Research Plan: Post-operative use of Game Ready cryocompression system versus conventional ice and compression for total knee arthroplasty (TKA): a prospective randomised controlled trial.

Investigators
Dr Mira Marinova MD
Dr Abayasankar Sundaram MBBS
Ms Katie Holtham (Hons) Sport and Exercise Sciences BSc (Hons) Physiotherapy
Dr Jay Ebert BExRehab (Hons)
Mr Ross Radic MBBS FRACS

1. BACKGROUND

Total knee arthroplasty (TKA) is a very commonly performed procedure for osteoarthritis of the knee. Over the course of a life time 1 in 11 Australians will develop osteoarthritis. According to data from the Australian Institute of Health and Welfare there has been a 38% increase in TKA from 2006-2016 with 54,277 being undertaken and reported to the registry in 2014. Arthritis is due to an increase in load through the weight bearing surfaces of the knee which over time causes the joint to wear away. Eventually the joint can wear out to such an extent that the thigh bone (femur) starts to grind on the shin bone (tibia). This loss of joint surface leads to the patient experiencing stiffness, pain and loss of function.

TKA is primarily performed to alleviate pain, improve function and some patients may find an improved range of movement. This is a major orthopaedic procedure involving the removal of the joint surface of the femur and tibia followed by their replacement with a metal prosthesis and a plastic insert. This operation causes a large amount of soft tissue damage and hence blood loss, pain and inflammation are to be expected during the recovery period. The severity of these outcomes and their effect on the patient during recovery often dictate the ultimate outcome of a TKA. Cryocompression therapy is a non-invasive and non-pharmacological modality used in managing acute inflammation. Cryotherapy promotes vasoconstriction, reduces blood flow, reduces inflammation, decreases muscle spasms, decreases metabolic demand and safely relieves pain without narcotics. Cryocompression is not routinely implemented postoperatively for TKA, but often cryotherapy or compression are used as separate modalities to help decrease a patient's post-operative pain and inflammation.

Previous orthopaedic research on the use of cryotherapy has shown positive outcomes in decreasing pain, inflammation, blood loss and improving range of movement. The Game Ready device is a cryotherapy system which provides concurrent compression over the desired area. There is limited research to evaluate the Game Ready system's effects. However, the two available studies that have employed the Game Ready device post-operatively after TKA have demonstrated that it is a safe, user friendly device with positive trends towards improved outcomes, but there is a need for further research to evaluate the use of the Game Ready system in post-operative TKA. This study seeks to investigate the benefit in using the Game Ready system post-operatively in TKA, aiming to reduce early post-operative pain, improve short and longer term patient outcomes, and ultimately returning to function faster with a minimally invasive low risk modality.

2. STATEMENT OF THE PUROPSE AND AIMS:

This is a prospective randomised control trial investigating the benefit of Game Ready cryocompression post TKA compared to conventional ice and compression.
The general aims of this project are to:

1. Compare post-operative patient-reported pain outcomes and use of PRN analgesia in patients following either use of Game Ready post TKA or conventional ice and compression.

2. Compare knee girth (i.e. knee effusion/swelling) and range of movement in patients following either use of Game Ready post TKA or conventional ice and compression.
3. Compare lower limb strength and functional outcomes in patients following either use of Game Ready post TKA or conventional ice and compression
4. Compare post-operative blood loss in patients following either use of Game Ready post TKA or conventional ice and compression.
5. Compare time to discharge from hospital in patients following either use of Game Ready post TKA or conventional ice and compression.
6. Compare patient satisfaction levels in patients following either use of Game Ready post TKA or conventional ice and compression.

3. METHODOLOGY

3.1 Study population, informed consent and recruitment

This is a prospective RCT investigating two different post-operative interventions and, therefore, all patients who are undergoing TKA surgery with Perth Orthopaedic and Sports Medicine Center's surgeons will be invited to participate in this trial. At this time, patients will provide written informed consent following discussion with the surgeon and reading the Patient Information Sheet (Appendix 1) and will be randomised to one of the two rehabilitation arms of the study (Game Ready or conventional ice with compression).

