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INTRAOPERATIVE INTRA-ARTICULAR INJECTION OF CORTICOSTEROIDS *VS.* SYSTEMIC INTRA-VENOUS ADMINISTRATION *VS.* NO ADMINISTRATION IN PATIENTS UNDERGOING TOTAL KNEE ARTHROPLASTY: STUDY PROTOCOL OF A TRIPLE-BLIND RANDOMIZED CONTROLLED TRIAL

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ABSTRACT – ***Objective:*** Total knee arthroplasty (TKA) is one of the most commonly performed orthopedic procedures, although postoperative pain control through the optimization of analgesia protocols remains a key aspect. Corticosteroids (CS) intraoperative administration has been suggested to decrease postoperative pain, reduce the incidence of nausea and vomiting, improve postoperative range of motion, and decrease the systemic inflammatory response, shortening overall hospital stay, and improving patient recovery without increasing the risk of complications. However, the literature still lacks trials directly comparing intra-articular (IA) and intra-venous (IV) steroid administration. The aim of this study is to compare the two delivery approaches to determine if they may yield different results.

Methods and Analysis: A triple-blind randomized controlled trial (RCT) was designed to investigate the effectiveness of IA (treatment group 1) or IV (treatment group 2) intraoperative CS administration in the immediate postoperative period and up to 10 years of follow-up for patients undergoing TKA, and to compare this to the standard perioperative analgesia protocol without CS administration (control group). The trial uses a 1:1:1 allocation ratio. The aim of this trial is to evaluate the safety and clinical benefit of CS administration, identifying the most suitable delivery approach. The hypothesis is that CS administration could provide superior pain relief in TKA patients, while showing the pros and cons of the administration routes. Secondary outcomes include length of hospital stay, postoperative nausea, opioid consumption, inflammatory response, glycemia, knee range of motion, time to mobilization, and patient-reported outcome measures (PROMs) over time.

Ethics and Dissemination: The study protocol was approved by the Cantonal Ethical Committee of Ticino, Bellinzona, Switzerland. All participants signed a written informed consent form before taking part in the study. The results of this trial will be disseminated through congress presentations and peer-reviewed publications.

Conclusions: The results of this trial will offer valuable insights into the effect of CS in TKA, evaluating both risks and benefits. The study findings will elucidate the optimal administration route and assess whether the safety and potential benefits of CS administration extend beyond short-term pain improvement, offering longer-lasting advantages for patients undergoing TKA.

Protocol Version: Version 2.0 (07 September 2022).

Trial Registration Number: NCT04432012, ClinicalTrials.gov.

KEYWORDS: Arthroplasty, Corticosteroids, Knee, Injection, Protocol, RCT.

INTRODUCTION

Total knee arthroplasty (TKA), the end-stage treatment of knee osteoarthritis, is one of the most commonly performed orthopedic procedures, with an increasing number of surgeries performed every year[1]. As a consequence, TKA has a significant impact on the healthcare system, both in terms of the number of treated patients and the economic burden[2]. In recent years, a significant effort has been made to alleviate patient discomfort and expedite recovery after the procedure, ultimately reducing the length of hospital stay and the cost of TKA[3].

Postoperative pain control, with the optimization of analgesia protocols, is a key aspect in quickening recovery and mobilization, thereby decreasing hospitalization length[4,5]. Traditionally, postoperative pain control heavily relied on opioids, but their adverse effects and the negative impact they have on patient recovery[6,7] encouraged the development of more effective solutions[8]. In this regard, corticosteroid (CS) supplementation is considered effective in decreasing pain and consequently the use of opioids in the postoperative period[9,10]. Moreover, positive effects have been documented in terms of lower incidence of nausea and vomiting, less postoperative range of motion limitation, and decreased systemic inflammatory response[9]. All these benefits led to a shortened hospital stay without an increased risk of complications such as local infections and hyperglycemia-related problems[9].

