction angiography		792.06	
Wound closure		68.22	
Operating room use		1239.25	
Observation period		100.14	
Healthcare personnel		140.94	
Follow-up		287.55	
GAE total cost (= incremental cost per patient)		**3432.37**	
Probabilistic sensitivity analysis			
Incremental total cost [95% CI]		€ 6741.84 [2992.10, 11 726.68]	
One-way deterministic sensitivity analysis			
Parameter	**Value in base case**	**New value**	**Cost of GAE (= incremental cost per patient). Euros**
Patients with allergy to antibiotics (%)	15	12 [Asm, -20%]	3426.67
		18 [Asm, +20%]	3438.07
Patients needed a vascular closure of the wound (%)	1	5 [Asm]	3433.86
		10 [Asm]	3435.71
GAE sessions (per year)	1	2 [Experts]	6577.20
		3 [Experts]	9722.02
GAE duration (hours)	1.5	1 [Experts]	2884.14
		2 [Experts]	3866.60
Observation period (hours)	4	3.2 [Asm, -20%]	3412.34
		4.8 [Asm, +20%]	3452.40
Follow-up visits	3	2 [Asm]	3336.52
		4 [Asm]	3528.22
Cost of usual embolizer (€ per vial)	10.10	8.08 [Asm, -20%]	3430.65
		12.12 [Asm, +20%]	3434.09
	200	160 [Asm, -20%]	3426.37

Cost of embolizer used in case of antibiotic allergy (€ per vial)		240 [Asm, +20%]	3438.37
Cost of anesthesia (€ per ampoule)	0.37	0.22 [Min[45]]	3432.22
		0.67 [Min[45]]	3432.67
Cost of wound closure by manual compression	67.85	54.28 [Asm, -20%]	3418.94
		81.42 [Asm, +20%]	3445.81
Cost of vascular closure of the wound	105	84 [Asm, -20%]	3432.16
		126 [Asm, +20%]	3432.58
Cost of digital subtraction angiography	792.06	428.85 [Min[46]]	3069.16
		1054 [Max[46]]	3694.31
Cost of 5Fr introducer	97.01	13.33 [Min[42–44]]	3348.69
		193.88 [Max[42–44]]	3529.24
Cost of 5Fr catheter (cobra)	38.17	19.27 [Min[42,44]]	3413.47
		111.63 [Max[42,44]]	3505.83
Cost of microcatheter	368.82	311.38 [Min[42,44]]	3374.92
		456.40 [Max[42,44]]	3519.95
Cost of 0.35 microguide	261.25	209 [Asm, -20%]	3380.12
		313.51 [Asm, +20%]	3484.62
Cost of the observation period (€ per hour)	25.04	4.67 [Min[46]]	3350.90
		51.46 [Max[46]]	3538.06
Labor cost (€ per hour)	31.32	25.06 [Asm, -20%]	3404.18
		37.58 [Asm, +20%]	3460.56
Cost of follow-up visit	95.85	40.02 [Min[46]]	3264.89
		153.04 [Max[46]]	3603.95
Cost of operating room (€ per session of 1.5 hours)	1239.25	991.4 [Asm, -20%]	3184.52
		1487.1 [Asm, +20%]	3680.22

Asm: Assumption; CI: Confidence interval; GAE: Genicular artery embolization; min: minimum; max: maximum

Figure Legends

Figure 1. Flow diagram of the selection process of effectiveness and safety studies

Figure 2. Risk of Bias in Included Studies

Figura 1 revisada (Figure 1)

Pulse aquí para acceder/descargar;Figura (Figure);Figure_1_.tiff

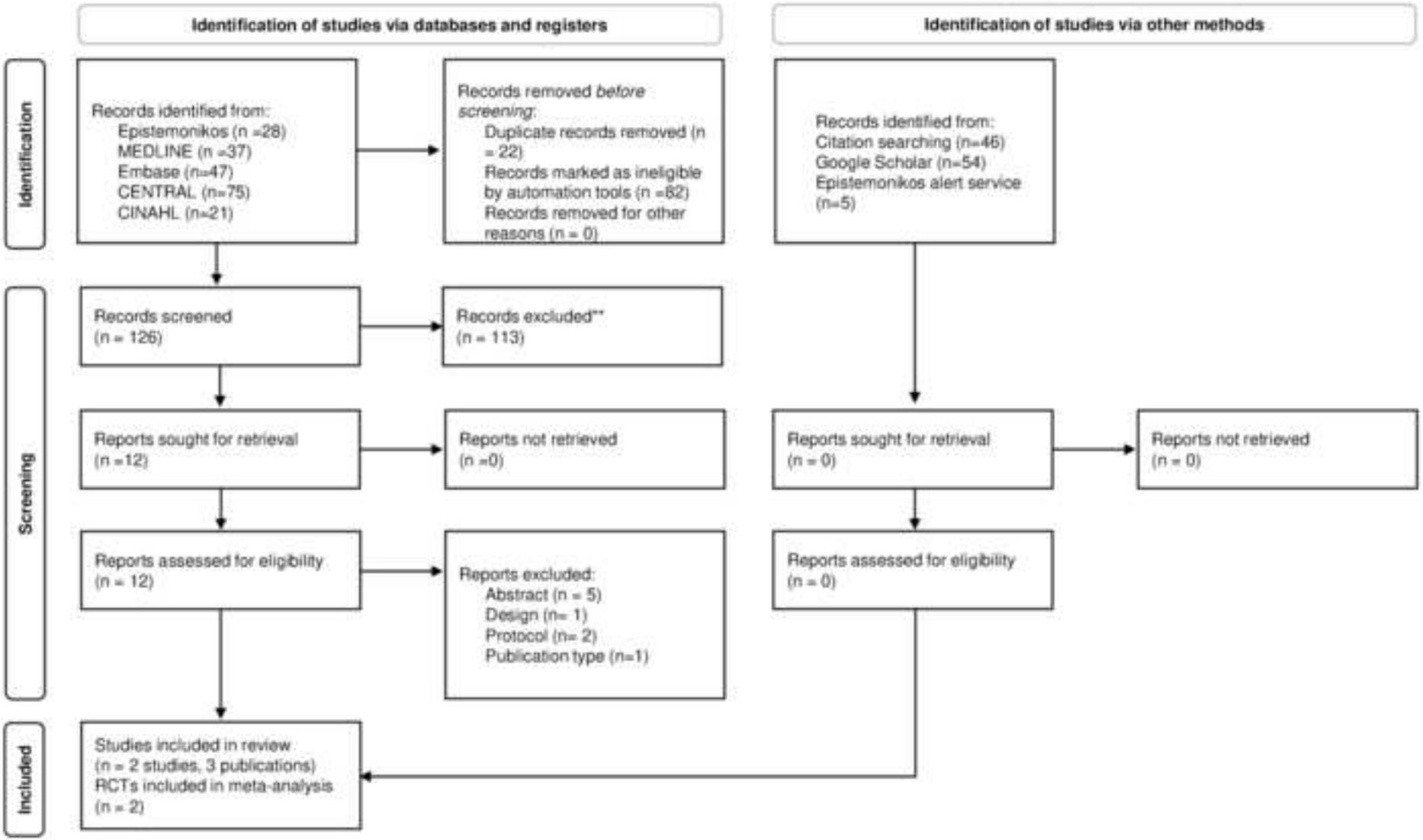
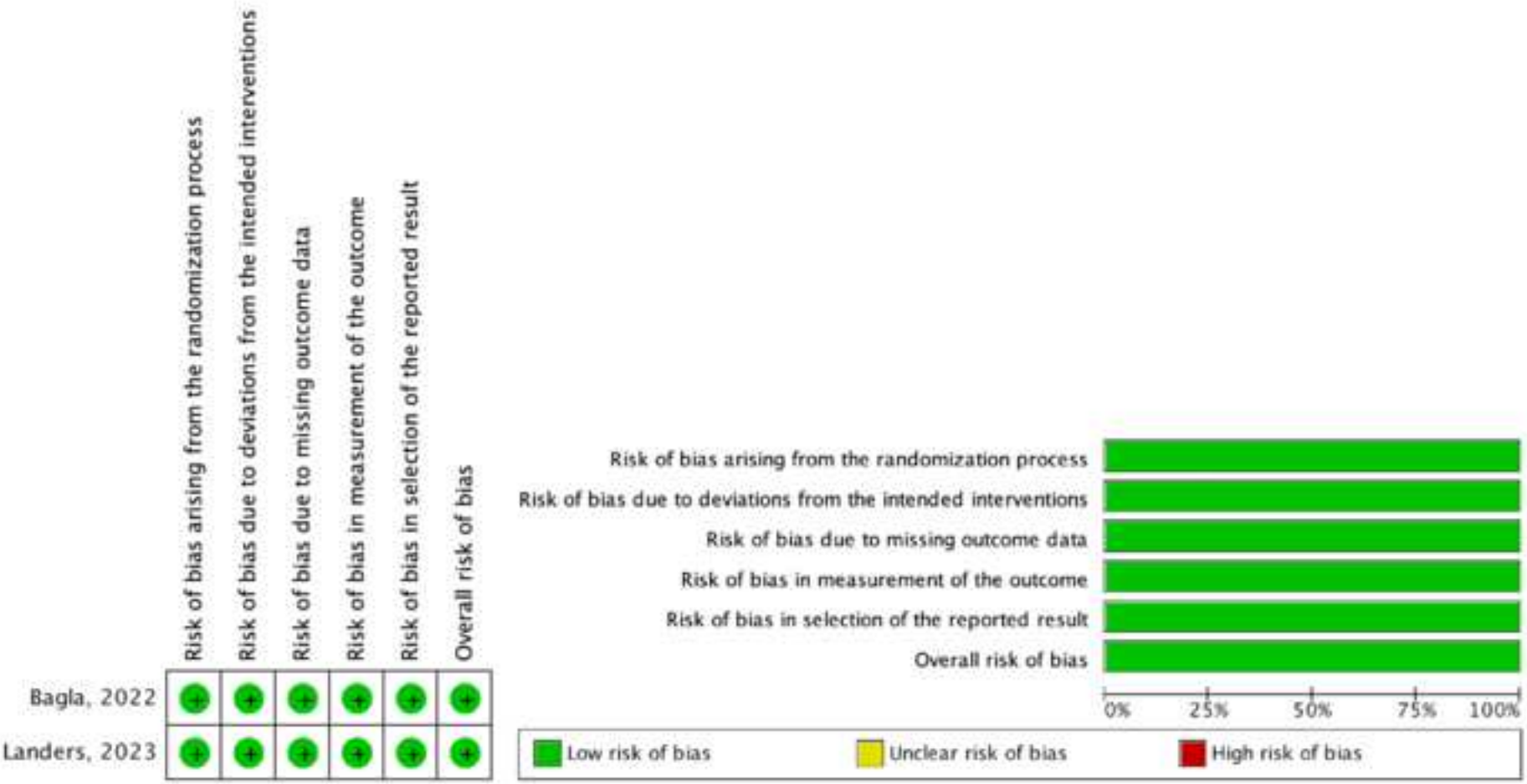


Figura 2 revisada (Figure 2)

Pulse aquí para acceder/descargar;Figura (Figure);Figure_2_.tiff



¿Qué se sabe sobre el tema?

