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Master thesis | Original study

Safety and efficacy of patient controlled analgesia using the Sublingual Sufentanil Tablet System (SSTS) in a fast track rehabilitation program after Total Knee arthroplasty

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Abstract

Background: **Postoperative pain can delay recovery after total knee arthroplasty (TKA). Currently, many postoperative TKA protocols rely primarily on multimodal analgesic tools with patient-controlled intravenous analgesia (PCIA) systems or nurse-controlled oral opioid tablets. However, both systems have disadvantages as to patient autonomy and mobility and may even create analgesic gaps. The sublingual Sufentanil tablet system (SSTS, Zalviso®, Grünenthal, Germany) could be beneficial in a fast track rehabilitation program, after total knee arthroplasty (TKA). SSTS is non-invasive and imposes no restrictions on patient mobility and improves patient autonomy.**
Objective: **The aim of this study was to investigate if SSTS provides effective and safe postoperative analgesia that allows early mobilization after TKA.**
Design: **Prospective cohort study**
Methods: **Sixty eight patients underwent TKA under spinal and locoregional anaesthesia. Postoperative analgesia consisted of IV paracetamol, oral NSAID's, supplemented with SSTS. The primary outcome was the absence of therapeutic failure, defined as the occurrence of consecutive NRS scores ≥4 despite optimal use of the SSTS. Discontinuation of study medication due to severe adverse events was also considered as therapeutic failure. Patient, Nurse and Physiotherapist- Ease- Of Care questionnaires were completed at the end of the study.**
RESULTS: Therapeutic success was achieved in 68% of the cases with a 95% Wilson Confidence Interval (56.3%-77.9%). No serious adverse events were reported. The Length of Hospital Stay was 2 days for all patients. The incidence of PONV was high: nausea in 19%, 26% and 10% on day 0,1 and 2 respectively; vomiting in 7%, 10% and 1% on day 0,1 and 2 respectively.
Conclusions: **The success rate of SSTS is similar to the reported success rates for parenteral PCA devices and oral opioids, providing adequate analgesia at rest and during mobilization after TKA. The system is safe and user friendly both for patients and health workers. The incidence of nausea and vomiting is high and needs to be anticipated. and oral opioids. A high incidence of nausea and vomiting is reported with the use of Zalviso.**
Trial registration: **The trial was registered at ClinicalTrials.gov (NCT04432428).**

Keywords: **knee arthroplasty, sublingual sufentanil tablet system (SSTS), postoperative pain.**

The study protocol was approved on 29 January 2020 by the local ethics board of University of Ghent (Corneel Heymanslaan 10, Ghent), chairman Prof. Dr. Deron (EC 2019/1741- BC 05063) and registered at the clinicaltrials.gov database (NCT04432428). Written informed consent was obtained from all patients prior to surgery. Patient enrollment occurred during the period June 2020 - October 2021.

Introduction

Total knee arthroplasty (TKA) is one of the major procedures performed today with a significant impact on health care budgets. In 2022 20, 300 TKA were executed in Belgium and predictions state the incidence in Belgium will double within 20 years due to the rapid aging population and the global burden of osteoarthritis[1]. In the United States, it is even estimated that the incidence of TKA in 2030 will be six times the incidence of 2005[2]. The vast number of these operations which are annually performed worldwide emphasize the importance of knowing whether one postoperative pain regimen has significant advantages over the other.

An Enhanced Recovery After Surgery (ERAS) protocol is a set of evidence-based guidelines designed to optimize the perioperative care of surgical patients. One of the major components of ERAS is early mobilization after a TKA[3-6]. Early mobilization is not possible without adequate pain control. In this context, the use of multimodal analgesia is pivotal. Suboptimal postoperative pain treatment leads to patient discomfort, delayed recovery and an increased length of stay[6-8]. It should be noted that 10% of the patients, who underwent a TKA, have a numeric rating scale (NRS) higher than 73 and up to half of the patients experience severe postoperative pain, despite the use of multimodal analgesia regimen[8]. Multimodal analgesia regimen consists of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, local infiltration analgesia (LIA) and adductor canal block[7,9].

Currently, Patient-Controlled analgesia (PCA) techniques, which are predominantly morphine based, are the gold standard after TKA. Problems with intravenous patient-controlled analgesia (IV PCA) are well known, including invasive access route, restriction of patient mobility and pump related technical errors. The sublingual sufentanil tablet system (SSTS, Zalviso®, Grünenthal, Germany) may overcome these shortcomings. It can be used as treatment for moderate to severe pain in hospitalized patients[4]. The SSTS consists of a small handheld device that delivers sufentanil tablets through a small tube under the patient's tongue. It contains a cartridge of 40 tablets sufentanil 15 micrograms (µg). To prevent overdose, a lock- out of 20 minutes is installed after each administration of a sufentanil tablet. The device uses an identifier tag so that only patients with a special thumb tag can release these tablets. They dissolve under the tongue and may not be chewed or swallowed. The SSTS provides a rapid onset of pain relief, has few adverse effects and can be used through physiotherapy exercises because there is no need for IV lines. The system provides autonomy and does not restrict mobility, which meets the condition of ERAS[4,9-11]. The equivalent dose of 15 µg sublingual Sufentanil is 2.5mg morphine intravenous or 5mg oral Oxycodone[12]. Morphine has the disadvantage that it has a slow onset of working and its active metabolite, morphine-6-glucuronide (M6G) occurs hours following the IV PCA dose and can result in delayed adverse events. Sufentanil lacks active metabolites, has a rapid equilibration half-life between plasma and central nervous system and due to its highly lipophilic nature, sufentanil can be rapidly absorbed following sublingual administration[13].

