Is the Rate of Early mobilization in Hip fracture patients using Alfentanil Better than standard opioid analgesia (REHAB)? A protocol for a prospective cohort study

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Aims

The primary aim of this study is to compare mobility status of patients receiving oral oxycodone with those receiving subcutaneous alfentanil as analgesic methods prior to mobilization to help physiotherapy compliance after hip fracture surgery. The secondary aims are to assess postoperative pain, health-related quality of life, in-hospital length of stay, total use of analgesia over postoperative days 1 and 2 (POD 1 and POD 2), complication rates within 30 days, and 30-day mortality rates.

Methods

A single-centre, prospective cohort study of 64 patients will be undertaken. Patients undergoing surgery for femoral neck fractures at the study centre will be recruited. Patients with a hip fracture meeting the inclusion/exclusion criteria will be enrolled on admission. Patients who have been administered oral oxycodone will be compared to those prescribed alfentanil for pain prior to mobilization with physiotherapists on POD 1 and POD 2. Which drug a patient receives is reliant of the prescriptions given by the medical team, and in current practice this varies at approximately 50:50. Mobilization will be defined as the ability to stand on and weightbear both feet with or without assistance.

Results

Visual analogue scale pain scores, mobility status, and total analgesia use will be assessed on POD 1 and POD 2. EuroQol five-dimension health questionnaire scores, complication rates, and mortality rates will be assessed up to 30 days following surgery (POD 1, 2, 7, and 30).

Conclusion

This study will help to build a wider protocol aiming to improve early mobilization after hip fracture surgery. The results of this study will provide pain scores and mobility status which will either support use of subcutaneous alfentanil as the standard analgesic modality prior to physiotherapy sessions, or highlight its limitations compared to the standard oral oxycodone. Secondary outcomes will also help to assess if early mobilization improves outcomes compared to delayed mobilization.

Take home message

- This study will help to build a wider protocol aiming to improve early mobilization after hip fracture surgery.
- The results will help to determine if alfentanil provides superior analgesia and therefore compliance with physiotherapy.
- If this is the case, this study will assess if this has any bearing on 30-day outcomes in morbidity and mortality.

Introduction

Hip fractures are among the most common orthopaedic injuries.[1] These fractures predominantly occur in the elderly

population, secondary to osteoporosis.[2] Projection studies from across the world suggest that incidence rates of hip fractures are set to increase. Worldwide projections indicate that hip fracture cases will double from 1.26 million in 1990 to 2.6 million by 2025, and to 4.5 million by 2050.[3] Furthermore, the Global Burden of Disease Study has identified that there was a 58% increase in hip fractures in 2017 compared to 1990.[4] In addition, data from the Scottish Hip Fracture Audit identified an increase from 6,369 hip fracture cases in 2007 to 8,380 in 2022.[5,6] Given the exponential rise in the frail elderly population, these numbers will likely continue to rise in the future.[7]

Hip fracture injuries are linked with increased morbidity, frailty, and mortality risk.[8-10] Moreover, there are significant social and economic costs on the healthcare system stemming from these injuries. In the USA, these costs are estimated to amount to more than $5.96 billion annually.[11] In the UK, these costs are approximately £1.1 billion.[12-14] Healthcare systems globally are becoming progressively more financially constrained, and the incidence of hip fractures is set to increase. Thus, further emphasis should be placed on interventions to reduce morbidity and mortality in this frail elderly patient group.

Early mobilization after hip fracture surgery is associated with reduced postoperative pain and complication rates, and reduced length of stay (LOS) in hospital.[15–21] Some studies have demonstrated that early ambulation also reduces 30-day mortality rates in this patient population.[18,20] Oldmeadow et al[22] demonstrated that early mobilization was also associated with an increased rate of discharges directly home, compared to those patients who mobilized late. Barone et al[23] indicated that although elderly patients have associated comorbidity and a higher risk of delirium, neither factor influenced the ability to mobilize early after surgery. They also found that a greater number of patients who mobilized early were able to be discharged directly home.[23]

Though early mobilization may provide numerous postoperative benefits, there are barriers to achieving this reliably and effectively. One such difficulty is pain secondary to the patient's injury. Studies have reported that pain is often a key obstacle to early ambulation after surgery.[24,25] Oral oxycodone is frequently employed as the analgesia of choice to help with postoperative pain in patients who have undergone orthopaedic trauma injuries. However, this analgesic modality is used to help with general postoperative pain rather than targeted abolition of pain prior to physiotherapy. Oxycodone has been used in clinical practice since 1917,[26] and there is in-depth literature on its pharmacokinetics. The onset of action of oral oxycodone is between ten and 30 minutes.[27,28] Peak onset occurs around one hour.[28-30] The plasma half-life is three to five hours, regardless of route of administration.[31] Alfentanil, by contrast, is a relatively new analgesic with limited literature in relation to its pharmacokinetic properties. There is consensus that onset of action of alfentanil is very rapid, with peak onset of intravenous alfentanil as quick as two minutes.[32–35] The plasma half-life of oral alfentanil is one to two hours.[34–36] Moreover, side effects of respiratory depression are lower than those of fentanyl or sufentanil.[35] The combination of rapid onset of pain relief, with an equally quick excretion, makes this medication appealing in palliative care medicine, in which patients are typically frail.[32,37] This is particularly the case in patients with renal impairment, since this medication is excreted by the liver.[38]