Despite the overall positive effect, it is still not clear which perioperative administration protocol provides the greatest benefit, with CS such as dexamethasone administered both systemically or locally[11-13]. In fact, the literature still lacks evidence directly comparing intra-articular (IA) and intra-venous (IV) CS administration, which may lead to different results. In particular, IV administration has a stronger systemic effect and seems to offer advantages in terms of postoperative pain and inflammatory response reduction[12,14]. On the other hand, IA administration, likely due to increased local action, may provide better results in terms of range of motion recovery[11]. Furthermore, the long-term results, as well as the influence of the administration protocol on the long-term follow-up, are poorly explored. This is a key issue, since unsatisfactory results are reported in up to 20% of the patients who underwent TKA[15-17], with pain persistence and limited functional improvement being the main reasons for complaints[18,19]. The intensity of acute postoperative pain has been related to the risk of developing chronic postoperative pain[20,21], and thus the advantages of intraoperative CS supplementation could be not only short-term, but even longer lasting.

This is a 3-arm study designed to compare IA and IV CS supplementation protocols and evaluate their potential advantages over routine analgesia protocols. The primary outcome is the acute postoperative pain. Furthermore, the influence of the administration route on knee range of motion, time to mobilization, patients' reported outcome measures (PROMs), patient satisfaction, postoperative nausea, opioid consumption, inflammatory response, glycemia, and length of hospital stay are evaluated. The long-term follow-up results and the complications of CS supplementation are documented as well. This randomized controlled trial (RCT) will thus contribute to defining how the perioperative analgesia protocol should be implemented, not only to improve acute postoperative recovery and shorten hospital stay, but also to optimize overall results after TKA.

Objective and Trial Design

A triple-blind RCT was designed to investigate the effectiveness of IA (treatment group 1) or IV (treatment group 2) intraoperative CS administration in the immediate postoperative period and

up to 10 years of follow-up for patients undergoing TKA, compared to the standard perioperative analgesia protocol without CS administration (control group). The trial uses a 1:1:1 allocation ratio. The aim of this trial is to evaluate the safety and clinical benefit of CS administration. The hypothesis is that CS administration could provide superior pain relief in TKA patients, while also providing information on the optimal administration route. Secondary outcomes include length of hospital stay, postoperative nausea, opioid consumption, inflammatory response, glycemia, knee range of motion, time to mobilization, patient satisfaction, and patient-reported outcome measures (PROMs) over time.

METHODS AND ANALYSIS

Study Setting

This is a triple-blind RCT based on two hospital centers, with all activities related to the study performed in two sites of the Ente Ospedaliero Cantonale, Lugano and Bellinzona, Switzerland. These are the two main hospital centers of the Ticino Canton and both have the same standard of clinical practice. This study protocol was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines[22] with trial registration number: NCT04432012.

Eligibility Criteria

Patients are enrolled based on the following criteria.

Inclusion criteria:

- Patients undergoing primary unilateral TKA.
- Age between 50 and 85 years old.
- Body mass index between 18.5 and 35 kg/m^2.
- Patients able to provide informed consent and follow all the study procedures as indicated by the protocol.

Informed consent documented by signature.

Exclusion criteria:

- Contraindications to CS.
- Revision TKA.
- Active CS therapy.
- Women who are pregnant or breastfeeding.
- Presence of other clinically significant concomitant disease states (ASA IV).
- Uncontrolled diabetes mellitus.
- Known or suspected non-compliance, drug or alcohol abuse.
- Inability to follow the procedures of the study, e.g., due to language problems, psychological disorders, dementia, etc., of the participant.
- Participation in another study with an investigational drug within the 30 days preceding and during the present study.
- Previous enrolment into the current study.
- Enrolment of the investigator, their family members, employees and other dependent persons.

Intervention

All patients undergo TKA implantation by experienced knee-specialized orthopedic surgeons. To minimize confounders, spinal anesthesia with sedation (propofol) is administered uniformly to all patients. Following sterile preparation and draping, surgical access is meticulously achieved to expose the knee joint. After bone cuts and thorough preparation of the femoral and tibial components for prosthetic implantation, the surgeon administers an intra-articular injection in the knee joint after prosthesis implantation and before wound closure. The injection syringe is prepared by the anesthesiologist based on the patient's randomization arm. For patients randomized in the IA CS administration group, a 50 mL syringe with 9 mg of dexamethasone is prepared using dexa-