Total knee arthroplasty (TKA) is a surgical procedure that involves the removal of a damaged knee joint and the replacement with an artificial joint, called prosthesis. The goal of a TKA is to relieve knee pain and improve quality of life[3]. The orthopaedic surgeon can choose between a total knee prosthesis or a unicondylar (unicompartmental) knee prosthesis to replace the damaged knee. A unicondylar knee prosthesis is a surgical procedure in which only the medial or lateral condyle of the knee is replaced instead of the entire joint. In this study a TKA includes unicondylar and total knee prosthesis.

Previous studies evaluated SSTS in orthopaedic and abdominal surgery in comparison to placebo or intravenous PCA but did not address analgesic efficacy during mobilization[2]. We hypothesize that the use of a sublingual sufentanil-based PCA device enables efficient and safe analgesia in patients undergoing TKA, allowing early postoperative mobilization in a fast track rehabilitation program.

Methods

This single center interventional prospective cohort study was conducted at Jan Yperman Hospital. Patients were enrolled between June 2020 and October 2021. The study protocol was approved on January,29 2020 by the local ethics board of the University of Ghent (Corneel Heymanslaan 10, Ghent), chairman Prof. Dr. Deron (EC 2019/1741-BC 05063) and registered in the clinicaltrials.gov database (NCT04432428). All participants gave their written informed consent. This study was carried out in accordance with the principles of the Declaration of Helsinki.

Possible candidates were signaled by orthopaedic surgeons to the principal investigators. Only patients who were capable of providing their written consent, of operating a SSTS device and who were undergoing a unilateral TKR under spinal anaesthesia were included. Exclusion criteria were history of substance abuse, hypersensitivity to sufentanil, pregnant or breast-feeding, severe kidney disease (eGFR <30ml/

min), liver impairment (INR>1,5 and/or AST/ALT above x3 highest normal value), sleep apnea, COPD gold III and IV, chronic pain conditions necessitating gabapentinoids, steroids or anti-inflammatory drugs, age <40 and >75 years and revision surgery.

During the study all patients received the same multimodal pain treatment. Preoperatively, patients were shown an instructing video on how Zalviso works. An intravenous line was placed prior to surgery in the C-lounge, a preparation room close to the operation room. Cefazolin 2 grams, a prophylactic antibiotic, was administered intravenously to the patient 30 minutes before skin incision. When the patient was allergic to penicillin, vancomycin 1g was chosen. In the C- lounge a tablet of Celebrex (celecoxib) 200mg was given preemptive.

In the operating room, spinal anaesthesia with 10-12.5 mg of hyperbaric Marcaine (Bupivacaine) was performed at L3-L4 or L4-L5 spinal level, no adjuvants were used. Peroperative, patients received 0.15 mg/kg (max 8mg) IV Dexamethason (Aacidexam) and at the end of the surgery 4mg IV Ondansetron (Avessa). During surgery 1gram of paracetamol (acetaminophen) was given intravenously and after the release of the tourniquet 1 gram tranexamic acid (1.5gram if the patient weighs >75kg) IV was administered. As part of the multimodal pain protocol, all patients received a saphenous (adductor canal) nerve block and LIA (local infiltration analgesia). The saphenous nerve block (10cc of ropivacaine 0.5%) was placed under echo guidance by a limited group of experienced anesthesiologists. LIA was placed by the surgeon at the end of the operation and a mixture of 200ml ropivacaine 0.2% (ropivacaine 1% 40 ml +160 ml saline) was used. A tourniquet was used during all surgeries, no drains were left in place.

The SSTS device was installed and started on arrival in the Post-Anaesthesia Care Unit (PACU). The PACU nurses repeated briefly how Zalviso works. Next to of the Sufentanil sublingual tablet system all patients received four times a day 1gram of paracetamol and two times a day Celebrex 200mg PO. On the third day Celebrex was reduced to once daily. A cold ice pack was applied to the wound area during the postoperative period. If a patient reported twice in a row an NRS ≥4, rescue medication had to be given. In the PACU Piritramide 2mg IV was used as rescue medication. The patients were discharged from the PACU to the ward if they reported a Bromage score≥ 3. Five hours after skin incision 1gram of transaminic acid IV (1.5gram if patients weighs >75kg) was readministered. A thrombophylactic dose of Enoxaparine 40mg was injected SC at 8 PM (10 hours postoperative). At the ward Oxynorm 5mg was prescribed as rescue therapy. The catheter patency device was removed on day 1 postoperatively.

Patients received the first physiotherapy sessions as early as3 hours after the end of surgery. SSTS could be used during the exercises and patients were advised to take 1 sufentanil tablet preemptively. On day 0 the exercises consisted of a 5 meter walk with support and training to assume a sitting position. On day1 physiotherapy was intensified to include active motion exercises adapted to the patient's condition. After discharge, physical therapy was continued at home or in an outpatient rehab facility.