What is known about the topic?

GAE has emerged as a promising minimally invasive procedure for refractory KO, but evidence on its safety, effectiveness and cost-effectiveness compared to standard care is still uncertainty.

¿Qué añade el estudio realizado a la literatura?

What does the study add to the literature?

GAE appears safe, but its effectiveness over standard treatment for KO is unclear, and its use generates and additional EUR 3432.37 per patient, requiring 0.137 QALYs improvement to be cost-effective.

¿Cuáles son las implicaciones de los resultados obtenidos?

What are the implications of the findings?

GAE is more costly than standard care in Spain and requires specific health improvements to be cost-effective; larger studies are needed to confirm its viability as a cost-effective treatment for KO.

Supplementary Material

Appendix A. Search strategies

Effectiveness and safety

Epitesmonikos (Systematic reviews)	
# 1	“Knee osteoarthritis”[EET]
#2	“Knee”[EET]
#3	knee* OR patell*
#4	“Osteoarthritis”[EET]
#5	osteoarthr* OR "osteo-arthritis" OR (arthrit* AND cartil* AND (damage OR repair)) OR (OA AND (joint OR cartilag* OR symptom* OR arthritis)) OR (degenerative AND joint)
#6	KOA OR gonarthr*
#7	(#2 OR #3) AND (#4 OR #5)
#8	#6 OR #7
#9	#1 OR #8
#10	“Geniculate artery embolization” [EET]
#11	“Genicular arteries” [EET]
#12	genicul*
#13	“Arteries” [EET]
#14	artery* OR arteri* OR vessel*
#15	(#11 OR #12) AND (#13 OR #14)
#16	“Embolization”[EET]
#17	(embolizat* OR embolisat*) OR embolotherap*
#18	GAE
#19	#15 AND (#16 OR #17)
#20	#19 OR #18
#21	#10 OR #20
#22	"Systematic review"[EET]
#23	"critical review" OR "electronic search" OR "evidence-based analysis" OR "evidence-based review" OR "literature search" OR "meta analysis" OR "meta synthesis" OR "meta-analyse" OR "meta-analytic review" OR "meta-study" OR "meta-synthesis" OR "metaanalysis" OR "metasynthesis" OR "meta-analysis" OR "pooled effect" OR "random-effects model" OR "systematic quantitative review" OR "systematically searched" OR "systemic review" OR (review AND randomized) OR (systematic AND review) OR MEDLINE OR "literature review" OR PubMed
#24	#22 OR #23
#25	#9 AND #21 AND #24#1 “Knee osteoarthritis”[EET]
-	2013-2023
Epitesmonikos (Randomized controlled trial)	
#1	“Knee osteoarthritis”[EET]
#2	osteoarthr* OR "osteo-arthritis" OR (arthrit* AND cartil* AND (damage OR repair)) OR (OA AND (joint OR cartilag* OR symptom* OR arthritis)) OR (degenerative AND joint)
#3	knee* OR patell*
#4	#2 AND #3
#5	KOA OR gonarthr*
#6	#4 OR #5
#7	#1 OR #6
#8	“Geniculate artery embolization” [EET]
#9	genicul* AND (artery* OR arteri* OR vessel*)
#10	embolizat* OR embolisat* OR embolotherap*
#11	#9 AND #10

#12	GAE	
#13	#11 OR #12	
#14	#8 OR #13	
#15	"Randomized trial"[EET]	
#16	randomi* OR RCT OR placebo* OR trial OR "controlled-trial" OR randomly*	
#17	#15 OR #16	
#18	#7 AND #14 AND #17	
-	2013-2023	

MEDLINE (Ovid)

1.	Embolization, Therapeutic/	36704
2.	(embolotherap* or emboliz* or embolisat* or GAE).ti,ab,kw.	65619
3.	(embozene* or emboGold* or embosphere* or microsphere* or cilastatin* or imipenem* or "embolic agent").ti,ab,kw.	49572
4.	(transcathet* adj5 arter*).ti,ab,kw.	7344
5.	1 or 2 or 3 or 4	126530
6.	exp Knee Joint/	72892
7.	Osteoarthritis, Knee/	27719
8.	((knee* or patella* or meniscal* or articular* or patellofem*) adj5 (joint or OA or osteoarthrit* or osteo-arthritis or arthrit* or degenerat* or diseas* or deteriorat* or injur* or defect* or degenerat* or symptom*)).ti,ab,kw.	89750
9.	((genicul* or knee* or patella* or meniscal* or articular* or patellofem*) adj5 (artery* or arteri* or vessel*)).ti,ab,kw.	2122
10.	(gonarthr* or KOA or genicul* or genual or genu).ti,ab,kw.	19456
11.	7 or 8 or 9 or 10	114583
12.	5 and 11	420
13.	Randomized Controlled Trials as Topic/	164537
14.	randomized controlled trial/	601324
15.	Random Allocation/	107031
16.	Double Blind Method/	176358
17.	Single Blind Method/	32982
18.	clinical trial/	538881
19.	clinical trial, phase i.pt.	25282
20.	clinical trial, phase ii.pt.	40345
21.	clinical trial, phase iii.pt.	22080
22.	clinical trial, phase iv.pt.	2445
23.	controlled clinical trial.pt.	95424
24.	randomized controlled trial.pt.	601324
25.	multicenter study.pt.	338883
26.	clinical trial.pt.	538881
27.	exp Clinical Trials as topic/	385201
28.	or/13-27	1579786
29.	(clinical adj trial$).tw.	490193
30.	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	200207
31.	PLACEBOS/	35933
32.	placebo$.tw.	250307
33.	randomly allocated.tw.	37147
34.	(allocated adj2 random$).tw.	40973
35.	or/29-34	797912
36.	28 or 35	1936677
37.	case report.tw.	407087
38.	letter/	1232768
39.	historical article/	369442
40.	or/37-39	1989945
41.	36 not 40	1893666

42.	(randomi?ed adj2 trial).ti.	143850
43.	trial registration*.ab.	102742
44.	42 or 43	212543
45.	41 or 44	1931597
46.	12 and 45	41
47.	2013-2023	37

Embase (Elsevier)

1.	'artificial embolization'/exp	117766
2.	embolotherap*:ti,ab,kw OR emboliz*:ti,ab,kw OR embolisat*:ti,ab,kw OR gae:ti,ab,kw	99249
3.	embozene*:ti,ab,kw OR embogold*:ti,ab,kw OR embosphere*:ti,ab,kw OR microsphere*:ti,ab,kw OR cilastatin*:ti,ab,kw OR imipenem*:ti,ab,kw OR 'embolic agent':ti,ab,kw	65100
4.	(transcathet* NEAR/5 arter*):ti,ab,kw	10925
5.	#1 OR #2 OR #3 OR #4	208068
6.	'knee joint'/exp	6236
7.	knee osteoarthritis'/exp	45774
8.	((knee* OR patella* OR meniscal* OR articular* OR patellofem*) NEAR/5 (joint OR oa OR osteoarthrit* OR 'osteo arthritis' OR arthrit* OR degenerat* OR diseas* OR deteriorat* OR injur* OR defect* OR degenerat* OR symptom*)):ti,ab,kw	124025
9.	((genicul* OR knee* OR patella* OR meniscal* OR articular* OR patellofem*) NEAR/5 (artery* OR arteri* OR vessel*)):ti,ab,kw	3001
10.	gonarthr*:ti,ab,kw OR koa:ti,ab,kw OR genicul*:ti,ab,kw OR genual:ti,ab,kw OR genu:ti,ab,kw	24458
11.	#7 OR #8 OR #9 OR #10	155145
12.	'clinical trial'/de	1085308
13.	'randomized controlled trial'/de	789844
14.	'controlled clinical trial'/de	441094
15.	'multicenter study'/de	374957
16.	'phase 3 clinical trial'/de	69981
17.	'phase 4 clinical trial'/de	5480
18.	'randomization'/exp	98978
19.	'single blind procedure'/de	52205
20.	'double blind procedure'/de	211996
21.	'crossover procedure'/de	75512
22.	'placebo'/de	410977
23.	'randomi*ed controlled trial*':ti,ab	327326
24.	rct:ti,ab	55089
25.	(random* NEAR/2 allocat*):ti,ab	55150
26.	'single blind*':ti,ab	31928
27.	'double blind*':ti,ab	247450
28.	((treble OR triple) NEAR/1 blind*):ti,ab	2073
29.	placebo*:ti,ab	369471
30.	'prospective study'/de	888013
31.	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	2978532
32.	'case study'/de	96989
33.	'case report':ti,ab	559131
34.	'abstract report'/de OR 'letter'/de	1305960
35.	'conference paper'/it	771278
36.	'conference abstract'/it	4939664
37.	'conference proceeding'/it	0
38.	'editorial'/it	777101
39.	'letter'/it	1283794
40.	'note'/it	949923

41.	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	5705375
42.	#31 NOT #41	2076303
43.	#5 AND #11 AND #42	52
44.	('randomi?ed' NEAR/2 'trial'):ti	177610
45.	'trial registration*':ab	81096
46.	#5 AND #11 AND #44	3
47.	#5 AND #11 AND #45	3
48.	#43 OR #46 OR #47	53
49.	2013-2023	47

CENTRAL (Wiley)