methasone sodium phosphate (4 mg/mL, corresponding to 3 mg of dexamethasone). Thus, 3 mL of Mephameson solution is drawn and mixed with 47 mL of saline solution (NaCl 0.9%) to obtain 50 mL of solution for injection. Conversely, for those randomized in the IV CS or no CS supplementation groups, the anesthesiologist prepares a 50 mL syringe containing only saline solution (NaCl 0.9%). The same process is performed for IV administration, with the anesthesiologist injecting the 9 mg of Dexamethasone in the IV CS group and only saline solution in the IA CS and no CS supplementation groups. The blinding of the surgeon is guaranteed by the fact that the two solutions in the syringe are visually indistinguishable. After the injection, the prosthetic components are implanted, and their alignment and stability are evaluated by the surgeon. Wound closure is performed through layer-by-layer suturing. To minimize confounders, a standardized postoperative analgesia protocol is uniformly followed for all patients in all three study groups, consisting of Paracetamol 1 g four times per day, Ibuprofen 400 mg three times per day, and, if needed, Morphine 5 mg subcutaneously, maximum 6 times per day. Postoperative CS use is avoided. Patients are normally discharged three to five days after TKA implantation according to their clinical status. Weight-bearing on the operated limb with the support of two crutches and physiotherapy is started on the first postoperative day. Thromboembolic prophylaxis and pain control with analgesics as necessary are prescribed for the first 6 postoperative weeks.

Outcomes

The primary outcome of the trial is the mean postoperative daily pain at rest in the first three postoperative days, quantified with the 0-10 numeric rating scale (NRS). The 0-10 NRS is a validated instrument for the self-assessment of symptoms, consisting of an 11-point numeric scale, with 0 indicating no pain and 10 reflecting the worst possible pain[23].

The secondary outcomes are:

- Postoperative knee pain reported on 0-10 NRS at 3, 6, 12, 24, 60 and 120 months.
- Postoperative knee function on 0-10 NRS in the first three postoperative days and at 3, 6, 12, 24, 60 and 120 months[24].
- Western Ontario and McMaster Universities Arthritis Index (WOMAC) at 2 and 6 weeks, and at 3, 6, 12, 24, 60 and 120 months: the WOMAC questionnaire is composed of 3 sub-scores that evaluate pain (5 questions, 0-20 points), stiffness (2 questions, 0-8 points), and function (17 questions, 0-68 points) and is a validated PROM to evaluate knee osteoarthritis[25].
- Knee Society score (KSS) at 2 and 6 weeks, and at 3, 6, 12, 24, 60, and 120 months: the original KSS has a “Knee Score” section (7 items) and a “Functional Score” section (3 items). Both sections are scored from 0 to 100, with lower scores being indicative of worse knee conditions and higher scores being indicative of better knee conditions[26].
- PainDETECT at 6, 12, 24, 60, and 120 months: PainDETECT consists of seven questions that address the quality of pain symptoms; it is completed by the patient, and no physical examination is required. A score ≤12 indicates that pain is unlikely to have a neuropathic component (<15%), while a score of ≥19 suggests that pain is likely to have a neuropathic component (>90%). An intermediate score (≥13, ≤18) indicates a possible neuropathic component[27].
- Patient satisfaction on a 0-10 NRS at 2 and 6 weeks, and at 3, 6, 12, 24, 60, and 120 months.
- Postoperative nausea during the first postoperative days: both incidence and intensity (on a 0-10 NRS) are evaluated. The 0-10 NRS is a valid and reliable instrument used for the self-assessment of symptoms[27]: it consists of a single 11-point numeric scale, with 0 indicating no nausea and 10 reflecting the worst possible nausea.
- Postoperative opioids and analgesic drug consumption: to evaluate analgesic drug consumption, the Medication Quantification Scale (MQS) score is used. It is calculated for each medication by taking a consensus-based detriment weight for a given pharmacologic class and multiplying it by a score for dosage. The calculated values for each medication are then summed for a total MQS score. The score can provide a useful point measure of medication usage for any pain medication regimen[28,29].
- Postoperative inflammatory response in terms of hematic C-Reactive Protein (CRP) and erythrocyte sedimentation rate (ESR) measured preoperatively and daily during the first three postoperative days (the medical charts are evaluated).
- Time from surgery to first mobilization. Early mobilization is one of the most important determinants of the length of hospital stay, but due to postoperative pain and symptoms, it is not always

possible to mobilize the patient on the first postoperative day[30]. The use of CS, reducing postoperative symptoms, may have a positive effect on this aspect.
- Time needed for climbing stairs the first time. The ability to climb stairs is considered the most important goal in the postoperative period to consider the patient as dischargeable.
- Length of hospital stay.