Heart rate (HR), oxygen saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBD), respiratory rate (RR) and Numeric rating scale (NRS) were taken on regular perioperative time points: The Numeric rating scale is a verbal 11-point scale, ranging from 0 ('no pain') to 10 ('worst imaginable pain'). Parameters were obtained by the investigators, ward nurses and physiotherapists. After the intake of a first sublingual sufentanil tablet, registrations were repeated every 30 minutes for the first hour and then hourly for the first 8 hours. After this, registrations were made at 4 hour intervals for the duration of the study. Pain scores were registered at rest, as well as during physiotherapy. For the latter, measurements were made at the start of physiotherapy, and 1 and 2 hours later. The physiotherapy session lasted 1 hour on average. If the patient reported an NRS score ≥4, the patient was instructed to take another sufentanil tablet to control the pain. After the intake of the extra Sufentanil tablet, the NRS score had to be rechecked 20 minutes later. If at any time the patients felt that pain control was insufficient, they were free to leave the trial. Study medication was discontinued if a severe adverse event occurred.

Our primary outcome was binary, ie either successful or unsuccessful analgesic therapy. When a patient reported two consecutive NRS scores ≥4, despite the intake of an extra sublingual sufentanil tablet, the treatment was considered unsuccessful. Discontinuation of study medication for SAE was considered as therapeutic failure.

Secondary outcomes were Length of Stay (LOS), incidence of nausea, vomiting, dizziness, constipation and pruritus and occurrence of severe adverse events. After completion of the study, nurses, physiotherapists and patients were asked to complete a questionnaire which focused on the convenience and efficacy in pain control of the device. Prior to the study, ward nurses and physiotherapists had been taught how to register pain scores and parameters, so uniformity in this study would be enhanced.

Statistical analysis

Sample size calculation was outsourced to a statistician, employed at HIRUZ (Health, innovation

and research institute). The study was originally designed as a two-center trial including one university hospital and one community hospital. Power analysis was done prior to the start of the study for a multicentric study design . In the literature IV PCA devices have a success rate of 75% and nurse controlled oral opioid have a success rate of 67%[13]. Based on the literature, we used the 95% Wilson Score Confidence Interval to evaluate the efficacy of SSTS in this trial. As lower limit we took 65% and a half-width of 10%. Targeting a success rate of 75%, 80 patients (or 40 patients in each center) is sufficient to achieve a 95% confidence interval with a confidence interval half-width less than 10% and a probability of 90%. After the statistical correction for center effect, a sample size of 68 patients was obtained for each center. The different parameters were registered and stored in REDCap (Research Electronic Data Capture), hosted by University Hospital of Ghent. REDCap is a secure, web-based software platform designed to support data capture for research-based studies[8]. Statistical processing was carried out on IBM® SPSS® statistics (Statistical Package for the Social Science). A total of 375 variables from 69 patients were analyzed. The software R, version 3.4.3 (R Core Team, 2017) was used to calculate the Wilson score Confidence interval. Variables were subjected to normality conformity assessment. Differences between groups were assessed using Student's T or Wilcoxon-Mann-Whitney tests.

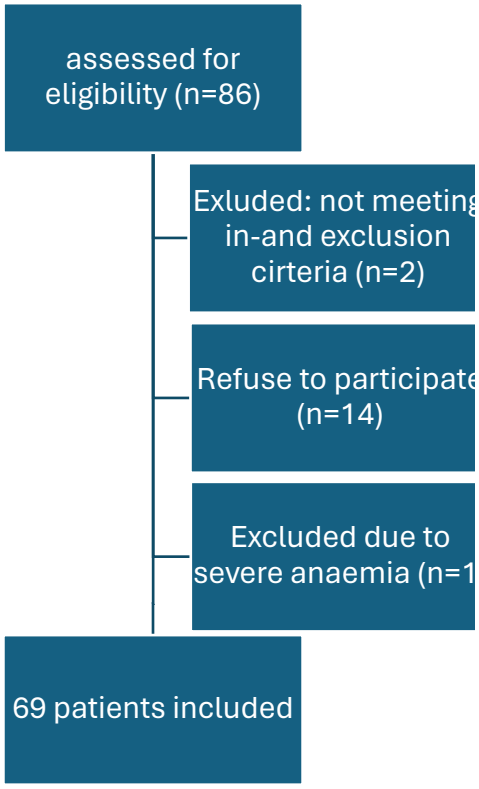

Fig. 1 — Flow diagram according to the Consolidated Standards of Reporting Trials (CONSORT).

Results

Study population

86 patients were assessed for eligibility. Two patients were excluded because they did not meet the required criteria and 14 patients did not want to participate in the study. 1 patient was removed from the study by the principal investigator because of serious anemia (not an official exclusion criteria). We enrolled 69 patients in this study (Figure 1). During the study no drop-outs due to malfunctioning of the SSTS device were mentioned. All patients, nurses and physiotherapists completed their questionnaire.

Demographics

The demographics of the study are shown in Table I; 44.9% of patients are male and 55.1% of patients are female. The median age of the study population is 61.5 years. Half of the study population has a BMI (body mass index) between 26.6 and 33 and a quarter of patients scores higher than 33. 98.6% of the study population has an ASA score of 1 or 2.

Primary outcome:

Pain score

22 patients out of 69 patients reported two consecutive NRS scores ≥4. The SSTS device had a success rate of 0,681 with a 95% Wilson Confidence Interval of [0.563-0.779]. No medical failure was due to discontinuation of study medication. Despite the study protocol, only 8 out of 22 patients took the rescue medication. The median intake of sufentanil tablets was 16 with an IQR of 12.

Patients reported for 87% of the time (registrations) an NRS score less than 4. When only the registrations after receiving an extra sufentanil tablet (because an NRS≥4 was reported) were taken into account,

Table I. — Demographics.

