SPIRIT-FULL PROTOCOL

Title:

MULLIGAN'S TECHNIQUE, TOPICAL NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs) OR BOTH FOR KNEE OSTEOARTHRITIS.

Trial Registration Reference number 48294

1. Administrative Information

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Funding:

No external funding.

2. Introduction

Knee osteoarthritis (KOA) is a leading cause of pain and disability in adults >45. Exercise is the recommended first-line conservative treatment, but pain often limits adherence. Mulligan Mobilization with Movement (MWM), as described by Mulligan, combines sustained accessory joint mobilization with active movement and may reduce pain through mechanical correction and neuromodulation. Topical diclofenac 2% is an effective and well-tolerated pharmacological treatment for knee OA with minimal systemic adverse effects.

However, no study has previously examined their combined effect.

3. Objectives

Primary Objective

To compare the effect of MWM, topical diclofenac 2%, and their combination—each delivered alongside a structured exercise program—on pain intensity (VAS) at 6 months.

Secondary Objectives

• To compare effects on knee function, ROM, strength, HRQoL.

• To compare responder rates using MCID.

• To determine the incremental benefit of MWM and diclofenac beyond best-practice exercise care.

Hypothesis

When delivered as adjuncts to structured therapeutic exercise, MWM and topical diclofenac 2% will exert additive and potentially synergistic effects. Their combined application is expected to produce significantly greater improvements in 6-month activity-related knee pain compared with exercise alone.

4. Trial Design

Four-arm, parallel-group randomized controlled trial.

Allocation ratio: 1:1:1:1.

5. Participants

5.1 Inclusion Criteria

• Age ≥ 45 years

• Clinical KOA (ACR criteria)

• Radiographic KOA Kellgren–Lawrence grade 1–3

• Activity-related pain ≥ 4/10

• Ability to perform a home-based exercise program

• Ability to understand procedures and provide written informed consent

5.2 Exclusion Criteria

• Inflammatory arthritis

• Intra-articular injections to the knee within the past 6 months

• Use of systemic corticosteroids within the last 4 weeks

• Prior knee surgery or planned arthroplasty

• Contraindications to manual therapy or topical NSAIDs

• Pain caused by malignancy, infection, or other serious systemic disease

• Clinically significant psychiatric disorder affecting participation

• PHQ-9 ≥10 (moderate to severe depressive symptoms)

Participants completed the PHQ-9 prior to enrollment; only individuals scoring 0–9 were included.

• DN4 ≥4 (neuropathic pain excluded)

Participants completed the DN4 to exclude neuropathic pain mechanisms.

6. Interventions

6.1 Exercise Program (Applied in All Groups)

All participants received the same structured therapeutic exercise program. Therapeutic exercise is considered core treatment by OARSI/ESCEO/NICE; thus, withholding exercise from a control group would be unethical.
The program was designed to provide standardized, evidence-based care so that the trial could evaluate the incremental benefit of MWM and topical diclofenac.

Components

- Walking: 10 → 40 minutes, progressing individually, 50–80% HRmax. Stationary cycling permitted when walking unsafe.

- Strengthening: isometric knee extensors/flexors, 10-s holds ×10, progressive overload.
- ROM exercises: extension→flexion ×10, flexion→extension ×10.
- Stretching: hamstrings + gastrocnemius, 30 s ×3 each.

Delivery & Monitoring

- All participants trained individually by the same physiotherapist.
- Daily home-based performance required.
- Safety guidance: avoid persistent pain, redness, swelling, warmth.
- In-person follow-up at week 2 for technique correction and adverse event monitoring.
- Periodic phone reminders to support adherence.
- Exercise program NOT performed on outcome assessment days.
- Adherence was recorded using participant diaries.
  Compliance was defined as ≥75% of prescribed sessions completed**.**

6.2 Group-Specific Interventions

Control Group

Structured therapeutic exercise program only.

Mulligan Mobilization with Movement (MWM) Group

Participants allocated to the MWM group received a standardized Mulligan Concept protocol delivered by a trained physiotherapist.
The intervention followed the established principles of Mobilization with Movement, combining a sustained accessory glide applied by the therapist with concurrent active movement performed by the patient. This approach aimed to correct subtle positional faults, restore pain-free movement, and reduce nociception.