The Game Ready system, manufactured by CoolSystems Inc. (Concord, California USA) now trading under Avanos Medical Inc. (Alpharetta, Georgia USA), received approval from the Australian Government Department of Health Therapeutic Goods Administration for clinical use from 13/08/2008.

Inclusion Criteria

- The individual is over 18 years of age
- The individual clinically qualifies for TKA surgery based on clinical examination and X-Ray
- The individual has not previously had TKA surgery (ie primary TKR only)
- The individual is not currently being treated for a psychiatric disorder, senile dementia, Alzheimer's disease, presence of alcohol/substance abuse.

Exclusion Criteria

- The individual is unable or unwilling to sign the Patient Informed Consent form, specific to this study, and approved by the Institutional Ethics Review Board.
- The individual is unable or unwilling to follow the designated Game Ready protocol (or conventional ice and compression).
- The individual is classified as morbidly obese (>40 BMI).

Withdrawal Criteria

As outlined on the Patient Consent Form, patients will be free to withdraw from the study without prejudice or altered post-operative care.

Ethical approval will be obtained from the Hollywood Private Hospital (HPH) Research Ethics Committee and the written, informed consent from each patient will be collected prior to surgery.

Sample Size Calculation

Sample Size Calculation

For this RCT, a priori power calculation has been determined based on the recommendations of Cohen, which indicates that for an anticipated large effect size (d = 0.80) in the primary outcome

variable (VAS – severity of pain 0-10 upon hospital discharge), a total of 52 patients (26 in each group) will be required to reveal differences at the 5% significance level, with 80% power. Therefore, 66 patients (33 per group) will allow for a 25% dropout over the trial period.

3.2 Procedures

3.2.1 Consent, Randomization and Surgical Procedures

Patients will be initially seen pre-operatively in the private rooms of their chosen orthopaedic surgeon at the Perth Orthopaedic and Sports Medicine Institute. Patients who meet the inclusion criteria for the study and are having TKA surgery will be offered participation in the trial. The Patient Information Sheet (Appendix 1) and a verbal summary of the study and the expected participation requirements will be presented to the patients. Those patients willing to participate will then complete the Patient Consent Form (Appendix 1) and will be booked accordingly for TKA. Pre-operative pain and knee girth measures will be taken for post-operative comparison. Patients will be randomly assigned into either Game Ready or ice and compression group following consent. Concealed allocation will be employed, whereby randomisation will be undertaken by a Research Coordinator using a 'random number generator' (undertaken prior to study recruitment) that will create a random list of numbers (1 = Game Ready, or 2 = Conventional Management).

TKA will be performed as per surgeon preference according to their specific regular protocol with a post-operative x-ray and routine bloods to be taken on day 1. All patients will have compression bandages over their operated knee in the form of a crepe bandage which is standard post-operative protocol for TKA and applied in theatre after the wounds have been sealed with dressings. Patients will go to recovery post-operatively for monitoring before they return to the ward. During their time in recovery they will then begin their randomised pathway, and will have either the Game Ready applied by the hospital physiotherapist to their knee or conventional ice over their compression bandage for a 20 minute period. Outside of the cryotherapy interventions, immediate post-operative in-patient (and out-patient) rehabilitation will be standardised across all patients, as per usual treatment.

3.2.2 Post-operative Procedure

The treatment regime will be as follows: Game Ready system applied to knee from day 0 in recovery and used daily for 2 weeks (spanning the in-patient and out-patient setting). Game ready setting will be for 20 minutes on low pressure (0-5 days) then medium/high from days 5-14 to be applied 6 times per day with at least a period of one hour off in between each usage. For the conventional group of ice with compression the same regime of cold/compression frequency and duration will be followed, employing ice-packs for 20 minutes on top of the post-operative compression dressings. From day 1 once the dressings are debulked, tubigrip (an elastic bandage) will be employed over the operated knee as compression and following the same cryotherapy time with the ice of 20 minutes, 6 times per day with at least an hour off time in between for a period of 2 weeks.

