DOI: 10.7860/JCDR/2026/81560.23759

Research Protocol

Ayurveda Section

Efficacy of *Baladi* Granules versus *Baladi Ksheerpaka* in Primary Knee Osteoarthritis: Protocol for an Open-label Multi-arm Non-inferiority Randomised Controlled Trial

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ABSTRACT

Introduction: Osteoarthritis (OA) is a major contributor to Years Lived with Disability (YLD) in the middle-aged and elderly population. The conventional approaches for OA management are not able to provide satisfactory relief due to associated Adverse Effects (AE). So, there is a critical need for safe and effective therapeutic options for OA management.

Need of the study: *Baladi Ksheerpaka*, indicated in Ayurvedic texts for *Vatavyadhi* such as *Sandhigatavata* (OA), contains *Bala* (*Sida cordifolia* Linn.) and *Brihat Panchamula*. Experimental studies have reported their anti-inflammatory and analgesic properties. For better adherence and compliance, the said formulation will also be administered as granules mixed with lukewarm milk in the present study, and their efficacy will be compared.

Aim: To compare the efficacy of Ayurveda interventions, *Baladi* granules, and *Baladi Ksheerpaka* in the management of primary knee OA.

Materials and Methods: This open-label, multi-arm, non-inferiority Randomised Controlled Trial (RCT) will be carried out at the Central Ayurveda Research Institute, New Delhi, India, from July 2025 to November 2025. Individuals of any gender aged 50 to 70 years diagnosed with primary knee OA as per the American College of Rheumatology (ACR) criteria, and having grade 1 to 3 radiographic changes in the affected knee, will be included. A total of 111 participants will undergo random assignment in a 1:1:1 ratio to receive *Baladi* granules or *Baladi Ksheerpaka*, or *Yograj Guggulu* (control group) for eight weeks. *Abhyanga* with *Nirgundi Taila* and hot fomentation will be advised in all three groups. The primary outcome is the change in knee pain score from baseline, assessed through the Knee Injury and Osteoarthritis Outcome Score (KOOS). The secondary outcome measures include the change in the score for other subscales of KOOS {other symptoms, function, and Quality of Life (QoL)}, the Numeric Pain Rating (NPR) Scale, and the pain disability index; change in the range of motion of the affected knee joint(s); and change in the need for rescue analgesic medication from baseline. The safety outcomes include the incidence of AE and changes in liver and Kidney Function Tests (KFT) from baseline. The results will be presented and analysed using appropriate statistical methods.

Keywords: *Brihat panchamula*, Knee injury and osteoarthritis outcome score, *Nirgundi Taila*, Osteoarthritis, *Sida cordifolia*, *Yograj Guggulu*

INTRODUCTION

Osteoarthritis (OA) is a chronic disease characterised by the degeneration of joint cartilage, osteophyte production, meniscal degradation, ligamentous laxity, and subchondral bone alterations [1-3]. The commonly affected joints due to OA are the knee, hands, feet, spine, shoulder, and hip. Joint pain, stiffness, functional disability, and impaired QoL are its characteristic features [2]. It has two predominant forms, viz., primary and secondary. Primary one occurs due to age-related degeneration, whereas injury, occupational stress on joints, and co-morbidities such as obesity or diabetes mellitus lead to secondary OA. OA accounts for 50% of the entire musculoskeletal disease burden [3]. Knee OA covers approximately 85% of the OA cases globally [3,4]. The significant increase in the prevalence of OA is a result of the ageing population and risk factors, including obesity [5]. It has been anticipated that OA will be among the top five reasons for YLD across the world shortly [6]. Worldwide prevalence of OA is estimated to be approximately 595 million in 2020, equivalent to 7.6% of the global population [7]. Out of which, about 303.1 million people worldwide have hip and knee OA, with an annual incidence of 181.2 per lakh [8]. In India, OA affects 62.35 million people as of 2019 [9].