1.	[mh ^"Embolization, Therapeutic"]	460
2.	embolotherap*:ti,ab,kw OR emboliz*:ti,ab,kw OR embolisat*:ti,ab,kw OR gae:ti,ab,kw	5419
3.	embozene*:ti,ab,kw OR embogold*:ti,ab,kw OR embosphere*:ti,ab,kw OR microsphere*:ti,ab,kw OR cilastatin*:ti,ab,kw OR imipenem*:ti,ab,kw OR 'embolic agent':ti,ab,kw	1891
4.	(transcathet* NEAR/5 arter*):ti,ab,kw	704
5.	#1 OR #2 OR #3 OR #4	7564
6.	[mh ^"knee joint"]	4175
7.	[mh ^"knee osteoarthritis"]	6144
8.	((knee* OR patella* OR meniscal* OR articular* OR patellofem*) NEAR/5 (joint OR oa OR osteoarthrit* OR 'osteo arthritis' OR arthrit* OR degenerat* OR diseas* OR deteriorat* OR injur* OR defect* OR degenerat* OR symptom*)):ti,ab,kw	23331
9.	((genicul* OR knee* OR patella* OR meniscal* OR articular* OR patellofem*) NEAR/5 (artery* OR arteri* OR vessel*)):ti,ab,kw	318
10.	gonarthr*:ti,ab,kw OR koa:ti,ab,kw OR genicul*:ti,ab,kw OR genual:ti,ab,kw OR genu:ti,ab,kw	2001
11.	#7 OR #8 OR #9 OR #10	23863
12.	#5 AND #11 in Trials	92
13.	2013-2023	75

CINAHL (EBSCOhost)

1.	((TI embolotherap* OR AB embolotherap*) OR (TIemboliz* OR AB emboliz*) OR (TI embolisat* OR ABembolisat*) OR (TI GAE OR AB GAE))	13518
2.	((TI embozene* OR AB embozene*) OR (TI emboGold*OR AB emboGold*) OR (TI embosphere* OR ABembosphere*) OR (TI microsphere* OR AB microsphere*)OR (TI cilastatin* OR AB cilastatin*) OR (TI imipenem* ORAB imipenem*) OR (TI "embolic agent" OR AB "embolicagent"))	3576
3.	((TI transcathet* OR AB transcathet*) N5 (TI arter* OR ABarter*))	1539
4.	(((TI genicul* OR AB genicul*) OR (TI knee* OR AB knee*)OR (TI patella* OR AB patella*) OR (TI meniscal* OR ABmeniscal*) OR (TI articular* OR AB articular*) OR (TIpatellofem* OR AB patellofem*)) N5 ((TI artery* OR ABartery*) OR (TI arteri* OR AB arteri*) OR (TI vessel* ORAB vessel*)))	560
5.	S7 OR S8 OR S9 OR S10	41949
6.	S5 AND S11	117
7.	(MH "Clinical Trials+")	353661
8.	PT Clinical trial	113801
9.	TX clinic* n1 trial*	467395
10.	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	15
11.	TX ((tripl* n1 blind*) or (tripl* n1 mask*))	1359
12.	TX ((doubl* n1 blind*) or (doubl* n1 mask*))	1321660
13.	TX ((singl* n1 blind*) or (singl* n1 mask*))	27115
14.	TX randomi* control* trial*	376959
15.	(MH "Random Assignment")	81747
16.	(MH "Random Assignment")	81747

17.	TX placebo*	142427
18.	(MH "Placebos")	14230
19.	(MH "Quantitative Studies")	36763
20.	TX allocat* random*	4680
21.	S13 AND S28	23
22.	2013-2023	21

Cost-effectiveness

MEDLINE (Ovid)		
1.	Embolization, Therapeutic/	36355
2.	(embolotherap* or emboliz* or embolisat* or GAE).ti,ab,kw.	64109
3.	(embozene* or emboGold* or embosphere* or microsphere* or cilastatin* or imipenem* or "embolic agent").ti,ab,kw.	48806
4.	(transcathet* adj5 arter*).ti,ab,kw.	7202
5.	1 or 2 or 3 or 4	124125
6.	exp Knee Joint/	71835
7.	Osteoarthritis, Knee/	27046
8.	((knee* or patella* or meniscal* or articular* or patellofem*) adj5 (joint or OA or osteoarthrit* or osteo-arthritis or arthrit* or degenerat* or diseas* or deteriorat* or injur* or defect* or degenerat* or symptom*)).ti,ab,kw.	87750
9.	((genicul* or knee* or patella* or meniscal* or articular* or patellofem*) adj5 (artery* or arteri* or vessel*)).ti,ab,kw.	2065
10.	(gonarthr* or KOA or genicul* or genual or genu).ti,ab,kw.	19133
11.	7 or 8 or 9 or 10	112255
12.	5 and 11	397
13.	Economics/	27502
14.	exp "costs and cost analysis"/	264817
15.	Economics, Dental/	1921
16.	exp economics, hospital/	25718
17.	Economics, Medical/	9248
18.	Economics, Nursing/	4013
19.	Economics, Pharmaceutical/	3105
20.	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	1039114
21.	(expenditure$ not energy).ti,ab.	36766
22.	value for money.ti,ab.	2116
23.	budget$.ti,ab.	35404
24.	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	1203722
25.	((energy or oxygen) adj cost).ti,ab.	4762
26.	(metabolic adj cost).ti,ab.	1710
27.	((energy or oxygen) adj expenditure).ti,ab.	29012
28.	25 or 26 or 27	34422
29.	24 not 28	1195765
30.	letter.pt.	1220130
31.	editorial.pt.	653538
32.	historical article.pt.	369323
33.	30 or 31 or 32	2221994
34.	29 not 33	1155771
35.	exp animals/ not humans/	5131837
36.	34 not 35	1080841
37.	bmj.jn.	88136
38.	cochrane database of systematic reviews.jn.	16318
39.	health technology assessment winchester england.jn.	1502

40.	37 or 38 or 39	105956
41.	36 not 40	1074038
42.	12 and 41	5
43.	2013-2023	5

Embase (Elsevier)

1.	'artificial embolization'/exp	115137
2.	embolotherap*:ti,ab,kw OR emboliz*:ti,ab,kw OR embolisat*:ti,ab,kw OR gae:ti,ab,kw	97249
3.	embozene*:ti,ab,kw OR embogold*:ti,ab,kw OR embosphere*:ti,ab,kw OR microsphere*:ti,ab,kw OR cilastatin*:ti,ab,kw OR imipenem*:ti,ab,kw OR 'embolic agent':ti,ab,kw	64120
4.	(transcathet* NEAR/5 arter*):ti,ab,kw	10717
5.	#1 OR #2 OR #3 OR #4	203837
6.	'knee joint'/exp	5673
7.	'knee osteoarthritis'/exp	44480
8.	((knee* OR patella* OR meniscal* OR articular* OR patellofem*) NEAR/5 (joint OR oa OR osteoarthrit* OR 'osteo arthritis' OR arthrit* OR degenerat* OR diseas* OR deteriorat* OR injur* OR defect* OR degenerat* OR symptom*)):ti,ab,kw	121134
9.	((genicul* OR knee* OR patella* OR meniscal* OR articular* OR patellofem*) NEAR/5 (artery* OR arteri* OR vessel*)):ti,ab,kw	2922
10.	gonarthr*:ti,ab,kw OR koa:ti,ab,kw OR genicul*:ti,ab,kw OR genual:ti,ab,kw OR genu:ti,ab,kw	24012
11.	#7 OR #8 OR #9 OR #10	151776
12.	#5 AND #11	665
13.	'health economics'	64980
14.	'economic evaluation'/exp	253249
15.	'health care cost'/exp	243583
16.	'pharmacoeconomics'	81786
17.	#13 OR #14 OR #15 OR #16	485755
18.	econom*:ti,ab OR cost:ti,ab OR costs:ti,ab OR costly:ti,ab OR costing:ti,ab OR price:ti,ab OR prices:ti,ab OR pricing:ti,ab OR pharmacoeconomic*:ti,ab	786783
19.	expenditure*:ti,ab NOT energy:ti,ab	30500
20.	(value NEAR/2 money):ti,ab	1852
21.	budget*:ti,ab	30086
22.	#18 OR #19 OR #20 OR #21	815755
23.	#17 OR #22	1044938
24.	letter:it	962456
25.	editorial:it	524662
26.	note:it	662311
27.	#24 OR #25 OR #26	2149429
28.	#23 NOT #27	955179
29.	(metabolic NEAR/1 cost):ti,ab	1149
30.	((energy OR oxygen) NEAR/1 cost):ti,ab	3727
31.	((energy OR oxygen) NEAR/1 expenditure):ti,ab	25419
32.	#29 OR #30 OR #31	29361
33.	#28 NOT #32	949067
34.	'animal'/de	1749759
35.	'animal experiment'/exp	2038962
36.	'nonhuman'/de	5013477
37.	rat:ti,ab,lnk OR rats:ti,ab,lnk OR mouse:ti,ab,lnk OR mice:ti,ab,lnk OR hamster:ti,ab,lnk OR hamsters:ti,ab,lnk OR animal:ti,ab,lnk OR animals:ti,ab,lnk OR dog:ti,ab,lnk OR dogs:ti,ab,lnk OR cat:ti,ab,lnk OR cats:ti,ab,lnk OR bovine:ti,ab,lnk OR sheep:ti,ab,lnk	3824591
38.	#34 OR #35 OR #36 OR #37	7976358
39.	'human'/exp	18010565

40.	'human experiment'	375681
41.	#39 OR #40	18012099
42.	#38 NOT (#38 AND #41)	6059572
43.	#33 NOT #42	870548
44.	'09598146':is	56876
45.	1469493x:is OR 13665278:is	16527
46.	17561833:is	22995
47.	#44 OR #45 OR #46	90196
48.	#43 NOT #47	1431374
49.	'conference abstract':it	2488117
50.	#48 NOT #49	1165462
51.	#12 AND #50	7
52.	2013-2023	7

Web of Science (Clarivate Analytics)