Recruitment

Patients are enrolled in the outpatient clinics of the Ente Ospedaliero Cantonale by trained medical staff from the orthopedic surgery team in the Department of Orthopedics and Traumatology. The enrolment is performed after screening of the eligibility criteria when a knee specialist schedules a patient for a TKA. The study procedures are accurately explained to the patient, including the planned 10-year duration of the study follow-up, to minimize the attrition rate. The patient then freely gives consent by signing the informed consent form (ICF).

Participant Timeline

After the ICF signature during the screening visit, the patient and the surgeon, in coordination with the research assistants, fill in the relevant questionnaires. The follow-up assessments are performed on the first three postoperative days, at discharge, and then at 2 weeks, 6 weeks, 3 months, 6 months, 1 year, 2 years, 5 years, and 10 years postoperatively. Each follow-up includes a physical examination, clinical questionnaires, and outcomes assessment as previously described. The detailed participant timeline is outlined in Table 1.

Blinding

This study is a triple-blind RCT, with participants, surgeons, and outcome-assessing physicians all blinded to treatment allocation. Only the anesthesiologists involved in the TKA surgery and preparing the syringes (with or without CS) are aware of the group allocation, and they are not involved in the follow-ups.

The patients' blinding is further ensured by the fact that the study arm does not affect the planned surgery. The radiological evaluations are conducted by experienced radiologists, who are also blinded to treatment allocation. Unblinding of the involved staff will be possible in case of adverse events requiring it. If unnecessary, the patients, the surgeons, the assessors, and all the study team members will remain blinded. The patients will be informed of their randomization group at the end of the trial or in case of suspension or premature study termination.

Allocation

A total of 159 patients are randomly allocated in a 1:1:1 ratio (53 patients per group) to receive either IA or IV CS administration concomitant with their TKA surgery or no administration. The randomization is performed according to a computer-generated sequence. The members of the orthopedic research team, dedicated to studying organization but not involved in the study procedures, conduct the randomization process for the enrolled patients. The randomization list is password-protected and accessible only to staff members with no direct involvement in the study.

Adverse Events

Adverse events (AEs) are monitored, both intraoperatively and at each follow-up, where patients are asked to report the occurrence of any AEs. AEs are documented in the patient case report form (CRF). Serious adverse events (SAEs) are defined as those resulting in death or those that are life-threatening, requiring hospitalization, or intervention to prevent permanent damage, according to the EC requirements.

Table 1. Participant timeline.

Study periods	Screening	Surgery	Discharge	Follow-ups							
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Time	≥ 2 w before V1	0	5 d ± 2 d	2 w ± 2 d	6 w ± 1 w	3 m ± 1 w	6 m ± 2 w	1 y ± 1 m	2 y ± 1 m	5 y ± 1 m	10 y ± 1 m
Informed consent form	x										
Demographics	x										
Medical history	x		x	x	x	x	x	x	x	x	x
In-/Exclusion criteria	x										
Physical examination	x		x	x	x	x	x	x	x	x	x
Knee swelling	x		x	x	x	x	x	x	x	x	x
Vital signs	x	x									
Laboratory tests	x										
Pregnancy test	x										
X-ray examination	x		x		x	x		x	x	x	x
Knee ROM	x		x	x	x	x	x	x	x	x	x
NRS 0-10 pain	x	x	x	x	x	x	x	x	x		
NRS 0-10 function	x		x	x	x	x	x	x	x		
WOMAC index	x			x	x	x	x	x	x	x	x
KSS	x			x	x	x	x	x	x	x	x
PainDETECT	x						x	x	x	x	x
Randomization		x									
Surgery		x									
CS supplementation		x*									
NRS 0-10 nausea		x									
CRP, ESR	x	x									
Glicemia		x									
MQS score	x	x	x	x	x	x	x	x			
Time to first mobilization			x								
Tim to first stairs climb			x								
Length of stay			x								
Patient satisfaction				x	x	x	x	x	x	x	x
Treatment-related AE		x	x	x	x	x	x	x			
SAEs		x	x	x	x						

AE: Adverse Event; CRP: C-reactive protein; CS: corticosteroids; d: day; ESR: erythrocyte sedimentation rate; KSS: Knee Society Score; MQS: Medication Quantification Score; NRS: Numeric Rating Scale; m: month; ROM: range of motion; SAE: Serious Adverse Event; w: week; y: year; *only if the patient is randomized in the CS supplementation arms.