The clinical presentation of OA is similar to *Sandhigatavata*, a particular type of *Vatavyadhi* (ailments due to vitiation of *Vata dosha*) described in Ayurveda. The symptoms of *Sandhigatavata* (~OA) are *Sandhishotha* (joint swelling) with *Vata Purna Druti Sparsha* (swelling feels like a bag filled with air on palpation), difficulty in joint movements, and painful movement of the joints [10]. Ayurveda interventions for OA management have shown promising outcomes in routine clinical practice. Further, a few clinical studies also reported the safety and beneficial effects of Ayurveda interventions in relieving symptoms of OA, promoting QoL, and limiting the analgesic requirement [11-19].

The present randomised controlled exploratory trial is designed to compare the efficacy of Ayurvedic interventions, *Baladi* granules, and *Baladi Ksheerpaka* with *Yograj Guggulu* in the management of primary knee OA. *Baladi Ksheerpaka* is described in classical Ayurveda texts for the management of *Vatavyadhi,* such as *Sandhigatavata* (~OA). Experimental studies reported the potential anti-inflammatory and analgesic activity of its ingredients (*Bala* and *Brihat Panchamula*). For ease of administration and to ensure participants' adherence and better compliance with the study intervention, the said formulation is also planned to be administered in the form of granules mixed with lukewarm milk in the present study.

The primary objective of this RCT is to assess the efficacy of *Baladi granules* and *Baladi Ksheerpaka* in managing knee pain in individuals with primary knee OA compared to *Yograj Guggulu*.

The key secondary objectives of this study include evaluating the efficacy of the trial interventions in managing other symptoms of

primary knee OA (stiffness, swelling, restricted range of motion, etc.,), and functional disability (activities of daily living and recreational activities), effect on the pain intensity score, pain disability score, and range of motion of the affected knee joint, need for rescue analgesic medication, and knee OA-specific QoL parameters, after eight weeks administration of study interventions. Another secondary objective is assessing the safety of trial Ayurveda interventions in managing knee OA.

Null Hypothesis (H0):

- *Baladi* granules and *Baladi Ksheerpaka* are inferior to *Yograj Guggulu* in improving the pain subscale score of KOOS in individuals with primary knee OA.
- Significant difference in the efficacy of *Baladi* granules and *Baladi Ksheerpaka* in improving the pain subscale score of KOOS in individuals with primary knee OA.

Alternate Hypothesis (H1):

- *Baladi* granules and *Baladi Ksheerpaka* are not inferior to *Yograj Guggulu* in improving the pain subscale score of KOOS in individuals with Primary Knee OA.
- No significant difference in the efficacy of *Baladi* granules and *Baladi Ksheerpaka* in improving the pain subscale score of KOOS in individuals with primary knee OA.

REVIEW OF LITERATURE

The OA is a major contributor to YLDs in the middle-aged and elderly population [20]. Management of OA includes combining non-pharmacological and pharmacological approaches aimed at preventing, lowering risk, and slowing the disease progression [21]. Acetaminophen and oral/topical non-steroidal anti-inflammatory medications are suggested as first-line OA management. However these medications have certain AE on long-term administration, such as gastrointestinal and renal toxicity, which limit their use over a long period [22]. Glucosamine alone or in combination with chondroitin is also prescribed for its effect on the structural progression of the disease, but its efficacy is uncertain [5]. Joint replacement surgery is considered for severe and advanced OA. So, it is imperative to search for safe and efficacious treatment options for OA management.

Ayurveda suggests various therapeutic options for OA management, including single herbs, herbal, herbo-mineral, and metallo-mineral compound formulations, and different *Panchakarma* (Ayurveda therapeutic procedures) procedures. Several clinical studies highlighted the safety and beneficial effects of Ayurveda interventions in relieving symptoms of OA, promoting QoL, and limiting the analgesic requirement [11-19]. However, most of these studies include *Guggulu Kalpa* or *Panchakarma* procedures. Guggulu-containing formulations are usually safe but are associated with a few AEs on long-term administration, such as abdominal pain, burning sensation in the epigastric region, loose stools, headache, skin rashes, etc., [23,24]. *Panchakarma* is a highly specialised Ayurveda treatment for the biopurification and rejuvenation of the body, senses, and mind. Yet there are certain functional limitations/challenges in terms of infrastructure, resources, medicine, and consumables supply, and trained staff in providing this specialised treatment facility at the primary level of healthcare, especially in rural and backward areas.