1.	TI=(embolotherap* or emboliz* or embolisat* or GAE) OR AB=(embolotherap* or emboliz* or embolisat* or GAE) OR AK=(embolotherap* or emboliz* or embolisat* or GAE)	65414
2.	TI=(embozene* or emboGold* or embosphere* or microsphere* or cilastatin* or imipenem* or "embolic agent") OR AB=(embozene* or emboGold* or embosphere* or microsphere* or cilastatin* or imipenem* or "embolic agent") OR AK=(embozene* or emboGold* or embosphere* or microsphere* or cilastatin* or imipenem* or "embolic agent")	77155
3.	TI=(transcathet* NEAR/5 arter*) OR AB=(transcathet* NEAR/5 arter*) OR AK=(transcathet* NEAR/5 arter*)	6792
4.	#1 OR #2 OR #3	143815
5.	TI=((knee* or patella* or meniscal* or articular* or patellofem*) NEAR/5 (joint or OA or osteoarthrit* or osteo-arthritis or arthrit* or degenerat* or diseas* or deteriorat* or injur* or defect* or degenerat* or symptom*)) OR AB=((knee* or patella* or meniscal* or articular* or patellofem*) NEAR/5 (joint or OA or osteoarthrit* or osteo-arthritis or arthrit* or degenerat* or diseas* or deteriorat* or injur* or defect* or degenerat* or symptom*)) OR AK=((knee* or patella* or meniscal* or articular* or patellofem*) NEAR/5 (joint or OA or osteoarthrit* or osteo-arthritis or arthrit* or degenerat* or diseas* or deteriorat* or injur* or defect* or degenerat* or symptom*))	100969
6.	TI=((genicul* or knee* or patella* or meniscal* or articular* or patellofem*) NEAR/5 (artery* or arteri* or vessel*)) OR AB=((genicul* or knee* or patella* or meniscal* or articular* or patellofem*) NEAR/5 (artery* or arteri* or vessel*)) OR AK=((genicul* or knee* or patella* or meniscal* or articular* or patellofem*) NEAR/5 (artery* or arteri* or vessel*))	2018
7.	TI=(gonarthr* or KOA or genicul* or genual or genu) OR AB=(gonarthr* or KOA or genicul* or genual or genu) OR AK=(gonarthr* or KOA or genicul* or genual or genu)	18039
8.	#5 OR #6 OR #7	117230
9.	#8 AND #4	377
10.	TI=(cost* or cost-effectiv* or costs or economic* or pharmacoeconomic* or price* or pricing* or "Resource Utilization" or "Resource Allocation" or Financi*)	1018053
11.	#10 AND #9	1
12.	2013-2023	1

Appendix B. Parameters of the economic evaluation

The parameters used in the analysis can be consulted in Table S1.

Use of resources

The use of resources related to the GAE technique and post-intervention follow-up was reported by experts.

The embolizers commonly used are a vial of antibiotic (imipenem-cilastatin 500 mg) or a vial of polyvinyl alcohol particles, in case of allergy to antibiotics. The proportion of target patients who are allergic was approximated using the value reported by the Spanish Society of Allergology and Clinical Immunology (SEAIC) in 2019 for general patients.[40]

This technique requires local anesthesia (for example, a lidocaine ampoule), and the performance of digital subtraction angiography, which serves as a guide for the correct administration of the embolizer. Other necessary instruments are a 5Fr introducer, a 5Fr catheter (cobra), a microcatheter and a 0.35 microguide.[47]

The wound is usually closed with manual compression, except in cases of elderly patients or patients with a contraindication, such as alterations in coagulation, in which a vascular closure, by means of a fibrin plug, is applied. According to experts, the average age of the target population is 55 years or older, so it was assumed that the percentage of patients who need a vascular closure should not be especially high, setting it at 1%.

Two nurses and an interventional radiologist are the responsible for carrying out the intervention. During the time the intervention lasts (1.5 hours), the operating room would be unavailable for other interventions, so this has also been considered. Once the intervention is finished, the patient remains under observation for four hours.

Regarding follow-up, the patient's evolution is measured at three, six, nine and twelve months from the interventional radiology unit. Given that the usual treatment is applied after

the technique, the visit when the hyaluronic acid is applied is considered common to both techniques, so only three follow-up visits were taken into account for the GAE strategy.

It was assumed, for the base case, that the technique is not repeated within the established time horizon. However, this value was varied in the sensitivity analysis assuming that the patient can receive GAE up to two additional times.

Unit costs

Unit costs were all extracted from Spanish data sources.

The prices of the antibiotic and anesthesia were obtained from the BotPlus database[45] to calculate the unit cost of the vial and the ampoule, respectively. The retail price (RPP) without Value Added Tax (VAT) was chosen. The costs of the vial of polyvinyl alcohol and the vascular closure were reported by experts. Regarding compression closure, its cost was extracted from the literature.[41] In the case of the instruments (introducer, catheter, micro-catheter and micro-guide), public tender documents from Spanish public hospitals were consulted.[42–44]

The costs of the digital subtraction angiography, the use of the operating room, the observation period, and the follow-up were average values of official tariffs of Spanish regions extracted from the CONCEPT-COSTS Database.[46] We assumed that the tariffs published in regional bulletins remained the same in 2023 because the bulletins were still in force. The cost of using the operating room came from the tariffs for surgical interventions and it was estimated as the cost per session, which depends on the duration of the intervention. Regarding the cost per hour of observation, this was estimated by dividing the cost of the hospital stay per day (€600.85/day) by 24 hours, and then multiplying it by the number of hours that the patient remains under observation. Finally, the number of follow-up visits was multiplied by the cost of a visit to the specialist estimating the cost of the follow-up.

The cost of the specialists was calculated considering the duration of the intervention. The monetary valuation was obtained by multiplying such time by the labor cost per effective hour, in 2022, for division 86 Health Activities of the National Classification of Economic Activities (CNAE)-09.[48] Subsequently, this value was multiplied by the number of clinicians involved in the GAE.

The Spanish consumer price index (CPI) was applied when necessary to update[26] the costs to Euros of 2023.

Table S1. Parameters used in the economic evaluation

Parameter	Value	Source	SE or min-max*
Percentages (Probabilistic distribution for the PSA: Beta distribution)			
Patients with allergy to antibiotics (%)	15	SEAIC [40]	0.03
Patients needed a vascular closure of the wound (%)	1	Assumption	0.01
Resource use (Probabilistic distribution for the PSA: Uniform distribution)			
GAE sessions (per year)	1	Experts	1 - 3
GAE duration (hours)	1.5	Experts	1 - 2
Usual embolizer (vial)	1	Experts	NA
Embolizer used in case of antibiotic allergy (vial)	1	Experts	NA
Anesthesia (ampoule)	1	Experts	NA
Digital subtraction angiography	1	Experts	NA
5Fr introducer	1	Experts	NA
5Fr catheter (Cobra)	1	Experts	NA
Microcatheter	1	Experts	NA
0.35 micro-guide	1	Experts	NA
Observation period (hours)	4	Experts	3.20 - 4.80
Healthcare personnel	3	Experts	NA
Follow-up visits	3	Experts	2 – 4
Operating room use (hours) (= GAE duration)	1.5	Experts	1 - 2
Unit costs (Euros of 2023) (Probabilistic distribution for the PSA: Gamma distribution)			
Usual embolizer (€ per vial)	10.10	BotPlus [45]	2.02
Embolizer used in case of antibiotic allergy (€ per vial)	200	Experts	40.00
Anesthesia (€ per ampoule)	0.37	BotPlus [45]	0.11
Wound closure by manual compression	67.85	García Díaz et al [41]	13.57
Vascular closure of the wound	105	Experts	21.00

Parameter	Value	Source	SE or min-max*
Digital subtraction angiography	792.06	CONCEPT-COSTS Database [46]	136.91
5Fr introducer	97.01	Tenders for public hospitals [42–44]	13.80
5Fr catheter (Cobra)	38.17	Tenders for public hospitals [42,44]	9.08
Microcatheter	368.82	Tenders for public hospitals [42,44]	20.32
0.35 micro-guide	261.25	Tenders for public hospitals [42]	52.25
Observation period (€ per hour)	25.04	CONCEPT-COSTS Database [46]	2.98
Labor cost (€ per effective hour)	31.32	INE [48]	6.26
Follow-up visit	95.85	CONCEPT-COSTS Database [46]	8.18
Operating room (€ per session of 1.5 hours)	1239.25	CONCEPT-COSTS Database [46]	247.85

GAE: genicular artery embolization; INE: Spanish National Statistics Institute; NA: not applicable; PSA: probabilistic sensitivity analysis; SE: Standard error; SEAIC: Spanish Society of Allergology and Clinical Immunology, from Spanish *Sociedad Española de Alergología e Inmunología Clínica*. * Values used in the probabilistic sensitivity analysis

Additional references

47. Monteverde Hernández FM, Portero Navarro J, Pantoja Ortiz V, Cabrera Rodriguez R, Souweileh Arancibia C, Medina Herrera R. Embolización de arterias geniculadas en el tratamiento analgésico de la patología degenerativa de rodilla. In: ; 2022.

48. Instituto Nacional de Estadística (INE). Coste laboral por hora efectiva por divisiones de la CNAE-09. Encuesta trimestral de coste laboral. Published online 2022. www.ine.es

Appendix C. Level of quality of the systematic reviews: AMSTAR-2 tool

Author, year	components of PICO	Deviations from the protocol	Study designs	Literature search strategy	Study selection	Data extraction	Excluded studies and justify the exclusions	Description of the included studies	RoB in individual studies (RCTs)	RoB in individual studies (nRCTs)	Sources of funding	Appropriate methods for statistical combination (RCT)	Appropriate methods for statistical combination (nRCT)	Potential impact of RoB in individual studies on the results of the MA	RoB when interpreting/ discussing the results	Heterogeneity observed in the results	Publication bias	Conflict of interest	Overall rating
Bhatia, 2023[14]	Y	No	Y	PY	Y	Y	No	PY	Y	Y	No	No	No	Y	Y	Y	Y	Y	**Critically low**
Casadaban, 2021[15]	No	No	No	PY	Y	No	No	PY	Y	NA	No	No MA	No MA	No MA	No	Y	No Ma	Y	**Critically low**
Epelboym, 2023[13]	No	No	No	PY	Y	No	No	No	No	No	No	No	No	No	No	No	Y	Y	**Critically low**
Guevara-Noriega, 2022[4]	Y	No	No	PY	Y	NA	No	No	No	No	No	No MA	No MA	No MA	No	No	No MA	Y	**Critically low**
Hindsø, 2021[16]	No	No	No	PY	Y	Y	No	No	Y	Y	No	No MA	No MA	No MA	Y	Y	No MA	Y	**Critically low**
Kishore, 2021[33]	No	PY	No	PY	Y	Y	No	Y	Y	Y	No	No Ma	No MA	No MA	Y	Y	No MA	Y	**Low**