Data Collection Methods and Management

Research-trained orthopedic surgery residents (blinded) collect the study data on paper-based CRFs. Subsequently, trained data analysts process the collected data into electronic forms. X-rays are stored at the Ente Ospedaliero Cantonale. Surgeons electronically collect the respective operative data shortly after TKA surgery. The study data are stored in a password-protected spreadsheet on a server hosted at the Ente Ospedaliero Cantonale. Only dedicated research personnel with study-specific authorization have access to the database.

Statistical Methods

The study hypothesis is that, thanks to an increased local concentration and effect, IA CS could achieve better results when compared to IV administration without increasing, or possibly decreasing, the risk of complications. A statistician performed a power analysis assuming 80% of power and 5% of probability of type 1 error (alpha=0.05). To detect with a one-way ANOVA a medium effect size (Cohen's f=0.25) with an α-error of 0.05 and a power of 0.8, a total of 159 patients are needed (53 patients per group). Quantitative variables will be expressed as means and standard deviations. The significance of the detected difference between groups for continuous variables will be tested using the *t*-test if normally distributed, otherwise with the Mann-Whitney U test. Dichotomous variables will be reported as absolute numbers and percentages, with the significance of the detected difference tested using the Chi-square test. In case of deviations from the original statistical plan, the protocol will be amended, and its validity will be evaluated by the EC. All the changes will be reported in the final publication report.

Data Monitoring

Specific authorized personnel from the Clinical Trial Unit of the Ente Ospedaliero Cantonale (CTU-EOC), an independent entity separate from the clinic and the medical personnel performing the study procedures, will conduct the monitoring activities. All the required source documents and trial essential documents will be available in case of inspections by competent authorities, and any critical issues will be addressed promptly. All parties involved will maintain the strict confidentiality of participants' data.

ETHICS AND DISSEMINATION

Research Ethics Approval

Ethical approval was obtained on 27 April 2020 from the Cantonal Ethical Committee of Ticino, settled at the Health Office, Via Orico 5, 6501 Bellinzona, Switzerland.

Confidentiality and Access to Data

Data are recorded using CRFs and centrally processed at the Department of Orthopedics and Traumatology, Ospedale Regionale di Lugano, Lugano, Switzerland. Hard copies of CRFs are stored in a locked area with restricted access. Electronic data are stored on password-protected servers and kept strictly confidential. Only authorized members of the research team have access to patients' information.

Scientific Relevance and Broader Impact

This study holds significant scientific and clinical relevance for the field of knee surgery and postoperative pain management. By investigating the effectiveness of IA, IV, or no CS administration in TKA surgery through a triple-blind RCT, a key gap in the current literature can be addressed.

Postoperative pain management represents a crucial aspect of TKA surgery, with implications for patient recovery, hospital stay duration, and healthcare costs. This study aims to provide solid evidence on the safety and effectiveness of this intervention, potentially offering a therapeutic strategy to improve postoperative pain management while minimizing opioid use and associated adverse effects. Moreover, by assessing a comprehensive set of outcomes, including PROMs, functional evaluations, and inflammatory markers, this trial aims to provide a global understanding of the impact of IA or IV CS administration on different aspects of patient recovery, both in the short term and at long-term follow-up. The findings of this study have the potential to inform clinical practice guidelines, optimize surgical protocols, and ultimately improve patient outcomes after undergoing TKA surgery.

CONCLUSIONS

The results of this trial will offer valuable insights into the effect of CS in TKA, evaluating both risks and benefits. The study findings will elucidate the optimal administration route and assess whether the safety and potential benefits of CS administration extend beyond short-term pain improvement, offering longer-lasting advantages for patients undergoing TKA.

Ethics Approval:

The study has been approved by the Cantonal Ethical Committee of Ticino (Study Identifier: ORL-ORT-13, BASEC-ID: 2020-00445, date of approval: April 27, 2020).

Informed Consent:

All patients provide informed consent to participate in this study as per the study protocol.

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Authors' Contributions:

All authors contributed to the definition of the study protocol, and will participate to the study execution, from treatment and follow-up to analysis and dissemination.

Conflict of Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No generative AI and AI-assisted technologies were used in the writing process of this manuscript.

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