For the present RCT, oral administration of *Baladi* granules/*Baladi Ksheerpaka* along with *Abhyanga* with *Nirgundi Taila,* followed by hot fomentation, is proposed for the management of primary knee OA. The proposed trial interventions are inexpensive, easily available, non-controversial, and possess potential therapeutic properties for effective management of OA. Further, the proposed interventions can be easily administered in remote clinical settings, where accessibility to effective treatment options for OA and the required infrastructure for *Panchakarma* therapies is not currently available. The palatability and ease of administration are the added advantages of the trial intervention (*Baladi* granules). These factors are crucial in ensuring patients' adherence and better compliance with the prescribed treatment.

Bala-BrihatPanchamula Siddha Ksheera is recommended for managing *Vatavyadhi* such as *Sandhigatavata* (~OA) in classical Ayurveda texts, *Chakradutta* (chapter 22, verse 81), and *Bhaishajya Ratnavali* (*Vatavyadhichikitsaprakarana*, verse 5) [25,26]. Its ingredients include *Bala* (*Sida cordifolia* L.) and *Brihat Panchamula* {*Bilva* (*Aegle marmelos* (L.) Corr.), *Shyonaka* (*Oroxylum indicum* (L.) Kurz), *Gambhari* (*Gmelina arborea* Roxb.), *Agnimantha* (*Clerodendrum phlomoides* Hort. Ital. ex DC.), *Patala* (*Stereospermum suaveolens* (L.f.) DC.)}. *Bala* and *Brihat Panchamula* have *Vatashamaka* (pacify vitiated *Vata Dosha*), *Vedanasthapana* (analgesic), and *Shothahara* (anti-inflammatory) properties [27]. Experimental studies also highlighted the potential anti-inflammatory and analgesic activity of *Bala* and *Brihat Panchamula* [28-33]. In addition, *Bala* and *Ksheera,* due to their *Balya* (provide optimal nutrition), *Dhatuposhana* (provide nutrition to the body tissues), and *Vayasthapaka* (slow down the degenerative process) properties, may slow down the degenerative changes observed in OA [27,34]. Acharya Charaka recommended milk among the suggested diet and lifestyle for *Vatavyadhi* [10]. Further, milk is a rich source of calcium and other essential nutrients, so it provides nourishment to the bones and joints. Due to its high fat and water content, milk can be both a polar and a non-polar solvent according to biochemical assays. As a result, active constituents extracted either in fat or water can be optimally extracted in the milk-containing formulation [35]. The interventions in the control group include *Yograj Guggulu* (Ayurvedic Pharmacopeia of India Part II Vol II), which is recommended in the Ayurvedic standard treatment guidelines issued by the Directorate General of Health Services, Government of India, for the management of OA [36]. Published clinical studies also reported significant and clinically relevant improvement in symptoms of knee OA with *Yograj Guggulu* [11,13,14].

Abhyanga and *Swedana* are included in all three study groups as such an approach reflects routine practice in Ayurvedic care. Further, *Abhyanga* and *Swedana* pacify the *Vata Dosha*, improve the blood circulation at the affected site due to their localized action, and alleviate pain and stiffness [19]. *Nirgundi Taila* is mentioned in Charak Samhita (*Chikitsasthana* chapter 28, verses 134-135) for topical application on the affected areas in *Vatavyadhi*-related pain [10]. The bioactive compounds present in *Nirgundi* (*Vitex negundo* L.) exhibit potent anti-inflammatory, analgesic, anti-osteoporotic, and antioxidant activities [37,38]. An exploratory clinical study on *Nirgundi Taila* has also reported its potential in managing OA [39].

Further, the present study has taken the KOOS as the primary outcome (one of the few clinical studies on Ayurveda interventions to utilise KOOS as a study outcome). It is a validated and reliable tool utilised for both short-term and long-term follow-up of subjects diagnosed with knee OA [40]. An advantage when using the KOOS for studies in physically active individuals is its ability to evaluate the sport and recreation-related functions, as well as knee-specific QoL {these two subscales are not available in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale}, and it has a better sensitivity in comparison to the WOMAC and SF-36 scales [40].