Sajan, 2021[34]	No	No	Y	PY	No	NA	No	No	No	No	No	No	No	No	No	No	Y	Y	**Critically low**
Taslakian, 2023[35]	No	PY	No	PY	Y	Y	No	No	No	No	No	No	No	No	Y	Y	No	Y	**Critically low**
Torkian, 2021[6]	No	No	No	PY	Y	No	No	No	Y	No	No	No MA	No	No	No	No	Y	Y	**Critically low**

MA: meta-analysis; NA: not applicable; nRCT: non-randomized controlled trial; PY: partial yes; RCT: randomized controlled trial; RoB: risk of bias; Y: yes

Appendix D. Excluded studies

Systematic Reviews (n = 9)	
Methodological quality (n = 9)	
1.	Guevara-Noriega KA, Chavez-Abiega R, Castro-Rios JG. Embolization of genicular arteries in patients with knee osteoarthritis as an alternative for refractory pain treatment: A systematic review. Med Clin. 2022;(159):592-597.
2.	Casadaban LC, Mandell JC, Epelboym Y. Genicular Artery Embolization for Osteoarthritis Related Knee Pain: A Systematic Review and Qualitative Analysis of Clinical Outcomes. Cardiovascular and interventional radiology. 2021;44(1):1-9.
3.	Torkian P, Golzarian J, Chalian M, Clayton A, Rahimi-Dehgolan S, Tabibian E, et al. Osteoarthritis-Related Knee Pain Treated With Genicular Artery Embolization: A Systematic Review and Meta-analysis. Orthop J Sports Med. 2021 jul;9(7):23259671211021356.
4.	Sajan A, Mehta T, Griepp DW, Chait AR, Isaacson A, Bagla S. Comparison of Minimally Invasive Procedures to Treat Knee Pain Secondary to Osteoarthritis: A Systematic Review and Meta-Analysis. Journal of vascular and interventional radiology: JVIR. 2021.
5.	Taslakian B, Miller LE, Mabud TS, Macaulay W, Samuels J, Attur M, et al. Genicular artery embolization for treatment of knee osteoarthritis pain: Systematic review and meta-analysis. Osteoarthritis and cartilage open. 2023;5(2):100342.
6.	Epelboym Y, Lee L, Okuno Y, Korchi A. Genicular artery embolization as a treatment for refractory osteoarthritis related knee pain. Skeletal Radiol. 52(11):2309-2321. doi: 10.1007/s00256-022-04208-0.
7.	Bhatia A, Bhatia S. The short-to-midterm outcomes of geniculate artery embolization for mild-to-moderate osteoarthritis of the knee: a systematic review. Journal of orthopaedics. 2023;39:30-41.
8.	Hindsø L, Riis RGC, Hölmich P, Petersen MM, Nielsen MB, Lönn L, Taudorf M. Current Status of Trans-Arterial Embolization in Pain Management of Musculoskeletal Inflammatory Conditions - An Evidence-Based Review. Cardiovasc Intervent Radiol. 202;44(11):1699-1708. doi: 10.1007/s00270-021-02948-5.
9.	Kishore S, Sheira D, Malin ML, Trost DW, Mandl LA. Transarterial Embolization for the Treatment of Chronic Musculoskeletal Pain: A Systematic Review of Indications, Safety, and Efficacy. ACR open rheumatology. 2021
Randomized controlled trials (n = 9)	
Abstract (n = 5)	
1.	Correa MP, Michelin A, Algarve R, Lugokenski R, Motta-Leal-Filho J. The Gaucho Trial: genicular Artery embolization Using imipenem/Cilastatin vs. mirospHere for chrOnic knee pain: a randomized controlled trial - preliminary clinical results of 3-months. Cardiovascular and interventional radiology. 2022, 45(4), S229.
2.	Padia S, Genshaft S, Plotnik A, Ryan T, Kim G, La Cava A, Stavrakis A. GRAVITY: genicular artery embolization versus observation for the treatment of symptomatic knee osteoarthritis: a randomized controlled trial. Cardiovascular and interventional radiology. 2022, 45(4), S198.
3.	van Zadelhoff TA, Oei EH, Moelker A, van der Heijden RA, Bos PK, Bierma-Zeinstra SM. Genicular artery embolization versus sham embolization for symptomatic osteoarthritis of the knee. Osteoarthritis and cartilage. 2023, 31(5), 694.
4.	van Zadelhoff T, Moelker A, Bierma-Zeinstra S, Bos P, Krestin G, Oei E. Genicular artery embolization for knee osteoarthritis: data from a randomized sham controlled trial. Cardiovascular and interventional radiology. 2022, 45(4), S299.
5.	van Zadelhoff, TA, Moelker, A, Bierma-Zeinstra, SM, Bos, KP, Krestin, GP, Oei. Safety of genicular artery embolization for the treatment of knee osteoarthritis: data from the Neo Trial. Osteoarthritis and Cartilage. 2022;30:S81eS438.
Design (n = 1)	
1.	Padia SA, Genshaft S, Blumstein G, Plotnik A, Kim GHJ, Gilbert SJ, Lauko K, Stavrakis AI. Genicular Artery Embolization for the Treatment of Symptomatic Knee Osteoarthritis. JB JS Open Access. 2021 Oct 21;6(4):e21.00085. doi: 10.2106/JBJS.OA.21.00085.
Protocol (n = 2)	
1.	Little MW, Harrison R, MacGill S, Speirs A, Briggs JH, Tayton E, et al. Genicular Artery Embolisation in Patients with Osteoarthritis of the Knee (GENESIS 2): Protocol for a Double-Blind Randomised Sham-Controlled Trial. Cardiovascular and interventional radiology. 2023 Sep;46(9):1276-1282. doi: 10.1007/s00270-023-03477-z.

2. van Zadelhoff TA, Moelker A, Bierma-Zeinstra SMA, Bos PK, Krestin GP, Oei EHG. Genicular artery embolization as a novel treatment for mild to moderate knee osteoarthritis: protocol design of a randomized sham-controlled clinical trial. Trials. 2022 Jan 8;23(1):24. doi: 10.1186/s13063-021-05942-x. PMID: 34998425; PMCID: PMC8742438.

Type publications (n = 1)

1. Padia SA. GENESIS 2 Trial: Unveiling the Potential of Genicular Artery Embolization. Cardiovascular and interventional radiology. 2023 Sep;46(9):1283-1284. doi: 10.1007/s00270-023-03516-9.

Appendix E. ***Characteristics of included studies***

One study, published in 2022, was conducted in the USA,[37] while the other, published in 2023, was conducted in Australia.[36] Landers et al. conducted a single-center, triple-blinded, parallel-arm RCT[36,38] while Bagla et al. conducted a multi-center, single-blinded, crossover RCT,[37] that included a treatment group (GAE) and a sham group. After the first month, the study was unblinded, the sham group crossed over to receive GAE, while the GAE group ceased to be treated. For this reason, due to the irreversible nature of the embolization in the treatment group, only data from the first period of the crossover RCT (1 month, prior to the crossing of the group) was included in this SR. The follow-up duration was 12 months in both studies, which involved collaboration with industry.

The sample sizes of both studies were small, with 21[37] and 59[36] participants, respectively. Both studies experienced the loss of one participant during the follow-up period. Both studies exclusively enrolled patients with mild to moderate KO, graded according to the Kellgren-Lawrence system.[49] Table 1 shows the selection criteria and the baseline characteristics of participants in the included studies.

All GAE procedures were performed by interventional radiologists. In Bagla *et al.*,[37] the procedural technique targeted the genicular arteries supplying the knee region with the most severe pain. In Landers *et al.*,[36] the initial plan was to embolize the major vessel primarily responsible for neovascularization. However, finally, all genicular arteries with collateral regional supply were sequentially assessed and embolized if neovessels were visible and accessible. The material used for GAE varied between studies, with absorbable particles[37] or imipenem/cilastatin sodium[36] being used. Light or moderate sedation was administered in both studies. Only one study reported that all patients received antibiotics before and for five days after the procedure.[37] In both studies, a sham procedure was used as the comparator, with the same type of sedation

administered by the same radiologists. Table 2 presents the characteristics of the GAE and control procedures in the included studies.

The effectiveness outcomes reported in the included RCTs were knee pain assessed using a visual analogue scale (VAS)[37] or the Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale;[36] overall functional improvement evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[37] and KOOS Function in Daily Living subscale (FDLS) and KOOS Function in Sport and Recreation subscale (FSRS);[36] HRQoL assessed using the European Quality of Life (EuroQol)-5 Dimensions (EQ-5D) and KOOS Quality of Life (QoL) subscale;[36] and the need for pain medication.[36] Knee pain, overall functional improvement and HRQoL were assessed at baseline, 1, 6 and 12 months. However, in the Bagla et al. study,[37] results at 6 and 12 months correspond to crossover-related measurements.