Patients will continue their allocated treatment for a total of 14 days, which will coincide with their first post-operative review.

All patients will engage in a standardised post-operative inpatient and outpatient rehabilitation protocols coordinated by physiotherapists, as per routine treatment.

3.2.3 Clinical Assessment

Patients enrolled in the study will have specific variables measured in order to assess whether there is any difference in the two treatment arms (Table 1). Patients will be given a booklet pertaining to

outcome measures which will contain questionnaires and charts where they can record pain levels throughout the monitoring period.

A range of patient-reported outcome measures (PROMs) will be employed to evaluate patient-perceived pain and function as follows.

Visual Analogue Scale (VAS):

- Will be used to assess patients' pain levels, on a whole number rating scale from 0 (no pain) – 10 (worst pain). Patients will be asked to circle the number that best corresponds to their knee pain level at that time-point.
- The VAS for pain will be assessed initially when the patient has returned to the ward (day 0), and then at 4pm on day 1, 2, 1 week, 2 weeks, 6 weeks, 3 months, 6 months, 12 months and 24 months after surgery.
- We have chosen 4pm as the uniform time of assessment as it is prior to dinner time, when most patients will often be taking their analgesics (in the early post-operative stages).
- While the in-patient VAS recordings (day 0, 1 and 2) will be assisted by the hospital physiotherapy and nursing staff. During the later stage VAS recordings (6, 12 and 24 months) will be facilitated by the research staff at follow-up time-points.
- Patients will also be provided with a set of charts in their study booklet with multiple VAS charts where they can provide their pain scores at the other non-facilitated designated study time-points (2 weeks, 6 weeks and 3 months).
- We will also be recording the amount of PRN analgesia used as in-patients, while analgesia usage following hospital discharge will also be documented.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

- The KOOS is a knee specific questionnaire which includes 42 questions in five individual subscales: Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation (Sport/Rec) and Knee Related Quality of Life (QOL). Each of these five subscales is scored from 0 (worst) to 100 (best).
- Will also be administered pre-surgery and at 3, 6, 12 and 24 months post-surgery.

Patient Satisfaction Questionnaire (PSQ)

- Will be employed to evaluate the patient's level of satisfaction with their surgery overall, as well as their satisfaction with surgery to relieve their pain, improve their ability to perform normal daily and work activities and improve their ability to return to recreational activities. The PSQ will also be used to assess their satisfaction with cryotherapy regime for ease of use and application, and perceived satisfaction on swelling control, sleep and mobility.
- A categorical tool was employed: 1 = very satisfied; 2 = somewhat satisfied; 3 = somewhat dissatisfied; 4 = very dissatisfied.

A number of objective measures will also be collected.

Oedema/swelling

- Will be evaluated pre-surgery, and then at day 0, 1 and 2, as well as 2 and 6 weeks post-surgery.
- Knee girth measurements will therefore be taken specifically at the knee joint line and 10cm above the superior aspect of the patella, with the knee flexed to 20 degrees, via a circumferential measurement with a tape measure.
- This process was undertaken twice for each site and the minimum value was recorded.

Knee Range of Motion

- Active knee flexion and extension range of motion (ROM) will be measured using a hand-held goniometer, creating an angle made by three anatomical landmarks; the greater trochanter of the femur at the hip, the lateral femoral condyle at the knee and the lateral malleolus at the ankle.
- Knee ROM will be evaluated pre-operatively and at day 0, 1 and 2, 2 and 6 weeks, and at 3, 6, 12 and 24 months after surgery.

Timed Up and Go (TUG) test

- TUG assesses functional ability by timing how fast the patient can get up off a chair walk 3m turn around and sit back down, using the walking aid they'd usually ambulate with.
- Will be undertaken in all patients to assess their functional capacity at 6 weeks, as well as 3, 6, 12 and 24 months post-surgery.