MATERIALS AND METHODS

This clinical study is an open-label, randomised controlled, multi-arm non-inferiority trial. The study will be carried out at Central Ayurveda Research Institute, New Delhi, India, from July 2025 to November 2025. The Institutional Ethics Committee of Central Ayurveda Research Institute, New Delhi, India, has approved the study protocol and related documents (vide letter no. I-12/2020-CARICD/Tech/IEC/111 dated May 14, 2025) to ensure compliance with ethical standards and safeguard the rights and well-being of the study participants. The study has been registered prospectively at

the Clinical Trial Registry of India (CTRI/2025/06/088460). The study protocol has been drafted following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [41].

Inclusion criteria: Individuals of any gender aged 50 to 70 years diagnosed with primary knee OA as per the American College of Rheumatology (ACR) criteria, grade 1 to 3 radiographic changes in the affected knee joint (as per Kellgren-Lawrence classification), pain score of at least 2 (as per numeric pain rating scale) in most days of the last month, and willing to provide written informed consent will be considered for enrolment in the study. ACR criteria for knee OA include pain in the knee along with any three of the following: age more than 50 years, less than 30 minutes of joint stiffness, crepitus, bony tenderness, bony enlargement, and no palpable warmth.

Exclusion criteria: Individuals with history of knee joint replacement (on one or both knee joints), intra-articular corticosteroids or hyaluronic acid administration or arthroscopy in the past six months, currently taking or in the last three months taken anticoagulants or oral corticosteroids; history of significant trauma to the affected knee within the preceding one year, history of rheumatoid arthritis, psoriatic arthritis, Systemic Lupus Erythematosus (SLE), gout, underlying diabetes mellitus, uncontrolled hypertension (more than160/100 mm Hg), gastrointestinal disease, cardiovascular disease, neurological disease, psychiatric disorder, coagulation disorders, endocrine disease, or malignancies; abnormal hepatic function {Aspartate Aminotransferase (AST) and/or ALT Alanine Aminotransferase more than three times the upper limit of normal} or abnormal renal function (serum creatinine more than 1.2 mg/dL); BMI $\geq$ 30 kg/m^2 will be excluded from the study. Similarly, those currently taking supplements that may affect the treatment outcome such as chondroitin and glucosamine, with history of hypersensitivity to the study interventions, history of alcohol use disorder, chronic smoking, or any other substance abuse; or presence of any other clinical condition which the investigator thinks may compromise the participant's safety or compliance, will not be considered for the study.

Sample size: This clinical study is proposed as a non-inferiority trial, and the primary outcome will be the change in knee pain score from baseline (assessed through KOOS). The non-inferiority margin between the new treatment group and control group for the KOOS pain subscale score is taken as 8, and the standard deviation as 11 (from a previously published study) [42,43]. For achieving a 90% power at the 5% level of significance with equal allocation in the study groups and an attrition rate of 10%, 37 participants in each of the three groups will be required in the study (111 study participants in total) [44].

Study Procedure

Study intervention: The eligible participants in trial Groups I and II will receive *Baladi* granules and *Baladi Ksheerpaka*, respectively, for eight weeks (56 days). The participants in the control group will be advised to take *Yograj Guggulu* for 56 days. *Abhyanga* with *Nirgundi Taila,* followed by hot fomentation twice daily, will be included in all three study groups. The details of the study interventions are provided in [Table/Fig-1]. The study interventions will be procured from Hans Herbals Pvt., Ltd., SIDCUL, Haridwar, Uttarakhand, India.

Discontinuation of the trial interventions: If any study participant develops any AE, the administration of the trial interventions would be temporarily halted, and the participant would be closely monitored. If symptoms recur after reintroducing the trial interventions, the participant will be withdrawn from the study, and an assessment of the causality of AE/Adverse Drug Reactions (ADR) will be done. All such events would be recorded in the AE/ADR reporting format and reported to the IEC.

Compliance with study interventions: All the participants will be provided with an information leaflet containing the instructions for the use (method of preparation, dose, frequency, time of administration) and storage of the study interventions. The participants would also be issued a compliance form during the baseline to subsequent follow-up visits to self-report their consumption of study interventions and to record any missed doses with remarks for missing, which would enable assessment of participants' adherence to the prescribed interventions as per the study protocol. During each follow-up visit, the participants would be asked to return the used/unused/partially used containers of the study interventions to the investigators to assess adherence and cross-check with the participant's self-reported compliance form.