The reported safety outcomes included adverse events and complication rates, such as knee pain[37], purpura, nausea/vomiting,[37] hematoma,[36,37] skin changes or ischemia,[37] pruritus,[37] ecchymosis,[37] osteonecrosis or ischemic complications.[37]

Additional reference

49. Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-Arthrosis. *Ann Rheum Dis*. 1957;16(4):494-502. doi:10.1136/ard.16.4.494

Appendix F. *Main data extracted from the included studies*

Bagla, 2022				
Geographic location and setting		USA Interventional radiology clinics		
Funder		Collaborator: Medtronic		
Objective		To assess the safety and efficacy of GAE compared with a sham procedure in the treatment of knee pain secondary to mild to moderate osteoarthritis		
Design		Design: A multicenter, single-blinded randomized controlled trial		
		No. of participating centres: 1		
		Follow-up (month): 1		
Participants	Selection criteria:	Inclusion criteria: 1. Kellgren– Lawrence grade 1–3 findings on knee radiography 2. A score greater than 50/100 on the VAS for pain 3. Pain refractory to 3 months of conservative therapies (medication, physical therapy, or intra-articular injection) 4. Age of >40 years		
		Exclusion criteria: 1. Local infection 2. Life expectancy of <6 months 3. Severe atherosclerosis seen on prior imaging 4. Rheumatoid arthritis 5. Infectious arthritis 6. Prior knee replacement surgery 7. International normalized ratio of >2.5 8. Platelets less than 30,000/μL 9. Iodinated contrast medium allergy resulting in anaphylaxis		
	No. patients recruited: 21			
	No. of randomized patients: 21			
		Intervention	Comparator	
	No. of patients	14	7	
	No. of lost patients	1	0	
	Females (%):	12 (85.71)	6 (85.71)	
	Age (mean ± SD):	63.9 ± 8.37	62.9 ± 7.13	
Intervention	Type of intervention: GAE			
	Professional applying the intervention: 3 interventional radiologists			
	Type of embolization (dose): Absorbable particles (100-300 micron)			
	Intervention duration (minutes): 29.9			
Comparator	Sham procedure			
Main results		Intervention	Comparator	DM (95% CI; p-value)
	Pain (VAS)	30.5 ± 28.0	78.4 ± 10.2	50.1 (29.0, 72.3; p< 0.01)
	Functional capacity (WOMAC)	34.7 ± 24.9	65.9 ± 11.3	25.2 (3.5, 45.9; p = 0.02)
	Knee pain*	1/14	0/7	NA
	Nausea/vomiting*	1/14	0/7	NA
	Purpura*	3/14	0/7	NA
	Hematoma*	0/14	1/7	NA
	Ecchymosis*	0/14	1/7	NA
	Bleeding at access site*	0/14	1/7	NA
	Skin changes*	0/14	0/7	NA
	Skin ischemia*	0/14	0/7	NA
	Pruritus*	0/14	0/7	NA

CI: confidence interval; DM: Mean difference; GAE: genicular artery embolization; NA: not applicable; SD: standard deviation; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; *: Events/total

Landers, 2023				
Geographic location and setting		Australia; A large regional public health service in Victoria		
Funder		Collaborator: Medtronic		
Objective		To investigate the effects of transcatheter arterial embolization on pain, function, and quality of life in people with early-stage symptomatic knee osteoarthritis compared to a sham procedure.		
Design		Design: A single-center, parallel-arm, triple-blinded (participant, assessor, statistician), randomized controlled superiority trial		
		No. of participating centres: 1		
		Follow-up (month): 1, 6, 12		
Participants	Selection criteria:	Inclusion criteria: 1.18–75 years 2. Kellgren– Lawrence grade 2 findings on knee radiography 3. Knee pain ≥ 6 months 4. Moderate to severe unilateral knee pain (≥3/10 knee pain on at least half the days in the preceding month according to an 11-point numeric scale) 5. Resistant to conservative treatment for at least 6 months (including medication, intra-articular injections, physiotherapy or exercise, or weight loss 6. Willing, able and mentally competent to provide informed consent		
		Exclusion criteria: 1. Local infection 2. Active malignancy 3. Rheumatoid arthritis or seronegative arthropathies 4. Prior ipsilateral knee surgery excluding arthroscopic surgery more than 6 months ago 5. Ipsilateral knee intra-articular injection in the previous 6 months 6. Grade 3 or 4 knee OA on X-ray as per Kellgren-Lawrence Grading Scale 7. Pregnant or trying to become pregnant during the study period 8. Allergy to contrast media 9. Reduced kidney function or failure 10. Body weight greater than 200 kg 11. Platelets <100×109/L 12. International normalized ratio >1.5 13. Approved for knee joint replacement surgery 14. Moderate to severe pain in other lower limb joints 15. History of allergy to carbapenem (e.g., imipenem, ertapenem or meropenem), or having an immediate or severe hypersensitivity reaction to a penicillin or cephalosporin antibiotic 16. History of seizures or use of valproate		
	No. patients recruited: 59			
	No. of randomized patients: 59			
		Intervention	Comparator	
	No. of patients	29	30	
	No. of lost patients	0	1	
	Females (%):	18 (62.06)	19 (63.33)	
	Age (mean ± SD):	61.1 ± 8.0	60.1 ±7.7	
Intervention	Type of intervention: Transcatheter arterial embolization			
	Professional applying the intervention: 1 interventional radiologist			
	Type of embolization (dose): Imipenem and cilastatin sodium (0.5g)			
	Intervention duration (minutes): 30-60			
Comparator	Sham procedure			
Main results		Intervention	Comparator	(95% CI)
		Median (IQR)	Median (IQR)	
	Pain (KOOS) – *1 month*	63.9 (52.7 – 75.0)	63.9 (44.4 - 75.0)	0 (-13.4 – 13.4)

	Pain (KOOS) – *6 months*	66.7 (44.4- 77.8)	70.8 (50.0 – 91.7)	-2.6 (-21.8 – 16.7)
	Pain (KOOS) – *12 months*	66.7 (52.8 – 88.9)	61.1 (47.2 – 88.9)	3.0 (-18.0 – 23.9)
	Physical function -KOOS FSRS- *1 month*	45.0 (25.0 -55.0)	42.5 (15.0 – 80.0)	0.4 (-23.2 – 23.9)
	Physical function -KOOS FSRS- *6 months*	40.0 (25.0 – 65.0)	50.0 (15.0 – 75.0)	4.3 (-20.1 – 28.7)
	Physical function -KOOS FSRS- *12 months*	45.0 (15.0 – 75.0)	35.0 (10.0 – 75.0)	12.5 (-15.8 – 40.8)
	Physical function- KOOS FDLS- *1 month*	72.1 (48.5- 85.3)	69.9 (54.4 – 89.7)	-1.5 (-18.2 -15.3)
	Physical function- KOOS FDLS- *6 months*	72.1 (54.4 – 88.2)	78.7 (60.3 – 95.6)	-6.1 (-23.9 – 11.6)
	Physical function- KOOS FDLS- *12 months*	72.1 (52.9 – 89.7)	70.6 (50.0 – 91.2)	7.4 (- 9.2 – 23.)
	QoL – KOOS- *1month*	50.00 (25.0 – 62.5)	50.00 (25.0 – 62.5)	6.3 (-5.5 – 18.0)
	QoL – KOOS- *6 months*	37.5 (25.0 – 56.3)	53.1 (18.8 – 68.8)	6.3 (-11.2 – 23.7)
	QoL – KOOS- *12 months*	43.8 (25.0 – 68.8)	43.8 (25.0 – 62.5)	16.7 (-0.7 – 34.0)
	QoL-EQ-5D-VAS- 1 month	80 (65- 90)	80 (60 – 90)	NA
	EQ-5D-VAS- 6 months	70 (55 – 80)	80 (65 – 90)	NA
	EQ-5D-VAS- 12 months	70 (55 – 90)	80 (70 – 90)	NA
		Intervention	Comparator	
		Events/total	Events total	
	QoL EQ-5D- Mobility - No/slight problem – *1 month*	17/29	21/30	NA
	QoL EQ-5D- Mobility - Moderate – extreme problem- *1 month*	12/29	9/30	NA
	QoL EQ-5D- Mobility - No/slight problem – *6 months**	18/29	20/30	NA
	QoL EQ-5D- Mobility - Moderate – extreme problem- 6 *months*	11/29	10/30	NA
	QoL EQ-5D- Mobility - No/slight problem- *12 months*	18/29	17/30	NA
	QoL EQ-5D- Mobility - Moderate – extreme problem – *12 months*	11/29	12/30	NA
	QoL EQ-5D- Self-care - No/slight problem- *1 month*	28/29	28/30	NA
	QoL EQ-5D- Self-care - Moderate – extreme problem – *1 month*	1/29	2/30	NA
	QoL EQ-5D- Self-care - No/slight problem- *6 months*	28/29	26/30	NA
	QoL EQ-5D- Self-care - Moderate – extreme problem – *6 months*	1/29	4/30	NA
	QoL EQ-5D- Self-care - No/slight problem – *12 months*	27/29	26/30	NA
	QoL EQ-5D- Self-care - Moderate – extreme problem – *12 months*	2/29	3/30	NA

	QoL EQ-5D- Usual activities - No/slight problem – *1 month*	17/29	22/30	NA
	QoL EQ-5D- Usual activities - Moderate – extreme problem – *1 month*	12/29	8/30	NA
	QoL EQ-5D- Usual activities - No/slight problem – *6 months*	16/29	20/30	NA
	QoL EQ-5D- Usual activities - Moderate – extreme problem – *6 months*	13/29	10/30	NA
	QoL EQ-5D- Usual activities - No/slight problem – *12 months*	19/29	19/30	NA
	QoL EQ-5D- Usual activities - Moderate – extreme problem – *12 months*	10/29	10/30	NA
	QoL EQ-5D- Discomfort - No/slight problem- *1 month*	13/29	14/30	NA
	QoL EQ-5D- Discomfort - Moderate – extreme problem- *1 month*	16/29	16/30	NA
	QoL EQ-5D- Discomfort - No/slight problem- *6 months*	14/29	15/30	NA
	QoL EQ-5D- Discomfort - Moderate – extreme problem- *6 months*	15/29	15/30	NA
	QoL EQ-5D- Discomfort - No/slight problem- *12 months*	15/29	15/30	NA
	QoL EQ-5D- Discomfort - Moderate – extreme problem- *12 months*	14/29	17/30	NA
	QoL EQ-5D- Anxiety - No/slight problem- *1 month*	23/29	25/30	NA
	QoL EQ-5D- Anxiety - Moderate – extreme problem- *1 month*	6/29	5/30	NA
	QoL EQ-5D- Anxiety - No/slight problem- *6 months*	21/29	27/30	NA
	QoL EQ-5D- Anxiety - Moderate – extreme problem- *6 months*	8/29	3/30	NA
	QoL EQ-5D- Anxiety - No/slight problem- *12 months*	23/29	22/30	NA
	QoL EQ-5D- Anxiety - Moderate – extreme problem- *12 months*	6/29	7/30	NA
	Access site hematoma*	4/29	1/30	NA

CI: confidence interval; EQ-5D: European Quality of life-5 Dimensions; FDLS: Function in Daily Living subscale; FSRS: Function in Sport and Recreation subscale; IQR: interquartile range; KOOS: Knee Injury and Osteoarthritis Outcome Score; NA: not applicable; QoL: quality of life; SD: standard deviation; VAS: visual analogue scale; *: Event adverse