Rationale

MWM techniques have been used widely for reducing pain and improving mobility in individuals with KOA.
The protocol in this study was based on the theoretical assumption that minor

positional faults may persist after injury, altering joint loading and contributing to ongoing pain.

Treatment Schedule

- 10 total sessions
- 3 sessions per week
- 30 minutes per session
- 4-week total duration
- All sessions were administered individually by the same physiotherapist.

Procedure

1. Assessment of painful direction
   At each session, the physiotherapist identified the painful or restricted movement (flexion or extension).
2. Systematic trial of glides
   With the participant in supine, the therapist tested:
   - medial tibial glide
   - lateral tibial glide
   - internal tibial rotation glide
   - external tibial rotation glide

Each glide was applied while the patient actively moved into the painful direction.

3. Selection of therapeutic glide
   The glide that produced the greatest pain reduction and ROM improvement was selected as the therapeutic technique for that session.
4. Progression
   - If movement became pain-free, overpressure was applied.
   - If still pain-free, the same technique was tested and applied in a weight-bearing position.
   - Progression occurred both within and between sessions.
5. Dosage

- 3 sets × 10 repetitions, remaining pain-free or pain-reducing.

6. Home-Based MWM Exercise
   After completing the 10 clinical sessions, participants were instructed in a simple home MWM mobility drill:
   - 3 sets × 10 repetitions daily
   - Performed immediately before their exercise program
7. Supervision and Correction
   A follow-up appointment at week 2 was scheduled to:
   - review home performance
   - correct improper execution
   - monitor adverse events (pain, swelling, warmth, redness)

Participants were advised to stop home MWM if symptoms worsened.

6.3 Topical Diclofenac Group

Participants allocated to the topical diclofenac group received a 4-week treatment using a 2% diclofenac dermal solution (PENNSAID). Topical NSAIDs are strongly recommended by international clinical guidelines (OARSI, ESCEO, NICE) as first-line pharmacological therapy for knee osteoarthritis due to their favorable balance of efficacy and safety. Evidence from multiple systematic reviews and meta-analyses supports the use of topical diclofenac for reducing pain, improving function, and decreasing stiffness in KOA.

Pharmacological Description

The diclofenac dermal solution used in this trial contained diclofenac sodium as the active ingredient. Its excipients included dimethyl sulfoxide (DMSO), ethanol, glycerin, propylene glycol, and purified water—agents that enhance transdermal absorption. Diclofenac exerts its therapeutic effect by inhibiting prostaglandin synthesis via irreversible inhibition of prostaglandin synthetase (cyclooxygenase), thereby reducing inflammation and nociceptive signaling.

Administration Protocol

Participants used the topical diclofenac solution for a total of 28 consecutive days. Detailed written and verbal instructions were provided at baseline.

Application Procedure

- The solution was applied directly to clean, dry skin over the affected knee.
- A total of 40 drops were applied to the affected knee at each use:
    - 10 anteriorly
    - 10 posteriorly
    - 10 on the medial side
    - 10 on the lateral side
- The solution was spread gently over the skin for approximately 1 minute, without massage.
- Participants allowed the area to dry for several minutes.
- The application was repeated 4 times per day, at approximately regular intervals.
- Contact with eyes and mucous membranes was avoided, and participants were instructed to wash hands thoroughly after each use.

Monitoring and Safety

Participants were informed about common local adverse effects, including:

- dry skin
- mild erythema
- localized rash
- pruritus
- paresthesia

They were instructed to contact the research center if any adverse reaction occurred, so that the physiotherapist could evaluate whether treatment continuation was appropriate.

To ensure correct and continuous application for the full 28 days:

- Telephone check-ins were conducted at regular intervals.
- Participants were welcome to attend the research center for clarification or safety concerns at any time.

Integration with the Exercise Program

Throughout the 4-week medication period, the structured exercise program was performed before each diclofenac application. After completion of the 28-day diclofenac regimen, participants continued the exercise program independently for the remainder of the 6-month study period.