Group	Intervention	Dosage with frequency	Anupana (vehicle of administration)	Duration
I	*Baladi* granules	10 gm twice daily, morning (after breakfast) and evening	100 mL of lukewarm milk	56 days
II	*Baladi Ksheerpaka*	150 mL twice daily, morning (after breakfast) and evening	--	56 days
III	*Yograj Guggulu*	1 g (2 tablets of 500 mg each) twice daily after food	Lukewarm water	56 days
Common in all three study groups (for 56 days): • *Abhyanga* with *Nirgundi Taila* twice daily (morning and evening), followed by • Hot fomentation (with hot water bottle/warm damp towel/heating pad) twice daily				

[Table/Fig-1]: Details of study interventions.

Withdrawal criteria: The participants who do not adhere to the study protocol, or do not have 80% or more compliance to the prescribed interventions, or those who develop any Serious Adverse Event (SAE) or Treatment-Emergent Adverse Events (TEAE) during the study, or those who withdraw their voluntary consent for participation in the study, will be withdrawn from the study. The Ethics Committee will be notified about the SAE/TEAE within two working days, along with appropriate justification.

Concomitant or rescue medication: The participants will be monitored for any concomitant or rescue medication they need during the study period. In case of the onset of any AE or increase in pain intensity, use of rescue medication, under the investigator's discretion, will be allowed. All instances of concomitant care would be carefully documented in the CRF.

Outcome measures: The primary outcome is the change in knee pain score from baseline, assessed through the KOOS. The secondary outcome measures include the change in the score for other symptoms of Primary Knee OA (stiffness, swelling, restricted range of motion, etc.,), and function (ADL and recreational activities) assessed through KOOS;change in the score of numeric pain rating scale, pain disability index, and KOOS QoL subscale (to assess knee OA-specific QoL); change in the range of motion of the affected knee joint(s) (assessed through goniometer); change in the need of rescue analgesic medication; and assessment of treatment adherence (through self-reported compliance form and used medication containers).

The outcomes will be evaluated on day 14, day 28, day 42, and day 56 from baseline. The range of motion will be assessed through a goniometer at baseline and day 56.

Safety outcomes: The safety of the study interventions will be determined by recording the incidence of AE, if any, during scheduled follow-up visits in a structured format. All AEs during the study would be recorded and monitored as per ICH-Good Clinical Practice guidelines. The safety would also be evaluated by assessment of Liver Function Tests (LFT) and Kidney Function Tests (KFT) at baseline and day 56.

Recruitment of study participants: During the study, individuals with clinical features of knee OA visiting the outpatient department of the study site will be screened by the investigators based on the defined inclusion and exclusion criteria. The eligible subjects would be allocated to one of the three study groups based on a computer-generated randomisation schedule.

Randomisation and allocation concealment: The eligible participants will be randomised into three parallel groups in a 1:1:1

ratio using the computer-generated random number sequence. Randomisation will be concealed by using Sequentially Numbered, Opaque, Sealed Envelopes (SNOSE).

Data collection: The data related to baseline demographics and clinical examination will be collected from the study participants and reported in a CRF and e-CRF designed for the purpose. The subjective and objective outcome assessments will be done as per the study protocol on baseline and follow-up visits at day 14, 28, 42, and day 56 [Table/Fig-2]. The investigators will ensure compliance with GCP principles regarding participant safety, data accuracy, and reliability.

	Screening	Baseline	Day 14	Day 28	Day 42	Day 56
Information and Written Consent	√					
Eligibility evaluation	√					
Numeric pain rating scale	√	√	√	√	√	√
BMI assessment	√					
LFT, KFT	√					√
X-ray Knee, FBS	√					
Demographics and Medical history		√				
Clinical examination		√	√	√	√	√
Assessment of KOOS and Pain Disability Index score		√	√	√	√	√
Goniometry		√				√
Issue of study interventions		√	√	√	√	
Assessment of drug compliance			√	√	√	√
Need for rescue analgesic medication			√	√	√	√
Assessment of Adverse Events (AE)			√	√	√	√

[Table/Fig-2]: Study schedule.