	SSTS (n =69)
Age (years) Median (Q1-Q3)	61.5 (57.5-68.0)
Sex, n(%) Male	31 (44.9%)
Female	38 (55.1%)
BMI Median (Q1-Q3)	29.3 (26.6-33.2)
Height (cm) Median (Q1-Q3)	169 (162-177.5)
Weight (kg) Median (Q1-Q3)	85 (74.5-95.0)
ASA, n (%) 1	17 (24.6%)
2	51 (73.9%)
3	1 (1.4%)

Abbreviations: BMI, body-mass index; ASA, American Society of Anaesthesiologists. Data are presented as median (25th and 75th percentile) or number of patients.

96.2% of the time an NRS ≤4 was registered. Figure 2 shows the 95% confidence interval plot of the mean of the NRS scores during rest after study initiation.

43 out of 69 patients reported once an NRS score ≥ 4 during physiotherapy. 12 patients out of 69 reported twice in a row an NRS score of ≥4 during mobilization. On day 0, 1 and 2 no correlation could be seen between the NRS scores at the start of physiotherapy and 1 and 2 hours later. Correlation was tested by using a logistic regression analysis. Figure 3 shows the 95% confidence interval plot of the mean of NRS scores during mobilization.

Seconary outcome:

Nausea and vomiting

On day 0,1 and 2 19, 26 and 12% of patients respectively suffered from nausea complaints and 7, 12 and 3% of patients suffered from vomiting. Only a fraction of these patients suffered from severe nausea and vomiting (Table II). During the study 6, 8 and 2 patients received an extra Ondansetron 4mg IV or Alizapride 50mg IV because of nausea complaints on day 0,1 and 2.

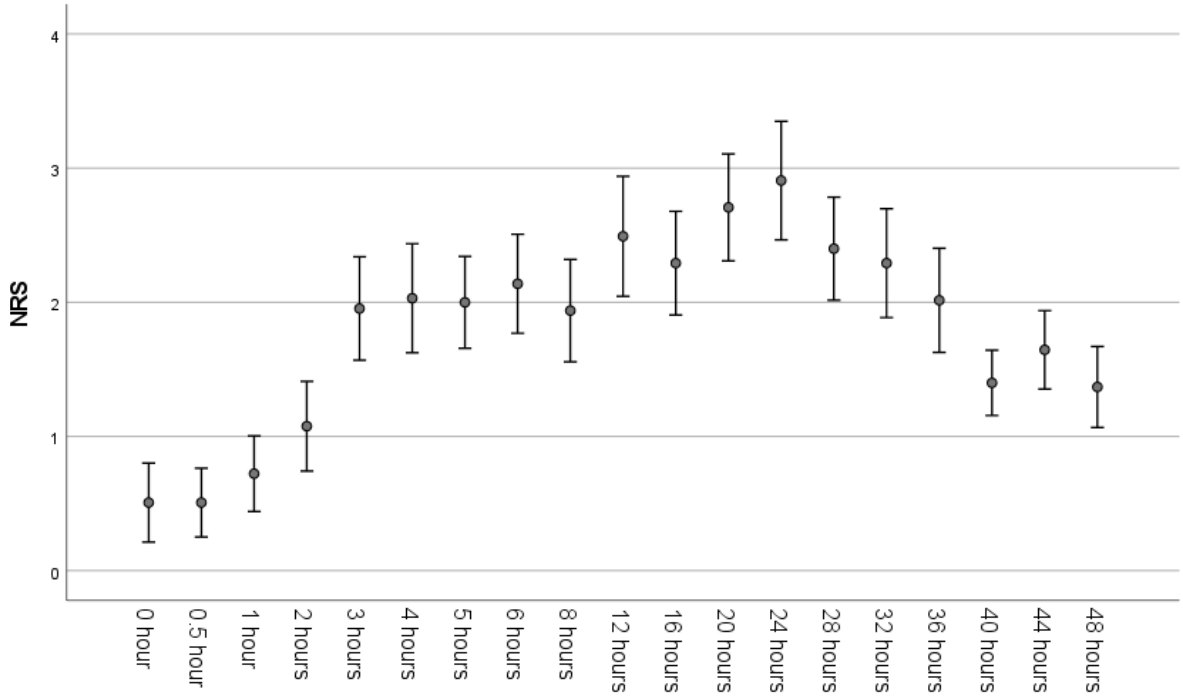

Fig. 2 — NRS scores in rest- 95% confidence interval plot.