Appendix G. Risk of bias of included studies

Bagla (2022)		
Domain 1: Risk of bias arising from the randomization process		
Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	A single-blinded randomized-controlled. Randomization using REDCap (Nashville,	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Tennessee) occurred prior to the subjects entering the procedure suite. A 2:1 allocation ratio was used with 14 subjects randomized to undergo embolization and 7 subjects randomized to undergo a sham procedure.	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No significant differences were noted when comparing the baseline attributes of the treatment and sham groups	N
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias arising from the randomization process?		NA
Domain S: Risk of bias arising from period and carryover effects		
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	A 2:1 allocation ratio was used with 14 subjects randomized to undergo embolization and 7 subjects randomized to undergo a sham procedure.	N
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?	Only data from the first period contribute to the result being assessed for risk of bias.	Y
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	Only data from the first period contribute to the result being assessed for risk of bias.	Y
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias arising from the randomization process?		NA
Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)		
Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Masking: Double (Participant and outcomes assessor) Appropriate measures will be taken to ensure patients and nursing staff caring for the patient are blinded to assignment.	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Due to the nature of the intervention, it is likely that the interventional radiologists could not be blinded.	PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the		N

intended intervention that arose because of the trial context?		
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favors experimental / Favors comparator / Towards null /Away from null / Unpredictable
Domain 3: Missing outcome data		
Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to missing outcome data?		NA
Domain 4: Risk of bias in measurement of the outcome		
Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed		N

between intervention groups?		
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Outcome assessors (patients) were blinded to intervention status	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias in measurement of the outcome?		NA
Domain 5: Risk of bias in selection of the reported result		
Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The researchers' pre-specified intentions are available (NCT03362957), and the planned outcome measurements and analyses are compatible with those presented in the protocol	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	Reported results for the outcome domain correspond to intended outcome measurements.	N
5.3 ... multiple eligible analyses of the data?	Reported results for the outcome measurement correspond to intended analyses	N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		NA
Overall risk of bias		
Risk-of-bias judgement		**Low risk**
Optional: What is the overall predicted direction of bias for this outcome?		NA

N: no; NA: not applicable; NI: not informed; PN; partial no; PY; partial yes; Y: yes

Landers (2023)		
Domain 1: Risk of bias arising from the randomization process		
Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Randomly allocated to either intervention or control groups with a 1:1 allocation ratio.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	The allocation sequence will be computer generated by the trial statistician (SEL) prior to trial commencement and uses randomly selected block sizes. Block sizes will not be disclosed to the interventionalist, assessors or other investigators. Allocation will be concealed until immediately prior to the participant's intervention, at which time the interventionalist will access the allocation code for that participant via the web-based project and data management tool.	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	At the baseline assessments were similar between the groups	N
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias arising from the randomization process?		NA
Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)		
Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	The participants, assessor, and statistician (SMG) were blinded to group allocation.	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Due to the nature of the intervention, the interventionalist could not be blinded.	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the		NA

result) of the failure to analyse participants in the group to which they were randomized?		
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA
Domain 3: Missing outcome data		
Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to missing outcome data?		NA
Domain 4: Risk of bias in measurement of the outcome		
Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Outcome assessor and patients (for participant-reported outcomes) were blinded to intervention status	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias		NA

in measurement of the outcome?		
Domain 5: Risk of bias in selection of the reported result		
Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The researchers' pre-specified intentions are available (Lander 2017 and ACTRN12616001184460), and the planned outcome measurements and analyses are compatible with those presented in the protocol	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	Reported results for the outcome domain correspond to intended outcome measurements.	N
5.3 ... multiple eligible analyses of the data?	Reported results for the outcome measurement correspond to intended analyses	N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		NA
Overall risk of bias		
Risk-of-bias judgement		**Low risk**
Optional: What is the overall predicted direction of bias for this outcome?		NA

N: no; NA: not applicable; NI: not informed; PN; partial no; PY; partial yes; Y: yes

Appendix H. Summary of findings of genicular artery embolization compared to standard treatment or drug therapy for the treatment of chronic pain secondary to knee osteoarthritis refractory to standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard treatment or drug therapy (no use of the GAE)	Risk with GAE				
Knee pain						
assessed with: VAS and KOOS QoL pain subscale follow-up: 1 month	In Bagla *et al.*, there was a statistically significantly more pain reduction assessed with VAS in the treatment group than in the sham group at 1 month (MD= 50.1 mm; 95% CI [29.0, 72.3]; 21 patients). However, the Landers *et al.* analyses showed a non-statistically significant difference in the level of pain between intervention groups at 1 month of follow-up.			80 (2 RCTs)[1,2]	⨁⨁◯◯ Low[a,b]	In the Bagla et al. study, the response rates at 1 month were 79% (11/14) and 0% (0/7) for the treatment and sham arms, respectively. However, in the Landers et al. study, global change in knee pain at 12 months indicated that 17 participants (58.6%) in the GAE group reported being moderately or much better, compared to 11 participants (37.9%) in the control group, though this difference was also not statistically significant.
assessed with: KOOS QoL pain subscale follow-up: 6 months	A non-statistically significant difference in the level of pain between intervention groups.			59 (1 RCT)[1]	⨁⨁⨁◯ Moderate[c]	
assessed with: KOOS QoL pain subscale follow-up: 12 months	A non-statistically significant difference in the level of pain between intervention groups.			59 (1 RCT)[1]	⨁⨁⨁◯ Moderate[c]	
Overall functional improvement						

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard treatment or drug therapy (no use of the GAE)	Risk with GAE				
assessed with: WOMAC and KOOS FDLS and KOOS FSRS follow-up: 1 month	-	SMD **0.18 lower** (0.62 lower to 0.27 higher)		80 (2 RCTs)[1,2]	⊕⊕⊕◯ Moderate[c]	
assessed with: KOOS FDLS and KOOS FSRS follow-up: 6 months		SMD **0.17 lower** (0.68 lower to 0.34 higher)		59 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	
assessed with: KOOS FDLS and KOOS FSRS follow-up: 12 months		SMD **0.07 higher** (0.44 lower to 0.58 higher)		59 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	
HRQoL						
assessed with: KOOS QoL scale and EQ-5D follow-up: 1 month	No effects were detected on the HRQoL.			59 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard treatment or drug therapy (no use of the GAE)	Risk with GAE				
assessed with: KOOS QoL scale and EQ-5D follow-up: range 6 months	No effects were detected on the HRQoL evaluated with the KOOS scale. However, when the HRQoL was assessed using the EQ-5D VAS, a difference in favor of the GAE group was detected at the 6-month follow-up (MD -10.00; 95% CI [-19.45, -0.55], 59 patients).			59 (1 RCT)[1]	⨁⨁◯◯ Low[b,c]	
assessed with: KOOS QoL scale and EQ-5D follow-up: 12 months	No effects were detected on the HRQoL.			59 (1 RCT)[1]	⨁⨁⨁◯ Moderate[c]	
Need for pain medication						
assessed with: number of participants taking analgesia follow-up: mean 12 months	467 per 1000	**243 per 1000** (112 to 513)	**RR 0.52** (0.24 to 1.10)	59 (1 RCT)[1]	⨁⨁⨁◯ Moderate[c]	
Adverse events and complications						
assessed with: number of participants follow-up: range 1 month to 24 months	No major adverse events or complications were found. No differences were observed in minor adverse events			(2 RCTs)[1,2]	⨁⨁⨁◯ Moderate[c]	No major adverse events were reported in either of the two studies. Specifically, Landers *et al.* reported that no evidence of osteonecrosis or ischaemic complications were found on magnetic resonance imaging up to two years following the procedure. No differences were observed in minor adverse events.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard treatment or drug therapy (no use of the GAE)	Risk with GAE				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its confidence interval).
CI: confidence interval; EQ-5D: European Quality of Life 5 Dimensions; FDLS: Function in Daily Living subscale; FSRS: Function in Sport and Recreation subscale; GAE: Genicular artery embolization; HRQoL: health related quality of life; KOOS: Knee Injury and Osteoarthritis Outcome Score; MD: mean difference; QoL: quality of life; RCT: randomized controlled trial; RR: risk ratio; SMD: standardized mean difference; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. The analyses of the level of pain at 1 month of follow-up showed very high heterogeneity rates (I^2= 91%), so the pooled data are not presented.
b. Inconsistent effects of the intervention across studies or across measurement scales.
c. Wide confidence interval and very small sample size.

References
1.Landers, S, Hely, R, Hely, A, Harrison, B, Page, RS, Maister, N, Gwini, SM, Gill, SD. Genicular artery embolization for early-stage knee osteoarthritis: results from a triple-blind single-centre randomized controlled trial. Bone and Joint Open; 2023.
2.Bagla, S, Piechowiak, R, Sajan, A, OrlandoJ, J, Hartman, T, Isaacson, A. Multicenter Randomized Sham Controlled Study of Genicular Artery Embolization for Knee Pain Secondary to Osteoarthritis. Journal of vascular and interventional radiology: JVIR; 2022.