Data management: Data management will adhere to stringent regulatory guidelines to ensure the accuracy, reliability, and integrity of collected data. After the participant's assessment, the investigators would promptly enter the data into CRFs and e-CRFs. The data entered in the CRFs and e-CRFs would undergo thorough cross-verification by the investigators, ensuring the reliability of the data.

STATISTICAL ANALYSIS

The data on categorical variables will be presented as numbers (percentages) and will be compared between groups using the Chi-square test, while within-group comparison will be done by using McNemar's/Cochran's Qtest. Continuous data will be checked for normality. The data following normal distribution will be presented as mean±SD and compared within the group using the Repeated Measures Analysis of Variance (rANOVA) test and between groups using One-way ANOVA with post hoc comparisons. Non-normal data will be presented as median (first quartile, third quartile) and will be compared within the group using the Friedman test. Between-group comparison will be done using the Kruskal-Wallis test. All the tests will be performed at a 5% level of significance. Statistical Package for Social Sciences (SPSS) version 29.0 will be used for statistical analysis.

Monitoring: Periodic monitoring of the study-related procedures to ensure compliance with good clinical practice guidelines and the study protocol will be done by the concerned study supervisors.

Trial audit: The investigators will ensure access to all the source documents, CRFs, and other study documents for any inspection by the regulatory authorities or IEC to monitor that the study procedures and data collection processes are as per the existing regulatory standards.

Ethical considerations: The study will be conducted following the ICMR's National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017), and Good Clinical Practice Guidelines for Clinical Trials on Ayurveda, Siddha, and Unani Medicines (GCP-ASU 2013), Ministry of Ayush, Govt. of India. All substantial amendments in the study protocol will be presented to the IEC for approval before implementation in the study. Before initiating the screening procedures, the potential participants would receive a participant information sheet in Hindi or their native language to provide the necessary information to decide their participation in the study. The written consent will be obtained from the eligible individuals, duly signed by the participant and the investigator.

Confidentiality: Strict measures will be taken to safeguard the confidentiality of participants' personal and medical information, both during and after their participation in the study. A coded enrolment identification number will be used to maintain participant confidentiality. All the consent forms, CRFs, and source documents will be stored securely at the study site in locked cabinets with restricted access. Electronic CRFs would be password-protected and stored in secure, access-restricted computer systems.

Ancillary and post-trial care: After the completion of the study, the participants will be provided with routine clinical care, as per their clinical condition. However, no ancillary studies are proposed with this study.

Protocol number: MGACHRC-OA-01 version: 5.0 dated 16.03.2025

Trial Registration: Clinical Trial Registry of India (CTRI/2025/06/088460)

Trial status: The recruitment of study participants has not started at the study site. The screening of eligible subjects is planned to be initiated by the first week of July 2025.

Source of support: Mahatma Gandhi Ayurved College, Hospital and Research Centre, Datta Meghe Institute of Higher Education and Research (Deemed to be University), Wardha, Maharashtra, India, provided technical support in conceptualising and designing the study.

Authors' contributions: AKR: Conceptualisation, Methodology, Investigation, Writing- original draft. BG: Project administration, Resources, Supervision, Writing- review and editing. VK: Conceptualisation, Project administration, Supervision, Writing-review and editing.

Data availability: This manuscript does not contain any data. However, the data related to the outcomes of this study will be available from the study investigators upon reasonable request.

Acknowledgement

The authors would like to acknowledge the Director-General, CCRAS, for providing administrative support to conduct this study. The authors are thankful to Dr. Sophia Jameela, Research Officer, CCRAS, for providing valuable technical insights, and Dr. Richa Singhal, Scientist-C, ICMR, and Dr. Arunabh Tripathi, Statistical Officer, CCRAS, for their statistical inputs while finalising this study protocol. The authors are also thankful to Hans Herbals Pvt., Ltd., Haridwar, Uttarakhand, India, for manufacturing the Ayurveda interventions for this study.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 26, 2025
- Manual Googling: Jan 05, 2026
- iThenticate Software: Jan 07, 2026 (17%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 25, 2025**
Date of Peer Review: **Oct 16, 2025**
Date of Acceptance: **Jan 09, 2026**
Date of Publishing: **Jul 01, 2026**