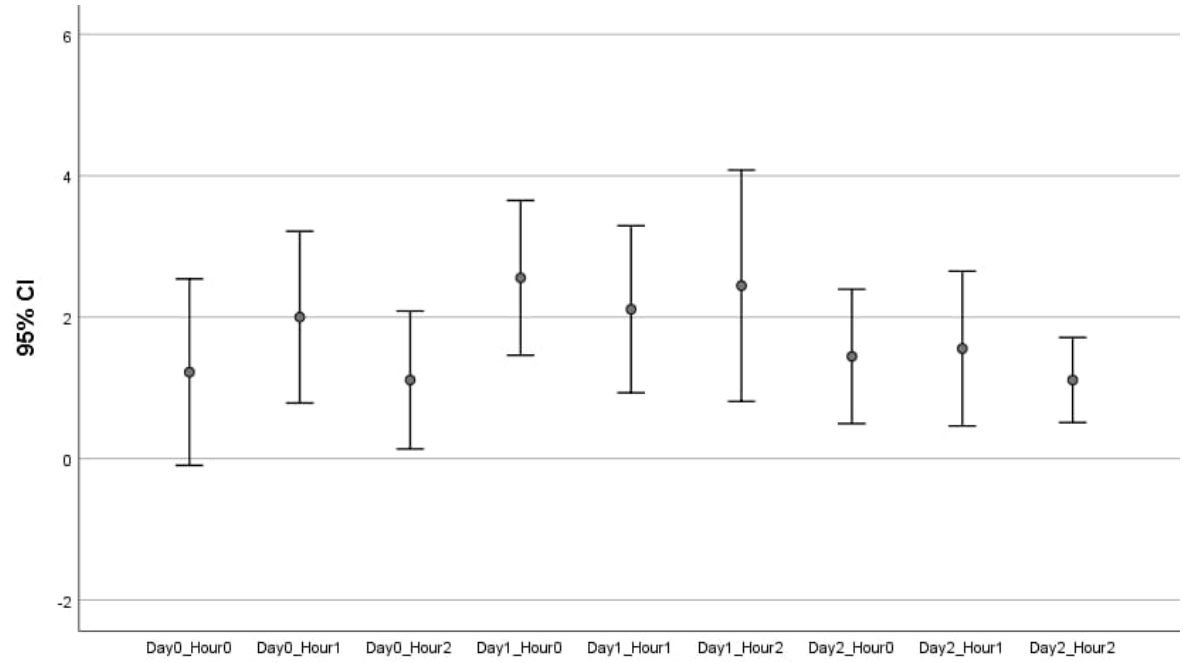

Fig. 3 — NRS during physiotherapy- 95% confidence interval plot.

Table II. — Incidence of side effects Zalviso.

(N=69)	Day 0	Day 1	Day 2
Nausea	n (%)	n (%)	n (%)
None	56 (81.2)	51 (73.9)	61 (88.4)
Mild	6 (8.7)	9 (13)	3 (4.3)
Moderate	6 (8.7)	5 (7.2)	4 (5.8)
Severe	1 (1.4)	4 (5.8)	0 (0)
Missing			1 (1.4)
Constipation	n (%)	n (%)	n (%)
None	69 (100)	65 (94.2)	63 (91.3)
Mild	0 (0)	2 (2.9)	2 (2.9)
Moderate	0 (0)	0 (0)	2 (2.9)
Severe	0 (0)	0 (0)	0 (0)
Missing		2 (2.9)	2 (2.9)
Vomiting	n (%)	n (%)	n (%)
None	64 (92.8)	61 (88.4)	67 (97.1)
Mild	3 (4.3)	3 (4.3)	0 (0)
Moderate	2 (2.9)	2 (2.9)	1 (1.4)
Severe	0 (0)	2 (2.9)	0 (0)
Missing		1 (1.4)	1 (1.4)
Pruritus	n (%)	n (%)	n (%)
None	65 (94.2)	67 (97.1)	67 (97.1)
Mild	2 (2.9)	0 (0)	1 (1.4)
Moderate	2 (2.9)	1 (1.4)	0 (0)
Severe	0 (0)	0 (0)	0 (0)
Missing		1 (1.4)	1 (1.4)
Dizziness	n (%)	n (%)	n (%)
None	59 (85.5)	56 (81.2)	63 (91.3)
Mild	7 (10.1)	7 (10.1)	2 (2.9)
Moderate	3 (4.3)	4 (5.8)	3 (4.3)
Severe	0 (0)	1 (1.4)	0 (0)
Missing		1 (1.4)	1 (1.4)

Constipation

None of the patients experienced constipation complaints on day 0. 2.9% of patients had a mild constipation on day 1, no treatment was needed. 2 patients had constipation symptoms on day 2 of which 1 had mild and 1 had moderate complaints. No treatment was needed on day 2.

Pruritus

5.8% of patients had pruritus on day 0, of which 1 patient received cetirizine 20 mg. On day 1, 1 patient (1.4%) had moderate pruritus complaints. No treatment was given. On day 2, 1 patient had mild symptoms of pruritus and received cetirizine 20mg.

Dizziness

The majority of patients (85.5%) had no complaints of dizziness after intake of Zalviso on day 0. However 10.1% of patients suffered from mild complaints and 4.3% had moderate symptoms. Only 1 patient asked for medication. On day 1, 81.2% had no complaints of dizziness; 10.1% had mild symptoms, 5.8% had moderate symptoms and 1.4% had severe symptoms. The patient with severe symptoms received an extra ondansetron 4mg. On day 2, 91.3% of patients had no complaints of dizziness, 2.9% had mild symptoms, 4.3% had moderate symptoms. No medication was given on day 2.

Patient, nurse and Physiotherapist Ease of Care questionnaire

The results from the patient and nurse, patient and physiotherapist EOC questionnaires are presented in Table III. Nurses and patients reported a high satisfaction score with the use of SSTS (Figure 4). Convenience scores were high among nurses to ambulate patients in a room or to transfer patients to a chair. Little to no time was needed by nurses and physiotherapists to educate patients or to solve side effects, related to the device. The SSTS device did not interfere with movement, according to the patients EOC questionnaire.

Adverse events

Neither ICU admissions, mortality, desaturation, hypotensive or bradycardia episode occurred during the study period. The occurrence of side effects did not lead to prolonged hospitalization stay. All patients had a Length of Hospital Stay (LOS) of two days.

Discussion

The major findings in this single centre cohort study, phase IV trial was a success rate of 68% of the cases with a 95% Wilson Confidence Interval [56.3%-77.9%]. The success rate of SSTS is similar to the reported success rates for parenteral PCA devices and oral opioids, providing adequate analgesia at rest and during mobilization after TKA[10,13]. Optimal pain management after TKA is essential. It permits early mobilization, improves patient satisfaction and economic savings[3-6]. A better postoperative pain relief leads to fewer complications, enhanced recovery and prevention of chronification of pain[3]. To our knowledge, this is the first study that investigated a SSTS device in a fast track rehabilitation program.