As with all groups, participants in the topical diclofenac arm attended an in-person follow-up visit at 2 weeks, during which:

- The exercise program was reviewed and corrected if necessary
- the application technique was reassessed
- the skin over the application area was checked for adverse signs (erythema, swelling, warmth, irritation)

6.4 Combination Group (MWM + Topical Diclofenac)

The combination of non-pharmacological and pharmacological treatments is commonly used in clinical practice for the management of knee osteoarthritis, although high-quality evidence supporting this strategy has been limited. It has been hypothesized that combining multiple first-line treatments for musculoskeletal disorders—such as Mulligan Concept mobilizations and topical NSAIDs—may enhance the beneficial effects observed with each therapy individually. However, prior to the present trial, no study had evaluated the effectiveness of combining these two important interventions. If a synergistic effect were confirmed, such findings could support the development of a new rehabilitation protocol for knee osteoarthritis.

Participants allocated to the combination arm received both the Mulligan Concept MWM protocol and the topical diclofenac 2% regimen exactly as described for the individual intervention groups, with a specific sequencing adaptation.

Treatment Sequencing

On Mulligan treatment days (10 total sessions):

- Participants completed the standardized MWM session (30 minutes, as described in the MWM section).

- Immediately after each MWM session, participants applied the topical diclofenac solution following the same procedure used in the topical diclofenac group.

On non-session days:

Participants followed the daily sequence below:

1. Home-based mobilization program
   (3×10 repetitions of the individualized MWM direction taught during supervised sessions)
2. Structured exercise program
   (same exercise protocol followed by all study groups)
3. Application of topical diclofenac
   (4 times/day, evenly spaced; same dosage and method as the diclofenac-only group)

The mobilizations and the exercise program were performed once daily, whereas the diclofenac application continued four times per day, every day during the 4-week treatment period.

Safety Monitoring and Adherence

As with the individual therapy arms:

- Participants received verbal and written instructions for both interventions.
- A mid-treatment in-person review at 2 weeks was conducted, during which the investigators checked:
    - correct execution of the mobilization program
    - correct exercise technique
    - skin integrity at the application site
    - adherence to the diclofenac regimen

Telephone check-ins were performed periodically throughout the 4-week combined intervention to reinforce adherence and identify potential adverse events.

7. Randomisation and Allocation Concealment

- Computer-generated random sequence
- Block size = 8
- Stratified by age, sex, baseline VAS, K–L grade
- Allocation via opaque, sealed, sequentially numbered envelopes
- Generated by independent statistician
- Assessors blinded
- Participants and therapists not blinded

8. Outcomes & Timepoints

Primary Outcome

VAS pain during activity (0–10)
Measured at:

- Baseline
- Post-treatment (Day 30 ±2)
- 3 months
- 6 months (primary endpoint)

MCID = 1.5 points.

Secondary Outcomes

- Range of motion (flexion/extension), digital goniometer
- Isometric strength (quadriceps & hamstrings), dynamometer
- Knee Society Score (Total)
- EQ-5D index (Greek version)
- Responder analysis: proportion achieving MCID ≥1.5 in pain

Measured at same timepoints.

9. Sample Size

G*Power: $\eta^2 = 0.25$, $\alpha = 0.05$, power 0.80
Required = 160
Recruited = 180 to account for attrition

9. Statistical Methods

- Analyses performed in Python (pandas, numpy, statsmodels)
- Linear mixed-effects models (REML)
- Fixed: group, time, group×time
- Random: participant intercept
- Covariates: age, sex, K–L grade, baseline value
- Missing data: maximum likelihood + multiple imputation (m=20)
- Effect sizes: Hedges g
- Primary contrast unadjusted
- Secondary contrasts Bonferroni-adjusted
- MCID responder analysis: RR, NNT
- Two-tailed $\alpha=0.05$

10. Ethics

Approval: Scientific Council, Protocol No. 10098/11-03-2021
Written informed consent obtained.

11. Dissemination

Results will be submitted for publication in peer-reviewed journals and presented at scientific conferences. Summary outcome data will also be uploaded to the ISRCTN registry in accordance with WHO requirements once all analyses are finalized and the study is formally completed.