Appendix I. Results of meta-analyses

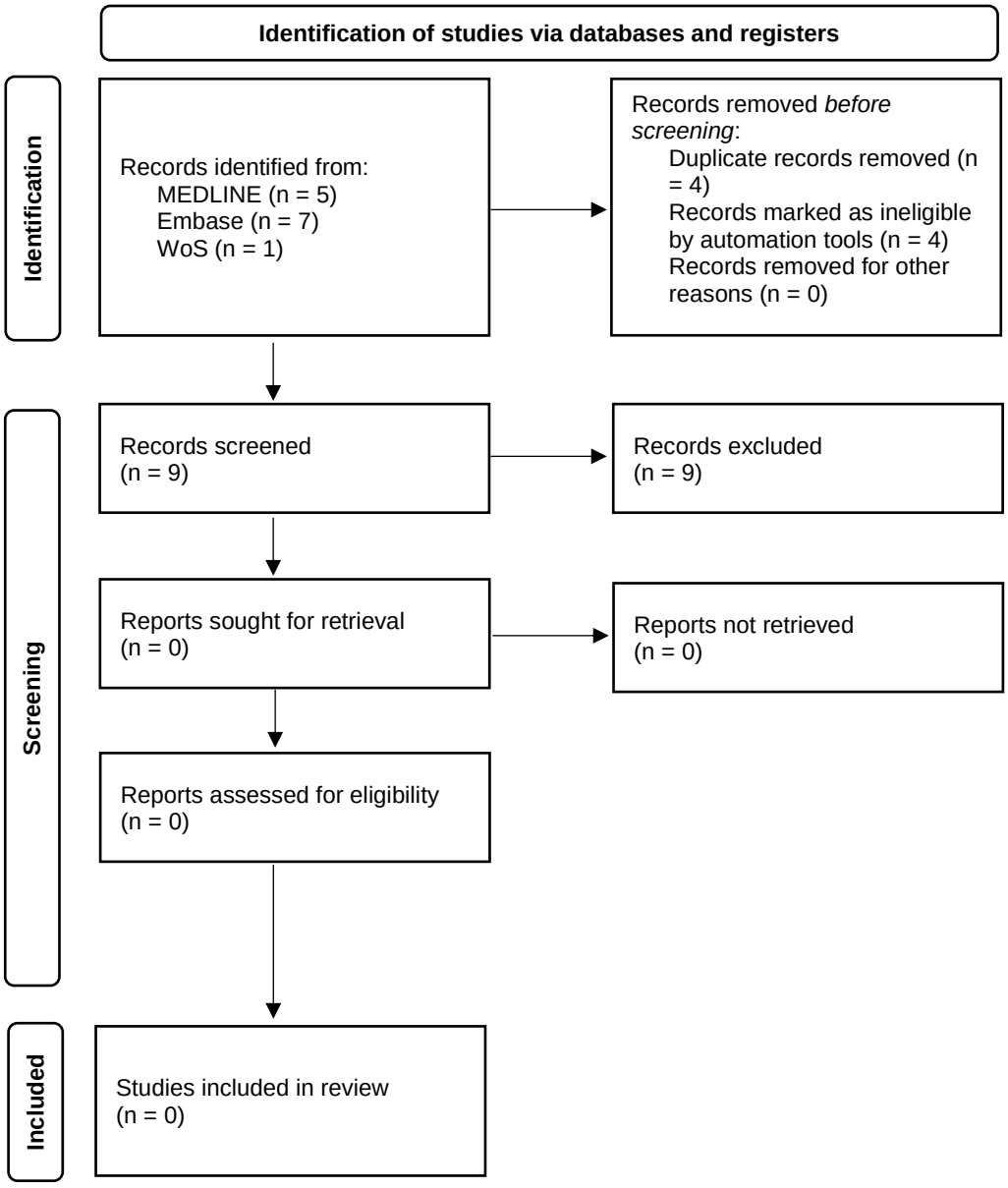
Genicular artery embolization vs. standard treatment or drug therapy

Outcome or Subgroup	K	N	Statistical Method	Effect Estimate
1.1 Pain	2		SMD (IV, Random, 95% CI)	Subtotals only
1.1.1 1 month	2	80	SMD (IV, Random, 95% CI)	-0.83 [-2.85, 1.19]
1.1.2 6 months	1	59	SMD (IV, Random, 95% CI)	-0.28 [-0.79, 0.24]
1.1.3 12 months	1	59	SMD (IV, Random, 95% CI)	0.13 [-0.38, 0.64]
1.2 Overall functional improvement	2		SMD (IV, Fixed, 95% CI)	Subtotals only
1.2.1 1 month	2	80	SMD (IV, Fixed, 95% CI)	-0.18 [-0.62, 0.27]
1.2.2 6 months	1	59	SMD (IV, Fixed, 95% CI)	-0.17 [-0.68, 0.34]
1.2.3 12 months	1	59	SMD (IV, Fixed, 95% CI)	0.07 [-0.44, 0.58]
1.3 HRQoL - KOOS	1		MD (IV, Fixed, 95% CI)	Subtotals only
1.3.1 1 month	1	59	MD (IV, Fixed, 95% CI)	3.33 [-9.13, 15.79]
1.3.2 6 months	1	59	MD (IV, Fixed, 95% CI)	-4.53 [-20.24, 11.18]
1.3.3 12 months	1	59	MD (IV, Fixed, 95% CI)	2.10 [-13.33, 17.53]
1.4 HRQoL - EQ-5D - VAS	1		MD (IV, Fixed, 95% CI)	Subtotals only
1.4.1 1 month	1	59	MD (IV, Fixed, 95% CI)	1.66 [-8.77, 12.09]
1.4.2 6 months	1	59	MD (IV, Fixed, 95% CI)	-10.00 [-19.45, -0.55]
1.4.3 12 months	1	59	MD (IV, Fixed, 95% CI)	-8.33 [-19.15, 2.49]
1.5 HRQoL - EQ-5D- Mobility - No/slight problem	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 1 month	1	59	RR (M-H, Fixed, 95% CI)	0.84 [0.57, 1.23]
1.5.2 6 months	1	59	RR (M-H, Fixed, 95% CI)	0.93 [0.64, 1.36]
1.5.3 12 months	1	59	RR (M-H, Fixed, 95% CI)	1.10 [0.72, 1.67]
1.6 HRQoL - EQ-5D- Self-care - No/slight problem	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.6.1 1 month	1	59	RR (M-H, Fixed, 95% CI)	1.03 [0.92, 1.16]
1.6.2 6 months	1	59	RR (M-H, Fixed, 95% CI)	1.11 [0.95, 1.30]
1.6.3 12 months	1	59	RR (M-H, Fixed, 95% CI)	1.07 [0.90, 1.28]
1.7 HRQoL - EQ-5D- Usual activities - No/slight problem	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 1 month	1	59	RR (M-H, Fixed, 95% CI)	0.80 [0.55, 1.16]
1.7.2 6 months	1	59	RR (M-H, Fixed, 95% CI)	0.83 [0.55, 1.25]
1.7.3 12 months	1	59	RR (M-H, Fixed, 95% CI)	1.03 [0.71, 1.51]

1.8 HRQoL - EQ-5D- Discomfort - No/slight problem	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 1 month	1	59	RR (M-H, Fixed, 95% CI)	0.96 [0.55, 1.68]
1.8.2 6 months	1	59	RR (M-H, Fixed, 95% CI)	0.97 [0.57, 1.62]
1.8.3 12 months	1	59	RR (M-H, Fixed, 95% CI)	1.03 [0.63, 1.71]
1.9 HRQoL - EQ-5D- Anxiety - No/slight problem	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.9.1 1 month	1	59	RR (M-H, Fixed, 95% CI)	0.95 [0.74, 1.22]
1.9.2 6 months	1	59	RR (M-H, Fixed, 95% CI)	0.80 [0.62, 1.04]
1.9.3 12 months	1	59	RR (M-H, Fixed, 95% CI)	1.08 [0.81, 1.44]
1.10 Need for pain medication	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 12 months	1	59	RR (M-H, Fixed, 95% CI)	0.52 [0.24, 1.10]
1.12 Knee pain	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.12.1 1 month	1	21	RR (M-H, Fixed, 95% CI)	1.60 [0.07, 34.93]
1.12 Purpura	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.12.1 1 month	1	21	RR (M-H, Fixed, 95% CI)	3.73 [0.22, 63.66]
1.13 Nausea/vomiting	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.13.1 1 month	1	21	RR (M-H, Fixed, 95% CI)	1.60 [0.07, 34.93]
1.14 Hematoma	2		RR (M-H, Random, 95% CI)	Subtotals only
1.14.1 1 month	2	80	RR (M-H, Random, 95% CI)	1.05 [0.05, 22.42]
1.15 Skin changes	1		RR (Non-event) (M-H, Fixed, 95% CI)	Subtotals only
1.15.1 1 month	1	21	RR (Non-event) (M-H, Fixed, 95% CI)	1.00 [0.82, 1.22]
1.16 Skin ischemia	1		RR (Non-event) (M-H, Fixed, 95% CI)	Subtotals only
1.16.1 1 month	1	21	RR (Non-event) (M-H, Fixed, 95% CI)	1.00 [0.82, 1.22]
1.17 Pruritus	1		RR (Non-event) (M-H, Fixed, 95% CI)	Subtotals only
1.17.1 1 month	1	21	RR (Non-event) (M-H, Fixed, 95% CI)	1.00 [0.82, 1.22]
1.18 Ecchymosis	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.18.1 1 month	1	21	RR (M-H, Fixed, 95% CI)	0.18 [0.01, 3.88]
1.19 Bleeding at access site	1		RR (M-H, Fixed, 95% CI)	Subtotals only
1.19.1 1 month	1	21	RR (M-H, Fixed, 95% CI)	0.18 [0.01, 3.88]

CI: confidence interval; EQ-5D: European Quality of life-5 Dimensions; IV: inverse variance: KOOS: Knee Injury and Osteoarthritis Outcome Score; VAS: visual analogue scale; HRQoL: health-related quality of life; K: Studies; N: Participants; M-H: Mantel-Haenszel model, MD: Mean Difference; RR: Risk Ratio; SMD: standardized mean difference

Appendix J. Flow diagram of the selection process of cost-effectiveness studies



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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ None	
		This study was commissioned and funded by the Spanish Ministry of Health in the framework of activities carried out by the Spanish Network of Agencies for Health Technology Assessment and Services for the National Health System (RedETS).	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
		This work received support from the Living Evidence to Inform Health Decisions (LE-IHD) program's project entitled "Strengthening decision-making capacity in the Spanish Health System through living evidence: An innovative framework" that has been funded by Instituto de Salud Carlos III (ISC-III) Grant PI21/01564.	

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6	Payment for expert testimony	☒ **None**	
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11	Stock or stock options	☒ **None**	
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13	Other financial or non-financial interests	☒ **None**	

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Authorship

Aránzazu Hernández-Yumar and Yadira González-Hernández participated in the design, acquisition, analysis, and interpretation of data, as well as drafting the work. These authors share first authorship. Tasmania del Pino-Sedeño, Cristina Valcárcel-Nazco, Aythami de Armas-Castellano, and Estefanía Herrera-Ramos participated in the design, acquisition, analysis, and interpretation of data, and reviewed the work. Julián Portero Navarro, Montserrat Carmona Rodríguez, María Ximena Rojas-Reyes, and María M. Trujillo-Martín participated in the design, and critically reviewed the work. Tasmania del Pino-Sedeño and María M. Trujillo-Martín also contributed to project administration. All authors read and approved the final manuscript.

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Conflict of interest

The authors have no conflict of interest with the subject matter or materials discussed in the manuscript.

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Role of the funding source

The study was conducted independently of study sponsors. There was no sponsor involvement in the study design; collection, analysis and interpretation of the data; in writing of the manuscript; or in the decision to submit the manuscript for publication.

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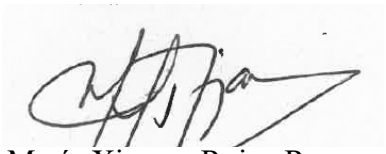

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