Sublingual sufentanil has a faster onset of analgesia time compared to classic IV morphine-based PCA devices and has no active metabolites. So a SSTS device reduces the risk of dose-stacking and delayed adverse events due to a decoupling of the patient's request for analgesia and the resultant

Table III. — Ease-of-Care (EOC) Questionnaire Results.

Patient EOC subscale results: Mean (SD)	**SSTS (n =69)**
Comfort with device	4.01 (1.1)
Ease of use	4.25 (1.5)
Interference with movement	0.16 (0.74)
Knowledge/understanding	4.12 (1.4)
Physiotherapist EOC subscale results: Mean (SD)	
Time efficiency:	
Attaining session goals	0.36 (1.1)
Ambulating patient outside the room	0.14 (0.7)
Convenience:	
Attaining session goals	4.77 (0.8)
Transferring patient to chair	4.63 (1.1)
Ambulating patient outside the room	4.74 (0.8)
Nurse EOC subscale results: mean (SD)	
Time efficiency:	
Educating patient the system	0.24 (0.8)
Solving side effects	0.20 (0.8)
Convenience	
Transferring patient to chair	4.73 (0.3)
Ambulating patient in room	4.81 (0.8)

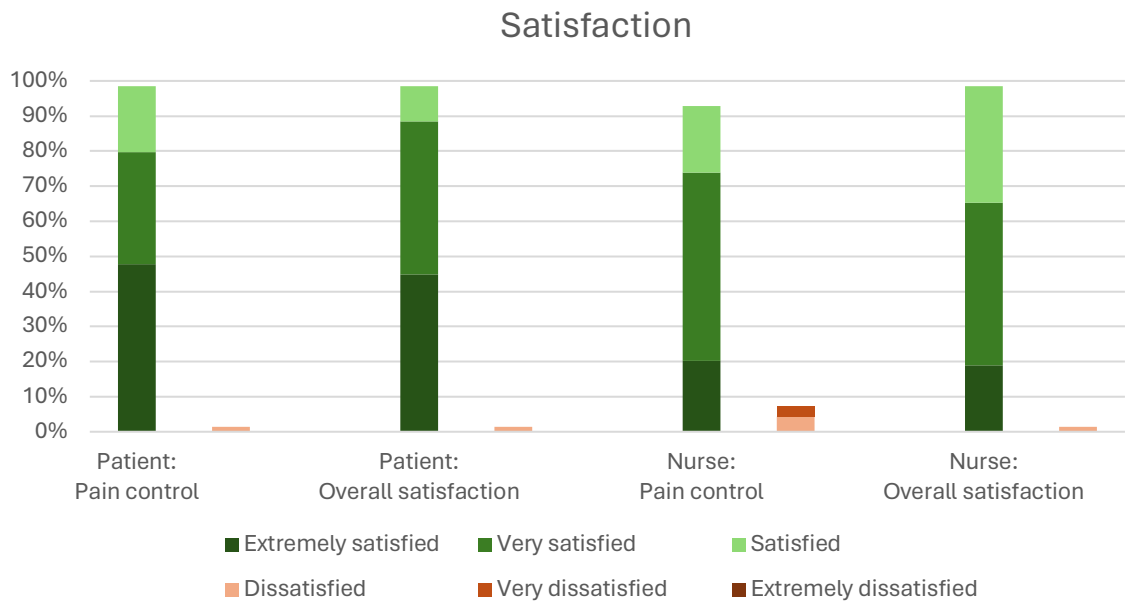

Fig. 4 — Overall satisfaction score among patients and nurses: pain control and overall satisfaction(%).

peak CNS concentration[13]. We did not observe any adverse events during our study. No supplement oxygen therapy was needed. The study group of Melson et al. showed fewer patients had desaturation events in the SSTS group, compared to IV morphine PCA devices.

The incidence of PONV was high during the study. We reported an incidence of nausea of 18.8%/26.1%/12.0% on day 0/1 and 2 respectively. In this study all patients received spinal anaesthesia and PONV prophylaxis (dexamethasone and ondansetron) was given perioperatively. The incidence of nausea is attributable to the intake of sufentanil tablets and was treated with alizapride 50mg.The occurrence of side effects did not delay rehabilitation exercises. The incidence of PONV in our study is comparable with the study group of Noel et al., which reports an incidence of 33%. Literature points out that the occurrence of nausea is more prevalent in the SSTS group compared to oral opioids[11-12]. Higher pain scores on day 1 could be explained by intense exercises during physiotherapy and elaborating analgesia of regional nerve blocks.

The study protocol was clear that rescue medication had to be taken when a patient reported twice in a row a NRS score ≥4. Despite the protocol only 8 out of 22 patients received rescue medication. Reasons were twofold. Firstly, some nurses forgot to offer the rescue medication to the patients. Secondly patients refused the intake of extra pain medication. In general an NRS score of 4 is seen as moderate pain and has to be treated in our trial, because this could interfere with the rehabilitation process of the patient. 98% of patients reported a high satisfaction score for pain control at the end of the study. A median intake of 16(40 mg morphine equivalent) sublingual sufentanil tablets with an IQR of 12 (30mg morphine equivalent) were taken during study period. The wide range in intake could be attributed to the fact that unicompartmental knee prosthesis is in general less painful than a total knee replacement, both type of operations were included in the study. In the literature Noel et al. had similar opioid consumption. Palanne et al. described a much higher opioid consumption during their trial.

