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LETTER

Bridging Evidence Synthesis and Clinical Relevance in Blood-Letting Therapy for Knee Osteoarthritis: Methodological Reflections on a Meta-Analysis [Letter]

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Dear editor

We appreciate the recent meta-analysis by Dong et al on blood-Letting therapy (BLT) for knee osteoarthritis (KOA).[1] A survey using data from the Osteoarthritis Initiative, a public database sponsored by the National Institutes of Health, reported that 47% of individuals with radiographic-confirmed KOA used complementary and alternative medicine (CAM).[2] Against this clinical background, the findings of Dong et al contribute valuable evidence regarding the potential integration of BLT into KOA management. Nevertheless, several methodological issues merit further discussion.

Choosing Clinically Meaningful Comparators for Control Groups

In the absence of an ideal placebo-BLT control, clinically informative comparisons for KOA generally include BLT versus conventional treatment (to evaluate its potential as an alternative therapy) or BLT plus conventional treatment versus conventional treatment alone (to evaluate its adjunctive value). However, Dong et al's meta-analysis included randomized controlled trials (RCTs) comparing BLT plus acupuncture with acupuncture alone.[1]

This comparison limits the clinical relevance of the findings. Acupuncture, though widely used in East Asia, is not an accepted standard KOA therapy, and its efficacy and safety remain debated.[3] Consequently, such comparisons cannot determine BLT's benefit over or in addition to standard care, thereby limiting their guidance for clinical decision-making.

We therefore strongly recommend that future meta-analyses prioritize RCTs using guideline-recommended standard therapies as comparators. Synthesizing effect sizes from such trials would ensure that conclusions directly inform clinical practice.

Addressing Clinical Heterogeneity in Comparators During Evidence Synthesis

Beyond control-group selection, substantial clinical heterogeneity among the control interventions appears underexplored.

For instance, in the comparison of "BLT plus Acupuncture versus Acupuncture", different acupuncture modalities, including manual-, warm-, and fire-acupuncture, were pooled under a single category of "Acupuncture"[1] despite differences in physical stimulation intensity, mechanisms of action, and physiological responses.[4] This assumes therapeutic equivalence across modalities, which is insufficiently supported and may partly explain the substantial heterogeneity observed for WOMAC outcomes (I^2 = 90%).

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A similar issue was observed in the comparison of "BLT versus Drugs", where oral Ibuprofen (an NSAID) and intra-articular injection of sodium hyaluronate were combined into a single "Medication" category.[1] These agents differ fundamentally in mechanism, route of administration, onset of action, and applicable disease stages. NSAIDs exert analgesic and anti-inflammatory effects primarily via COX inhibition in peripheral tissues and the central nervous system,[5] whereas intra-articular sodium hyaluronate acts through receptors such as CD44, ICAM-1, and RHAMM on synoviocytes or chondrocytes, mediating anti-inflammatory, analgesic, chondroprotective, and lubricating effects, as well as promoting proteoglycan synthesis and influencing subchondral bone.[6] Thus, even if statistical heterogeneity were low, the clinical heterogeneity alone sufficiently undermines the interpretability of the pooled estimate. The resultant effect size reflects BLT's performance against an artificially constructed "average drug control", failing to address the clinically relevant question of which specific drug BLT outperforms.

Notably, the meta-analysis included multiple intervention comparisons, including BLT (or BLT plus Drugs) versus Drugs, BLT plus Rehabilitation versus Drugs plus Rehabilitation, and BLT plus Acupuncture versus Acupuncture.[1] Given this multiplicity, a network meta-analysis may have been more appropriate than the pairwise meta-analysis currently employed, as it allows simultaneous comparison and ranking of multiple interventions, thereby providing evidence with greater clinical utility[7]—for instance, clarifying the relative standing of BLT among available options and identifying optimal therapeutic strategies.

Stratifying Effect Estimates by Treatment Duration/Sessions

Included RCTs had treatment durations ranging from nine days to eight weeks,[1] yet no stratification by treatment duration was conducted. For a chronic degenerative disease like KOA, treatment duration critically influences therapeutic effects:[8] a nine-day regimen predominantly captures short-term stimulatory effects, whereas an eight-week protocol more likely reflects cumulative treatment effects—these are not biologically equivalent. Nevertheless, Dong et al extracted end-of-treatment outcomes from each RCT without standardizing assessment time points, thereby pooling short- and medium-term effects within a single estimate. The resulting effect size represents a weighted average across heterogeneous time windows and does not correspond to any specific clinically meaningful time point. Consequently, it cannot answer when BLT effects emerge or how long they persist.

Future meta-analyses would benefit from incorporating prespecified subgroup analyses based on treatment duration or sessions, or using meta-regression to examine dose-response relationships between treatment intensity and effect size.[7] When data allow, meta-analysis of repeated-measures studies[9] could also be considered to chart the temporal trajectory of BLT effects over time, identifying onset, peak, and duration of therapeutic benefit, and thus offering more actionable evidence for clinical regimen design.