Peak Strength

- Peak knee extensor and flexor strength will be assessed in patients at 6, 12 and 24 months post-surgery, using an isokinetic dynamometer.
- Peak concentric knee extension and flexion strength will be measured through a range of 0-90˚ of knee flexion, at a single isokinetic angular velocity of 90°/s.
- Patients will be informed that each trial will consist of four repetitions on the same leg: three low intensity repetitions of knee extension and flexion, immediately followed by one maximal test effort which is recorded.
- Standardized verbal encouragement will be provided across all trials. Each test will be initiated on the unaffected leg, and then alternated between the unaffected and operated limb until three valid trials on each limb are completed. Patients will be given adequate rest in between trials to minimize fatigue.

Blood loss and hospital length of stay

- Will be measured by recording the post-operative haemoglobin levels of the two groups. Length of stay in hospital will also be recorded for all patients in the study.

The knee girth, ROM, strength and functional measurements will be recorded by the physiotherapist and added to a password protected word document that only the research team will have access to. Pre- and post-operative clinical assessments will be undertaken by a blinded therapist and at a variety of locations given the equipment required and patient ease, which will include the hospital (i.e. Hollywood Private Hospital), the Perth Orthopaedic and Sports Medicine Centre, Beatty Park Physiotherapy and the HFRC Rehabilitation Clinic.

Table 1. Timeline of patient evaluation throughout the study.

Measure	Pre-surgery Assessment	Post-operative Clinical Assessments						
		In-patient			Out-patient			
		Day 0	Day 1	Day 2	Week 1	Week 2	Week 6	3, 6, 12 and 24 months
VAS (Pain)	x	x	x	x	x	x	x	x
Analgesia Usage		x	x	x	x	x	x	

Swelling	x	x	x	x	x	x	x	
KOOS	x							x
Satisfaction	x					x	x	x
Knee ROM	x	x	x	x		x	x	x
TUG	x						x	x
Knee Strength								x

3.3 Adverse Events

For this study, an adverse event has been defined as a clinical sign, symptom or condition that is causally related to the surgery and/or subsequent rehabilitation intervention. Irrespective of the severity of adverse event, all events will be documented accordingly, along with relevant treatment(s), within the individual's patient file and within the study database. Information on adverse events will be collected at each post-operative visit. Specific information will be solicited from participants at each study visit and via physical examination to capture adverse events associated with study treatment.

Adverse events will be graded as follows:

- Mild (Grade 1): Transient or mild discomfort; no limitation in activity; no intervention or therapy required.
- Moderate (Grade 2): Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe (Grade 3): Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalisation possible.
- Extreme (Grade 4): Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalisation or hospice care probable; potentially life-threatening.

All adverse events deemed to be severe or extreme will be reported accordingly to the relevant ethics board, and treated accordingly.

3.4 Interim analysis

While we do not anticipate an adverse event as a direct result of the accelerated rehabilitation intervention proposed in this study, periodic interim analysis will be undertaken on the study data to ensure patients are not adversely affected by the accelerated treatment arm. This will be made with particular reference to adverse events and episodes of re-injury/re-tear. Interim analysis will be undertaken by investigation team every three months and/or specifically after the report of an adverse event deemed attributable to the rehabilitation intervention.

3.5 Data handling, statistical analysis and reporting of results

Paper records will be kept under lock and key in a metal filling cabinet at the Perth Orthopaedic & Sports Medicine Centre. Computer records will be stored in the assessor database and will be password protected. No patient names will be saved in the computerised records as all patients will be assigned a number which their results will be recorded under. The patients consulting surgeon and the study investigators will only have access to hand written and electronic records. Records will be kept for 15 years after which, paper records will be shredded and computer records will be

permanently deleted including back-up copies. The result of the research will be made available through medical journals or meetings, but all patient information will be de-identified and no private information will be identified outside the investigator office.

Statistical analysis will be performed using SPSS software (SPSS, Version 11.5, SPSS Inc., USA). A series of repeated measures ANCOVAs will be used to investigate clinical outcomes between the two patient groups. A Tukeys post-hoc statistic will be used to determine time-points at which the two groups differ, given any significant main effects.

Relevant results will be reported at the state meeting of the Western Australian Orthopaedic Association and results published in peer reviewed journals.

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