Patient EOC questionnaire results show a high score for all aspects of the SSTS device (comfort with the device, ease of use, pain control, understanding). The SSTS is a hand-held device and easily accessible, it is stored in a bedside holster within clear view of the patient. The device has lights indicating lockout status, the dosing button lights up and flashes when it recognizes the thumb tag and emits a positive dosing sound when the device has dispensed a tablet. The convenience, the higher degree of feedback compared with IV PCA devices may explain the high satisfaction scores among patients[13]. Note that a part of the high satisfaction score among patients could be attributed to the Hawthorne effect. Patients were visited on a regular basis by nurses to fill in all parameters. The overall satisfaction grade was also very high among nurses. In general nurses were satisfied with the efficacy of pain control and convenience of the SSTS device, however some problems during the study were reported with the loosening of the thumb tag. In general, Zalviso is intuitive and easy to use. The study group of Scardino et al. measured that the installing time of Zalviso is on average 2.4 minutes. These aspects may appear trivial, from an operation point of view they translate in saving time, easier streamlining of procedures, and better prevention of human error. PCA devices are associated with errors linked to medical prescriptions, drug combinations, dose titrations and pump programming[16]. The SSTS device gave a great autonomy to the patients on their own pain management. Physiotherapist have a pivotal role in the rehabilitation process after total knee arthroplasty. The questionnaires show that physiotherapists are very satisfied with the convenience and analgesic effect of the SSTS device.

Further studies are needed to investigate the cost effectiveness of SSTS with conventional pain medications. Unfortunately Zalviso is no longer on the market. Since December 2022 Dzuveo is the successor of Zalviso, which consists of sublingual tablets of 30µg Sufentanil and is administered to the patient with a small applicator.

Limitations

This study is a single centre cohort study, conducted in a community hospital. The study was originally designed as a two-center trial including one university hospital and one community hospital in order to maximize external validity of the data. As a consequence, statistical power calculation had to incorporate a correction for center effect. For a variety of reasons, the inclusion of patients was slower in the academic centre (sicker patient profile with more exclusion criteria, competitive study launched by surgeons in similar patient cohort, COVID pandemic reducing case load…). An abrupt decision from the supplying company to withdraw the product from the international market subsequently forced an early termination of the study. At that time, only one hospital had completed the patient recruitment hence a 2-centre statistical analysis would be underpowered. To overcome this limitation we decided to proceed with a single centre analysis. Due to the small sample size rare complications, such as intensive care admission or mortality would not be picked up.

Secondly in this study we defined failure when a patient reported twice in a row a pain score of ≥4. This definition may be too strict. It is always hard to compare different pain studies, given that many studies use a different study design, outcome or surgical technique (for example robotic assisted knee surgery). In addition quantification of 'pain' by using NRS score is interpretable. It depends on the enquiry method, support and interaction with the interrogator. In this study we tried to limit the number of nurses who registered the parameters and gave before the study of the study a lecture to the nurses on 'how to register the parameters in the ward'. However, interprofessional differences could not be excluded.

Thirdly, in this study we included both unicondylar knee replacement and total knee replacement. Although similar, these operations differ nevertheless in surgical stress and postoperative pain scores. In this study we could not perform sub-analysis between the two different operations. The TKA was performed by three

different surgeons. The overall surgical technique was the same. Nonetheless differences in speed, quality of execution and LIA placement could not be totally excluded.

Fourthly, the design of the study contains a lot of in- and exclusion criteria. 98.6% of patients had an ASA score lower or equal to two and the median age was 61.5 years. No patients with liver or renal abnormalities were selected. Sufentanil could accumulate in patients with liver and renal impairment. It would be interesting to investigate if the SSTS device is also effective after a general anaesthesia and should be used in a more fragile study population, considering ERAS pathways should be applicable to all patient groups. The vast number of TKA performed worldwide emphasize the importance of knowing the ideal pain treatment.

Conclusions

For a long time, PCA devices were considered the gold standard to provide effective pain control post TKA. However such systems have their shortcomings. They are often defective, time consuming and require intravenous access, which hampers mobilisation of the patient. In this study, 68.1% of patients did not report two consecutive NRS scores of $\geq$4 during early mobilisation after TKA. The success rate of SSTS is similar to the reported success rates for parenteral PCA devices and oral opioids. However this is the first study, to our knowledge, that provided this success rate in a fast track rehabilitation program, focusing on early mobilisation after TKA. A high satisfaction score for convenience and pain control was noted among patients, nurses and physiotherapists. During the study period no adverse events occurred. Despite spinal anaesthesia and PONV prophylaxis a high incidence of PONV is reported. On day 1 postoperative, 26.1% of patients reported nausea.

Conclusion

Low flow anesthesia reduces the environmental impact of inhaled anesthetics. Understanding the effects of lowering FGF on the difference between the dialed and end-expired agent concentration empowers the clinician to lower FGF. It also provides the rationale for the further development and use of target controlled low flow delivery. To maximally reduce agent use with automated target controlled low flow delivery systems, one further has to consider the factors affecting target selection (patient age, opioid use) and hysteresis (slow wash-in, slow wash-out). The combined use of these factors can have a pronounced effect on agent use and waste. Lowering FGF is only one part of a larger puzzle to reduce the environmental impact of inhaled anesthetic agents. The quantitative aspects outlined in this manuscript should be part of any life cycle analysis of inhaled anesthetic agents.