Pooling Response Rates Only Under Uniform Grading Criteria

The authors used "inefficient rate" and "response rate" as outcome indicators and calculated risk ratios accordingly, concluding that BLT-based interventions reduced the inefficient rate and increased the response rate compared with control interventions.[1] This inference is methodologically fragile, as the definitions of "Clinical Cure/Control", "Effective", and "Ineffective/Non-Response" varied across included trials.

Taking the meta-analysis of overall response rate under the "BLT plus Acupuncture versus Acupuncture" comparison as an example, six RCTs were pooled. Among them, three trials adopted entirely different grading criteria. Bu defined response levels based on percentage reduction in WOMAC score: ≥95% as clinical control, 70–95% as markedly effective, 30–70% as effective, and <30% as ineffective.[10] In contrast, Wang used a composite of symptom resolution, joint range of motion (0°–135°), and impact on daily activities to define clinical cure, markedly effective, effective, and ineffective.[11] Xu employed yet another set of criteria, categorizing outcomes based on the presence of pain at rest and during activity.[12] These disparate standards are not interchangeable; pooling response and non-response rates across them introduces significant measurement heterogeneity, likely distorting the pooled effect estimate and compromising outcome comparability.[7]

Greater reliance should be placed on internationally accepted core outcome sets—such as VAS, WOMAC, and KOOS-PS—as primary analysis indicators, with pain sub-scores further evaluated according to the composite

OMERACT-OARSI response criteria.[13] Composite outcomes like overall response rate should be relegated to secondary analyses, and their pooling strictly confined to RCTs that adopt identical efficacy grading criteria. Such an approach would enhance the comparability and reproducibility of findings, while also improving both the internal validity and external generalizability of evidence synthesis results.

Examining Technical Parameters of Blood-Letting via Meta-Regression

The authors classified blood-letting methods into three types (pricking BLT, wet cupping therapy, and needle-scraping therapy), yet the instruments and procedures employed actually vary considerably.[1] This inconsistency may introduce intervention heterogeneity across included RCTs and affect the stability of pooled estimates. Moreover, different techniques differ substantially in puncture depth, tissue trauma, blood volume control, local damage extent, infection risk, and patient tolerability—implicating both efficacy and safety dimensions. However, no subgroup analyses or focused discussion on these differences appear to have been conducted.

A more refined analytical approach would treat blood-letting modality as a prespecified subgroup factor or include it as a covariate in meta-regression to examine its influence on efficacy and safety outcomes. Such analyses would help clinicians clarify the relative merits of different BLT procedures and provide more operationally instructive recommendations for subsequent clinical practice guidelines.

Strengthening Publication Bias Assessment in Small-Sample Meta-Analyses

The authors prespecified that funnel plots would be used to detect publication bias when more than 10 trials were available per comparison. As this threshold was not met for any comparison, no such testing was performed.[1]

While we agree that funnel plots and Egger's test have limited statistical power in small-sample meta-analyses, this does not justify omitting consideration of publication bias.[7] This concern is further highlighted by the fact that the included RCTs were almost exclusively from China and predominantly reported positive findings. This geographic concentration and consistent directional pattern themselves constitute a risk signal for publication bias.

For meta-analyses with fewer than 10 original studies, alternative methods such as Doi plots and the Luis Furuya-Kanamori Index may provide more informative assessments of publication bias.[14] More importantly, the authors applied the GRADE approach, which explicitly requires consideration of publication bias as one of its core domains.[15] Failure to address this domain may lead to incomplete certainty assessments and affect the overall grading of evidence quality.

Conclusion

In summary, Dong et al's meta-analysis provides a timely synthesis of evidence on BLT for KOA. However, the issues discussed above collectively underscore a broader methodological challenge in CAM research, namely the tension between increasingly sophisticated quantitative synthesis and clinical interpretability. We therefore advocate for more clinically structured and methodologically rigorous analytical frameworks, including appropriate comparator selection, standardization of interventions and outcome definitions, and, when appropriate, network meta-analysis. Such improvements are not merely technical refinements, but constitute a critical pathway for transforming fragmented and heterogeneous clinical trial data into evidence that is truly meaningful for clinical decision-making.

Abbreviations

BLT, Blood-Letting Therapy; CAM, Complementary and Alternative Medicine; COX, Cyclooxygenase; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; ICAM-1, Intercellular Adhesion Molecule 1; KOA, Knee Osteoarthritis; KOOS-PS, Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-form; MD, Mean Difference; NSAID, Non-Steroidal Anti-Inflammatory Drug; OMERACT-OARSI, Outcome Measures in Rheumatology-Osteoarthritis Research Society International; RCT, Randomized Controlled Trial; RHAMM, Receptor for Hyaluronan-Mediated Motility; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Data Sharing Statement

Data availability is not applicable as no new data was generated or analyzed in this communication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no competing interests in this communication.

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