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References

1. Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am. 2018 Sep 5;100(17):1455-1460.
2. Hertog den a, Gliescche K, Timm J. Pathway controlled fast-track rehabilitation after total knee arthroplasty: a randomized prospective clinical study evaluating the recovery pattern, drug consumption, and length of stay. Arch Orthop Trauma Surg;2012 Aug. 138 p.
3. Kalmar A, Van Overschelde P, Byn P, Pennynck S, Vanoverschelde H (2020). A neuro-anatomically grounded scheme for LIA gives superior analgesia and comfort levels compared to epidural analgesia until seven days after total knee arthroplasty. Acta orthopaedica Belgica; 2020 Dec; 86(4):688-696.
4. Jove M, Griffin DW, Minkowits HS, Ben-David B, Evashenk MA, Palmre PP. Sufentanil sublingual tablet system for the management of postoperative pain after knee or hip arthroplasty: a randomized, placebo-controlled study. Anesthsiology; 2015 Aug;123(2):434-43.
5. Jones EL, Wainwright tW, Foster JS, Smith JRA, middleton RG (2014) A systematic review of patient reported outcomes and patient experience in enhanced recovery after orthopaedic surgerty. Ann R Coll Surg Engl; 2014 Mar;96(2):89-94.
6. Kehlet H, Wilmore DW. Fast-track nee arthroplasty-status and future challenges. Knee20(suppl1); 2013 Sep;20:S29-33.
7. Soffin EM, YaDeau Jt. Enhanced recovery after surgery for primary hip and knee arthroplasty: a review of the evidence. Br J Anaesth 117; 2016 Dec;117(suppl 3):iii62-iii72.
8. Chan EY, Blyth FM, Nairn L, Fransen M. Acute postoperative pain following hospital discharge after total knee arthroplasty. Osteioarthritis Cartilage;2013 Sep;21(9):1257-63.
9. Turnbull ZA, Sastow D, Giambrone Gp, Tedore T. Anesthesia for the patient undergoing total knee replacement: current status and future. Local Reg Anesth; 2017 Mar 8;10:1-7.
10. Noel E, Miglionico L, Leclercq M (2020) Sufentanil sublingual tablet system versus oral oxycodone for management of postoperative pain in enhanced recovery after surgery pathway for total knee arthroplasty: a randomized controlled study. Journal of experimental orthopaedics. J Exp Orthop; 2020 Nov 20;7(1):92.
11. Hused H, Otte KS, Kristensen BB, Orsnes T, Wong C, Kehlet H(2010) Low risk of thromboembolic complications after Fasttrack hip and knee arthroplasty. Acta Orthop; 2010 Oct;81(5):599-605.
12. Rineau E, Dumartinet B, Samson E, Dollfus A, Aubourg C, Lasocki S (2022) Sufentanil sublingual tablet system for enhanced recovery after total knee arthroplasty: a prospective observational case study. Perioperative Medicine; 2022 Oct 4;11(1):50.

13. Melson T, Boyer D, Minkowitz H, Turan A, Chiang Y, Evashenk M, Palmer P. (2014) Sufentanil Subingual Tablet System vs. Intravenous Patient-Controlled Analgesia with Morphin for Postoperative Pain Control: A Randomized, Active-comparator Trial. Pain Practice.
14. Kuang M-J, Ma J-X, Fu L, He W-W, Zhao J, Ma X-L (2017) Is adductor canal block better than femoral nerve block in primary total knee arthroplasty? A GRADE analysis of the evidence through a systematic review and meta-analysis. Journal of Arthroplasty;2017 Oct;32(10):3238-3248.
15. Gonvers E, Il-Boghdadly K, Grape S, Albrecht E. Efficacy and safety of intrathecal morphine for analgesia after lower joint arthroplasty: a systematic review and meta-analysis with meta-regression and trial sequential analysis. Anaesthesia; 2021 Dec;76(12).
16. Palanne R, Rantasalo M, Vakkuri A, Madanat R, Olkkola K, Lahtinen K (2020) Effects of anaesthesia method and tourniquet use on recovery following total knee arthroplasty: a randomised controlled study.Br J Anaesth; 2020 Nov;125(5):762-772.
17. Scardino M, D'Amato T, Martorelli F, Fenocchio G, Simili V, Di Matteo B, Bugada D, Kon E (2018) Sublingual sufentanil tablet system Zalviso for postoperative analgesia after knee replacement in fast track surgery: a pilot observational study; J Exp Orthop. 2018 Dec; 5: 8.
18. Van Veen D, Verhelst C, Van Dellen R, Koopman J(2018) Sublingual sufentanil (Zalviso) patient-controlled analgesia after total knee arhtroplasty: a retrospective comparison with oxycodone with or without dexamethasone. Journal of pain research; Journal of pain research;2018 Dec 14;11:3205-3210.
19. Frampton J (2016) Sublingual Sufentanil: a review in acute postoperative pain. Adis Drug evaluation; Drugs. 2016 Apr;76(6):719-29.
20. Vergari A, Coregiani A, Rispoli M, Coluzzi F, Deni F, Leykin Y, Lorrini L, Martorano PP, Paolicchi, Polati E, Scardino M, Corcione A, Giarratono A, Rossi M (2020) Sufentanil Sublingual Tablet system: from rationale of use to clinical practice. European Review for Medical and Pharmacological Sciences. Journal of clinical medicine; 2022 Nov; 11(22): 6864.

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