Many studies have identified pain as a barrier to early mobilization after hip fracture surgery. However, to the authors' knowledge, there are no studies or reviews in the literature which have specifically investigated this, nor provided a systematic strategy to tackle postoperative hip pain, to help facilitate early mobilization. A preliminary audit conducted at the Royal Infirmary of Edinburgh identified that use of subcutaneous alfentanil provides superior analgesia compared to the use of routine oral oxycodone as part of a quality improvement project.[39] A total of 36 postoperative hip fracture patients were included, of whom 22 required analgesia to aid in physiotherapy.[39] There were 12 patients who received alfentanil, and eight who received oxycodone.[39] Out of the 36 patients, 26 were mobilized.[39] Successful postoperative day (POD) 1 mobilization was higher in patients receiving subcutaneous alfentanil (10/12) compared with oral oxycodone (3/8), with an odds ratio of 8.33 (95% CI 1.03 to 67.14, $p = 0.040$).[39] Given the significantly longer peak onset time of oxycodone compared to alfentanil, physiotherapists who cannot wait one hour per patient risk mobilizing patients with subtherapeutic analgesia. The short half-life, combined with the fast onset of analgesic effect, makes alfentanil a promising analgesic option to reduce pain before physiotherapy and therefore facilitate more engaging sessions.

Study objectives and endpoints

Our research hypothesis is that subcutaneous alfentanil provides quicker analgesic benefits compared to oral oxycodone, thereby allowing better pain-free physiotherapy, which would facilitate a greater rate of early mobilization after hip fracture surgery. Our primary objective is to compare the rate of POD 1 and POD 2 mobilization between patients receiving oral oxycodone with receiving subcutaneous alfentanil as analgesic methods prior to physiotherapy after hip fracture surgery. Our secondary objectives are to assess POD 1 and POD 2 pain before and after physiotherapy, health-related quality of life (HRQoL), in-hospital LOS, total use of analgesia over POD 1 and 2, 30-day complication rates, and 30-day mortality rates.

Our primary endpoint is mobility status on POD 2; secondary endpoints are 30-day HRQoL, and complication and mortality rates after surgery.

Study design

This will be a single-centre, observational prospective cohort study. This is a 30-day study of oral oxycodone compared to subcutaneous alfentanil as part of post hip fracture treatment at the Royal Infirmary of Edinburgh (RIE), NHS Lothian, UK. Both analgesic methods will be compared to assess which is superior in facilitating early mobilization after surgery. Patients listed for an operation to treat a hip fracture who meet the inclusion criteria will be highlighted on admission, and consented for recruitment into the study. After surgery, participants will then be encouraged to mobilize at POD 1 and POD 2, which is standard practice for all patients undergoing hip fracture surgery at RIE. Current practice is for patients to undergo a pain assessment with physiotherapists prior to attempted mobilization. This is assessed at rest and on passive hip flexion, using the visual analogue scale (VAS) for pain.

Patients who report a score of 5/10 or higher at rest or on passive hip flexion are provided with the analgesia, either oral oxycodone or subcutaneous alfentanil. The type of analgesia given is left to the discretion of the medical team caring for the individual and patient preference. Those who receive oral oxycodone will then be placed into Group 1. Those who receive subcutaneous alfentanil will then be placed into Group 2. They will then undergo the routine physiotherapy assessments to encourage mobilization in POD 1 and POD2. Patients will receive the same analgesia as POD 1 on POD 2 to allow for uniformity. Furthermore, all patients will be assessed by the physiotherapy team within 30 minutes of the patient receiving analgesia, which is standard practice within our department, to ensure continuity of care between the groups.

Patient-reported outcome measures (PROMs) in the form of the EuroQol five-dimension five-level questionnaire (EQ-5D-5L) [40] will be assessed at POD 1, 2, 7, and 30. Complications will also be assessed at the same intervals. Participants will be followed up to 30 days postoperatively to determine mortality and complication rates.

Study population

A total of 64 patients undergoing surgery for their hip fracture will be recruited at the study centre. Inclusion criteria are patients undergoing dynamic hip screw/cannulated hip screw/hemiarthroplasty/total hip arthroplasty/intramedullary nail for insufficiency-type neck of femur fractures, who are aged over 60 years, willing and able to comply with the study protocol, and provide informed consent. Exclusion criteria are patients who do not meet the study's inclusion criteria, prosthetic or pathological hip fractures, high-energy mechanism of injury, and patients who were not able to mobilize prior to injury, e.g. wheelchair-bound.

Participant selection and enrolment

The majority of patients who present to the RIE with a hip fracture are seen in the emergency department (ED). They are then seen by the orthopaedic surgical registrar on call, who will accept the patient into the orthopaedic service if appropriate. Some patients will fall in the hospital or be transferred directly to the orthopaedic ward when being transferred from another hospital. The research team will liaise with the orthopaedic surgical registrar on call, to highlight all patients admitted to the orthopaedic ward with a hip fracture that requires surgery.

When the patient is assessed by the orthopaedic registrar on admission (either in the ED or orthopaedic ward), they will seek permission for the patient to be approached by the research team. A member of the research team will then meet with the patient and provide the patient information leaflet (PIL), explain the justification of the trial, and what this would entail for the patient.

After the initial approach, a member of the research team will meet with the patient again to further discuss the study, answer any questions, and ask if the patient is happy to consent for inclusion into the trial. Ideally, 24 hours will be given between the initial approach and provision of the PIL to re-discussion and potential consenting. However, should these patients undergo surgery before this time, they will be seen sooner to ensure that consent is gained prior to surgery. Should the patient feel that sufficient time has not been provided, they will be revisited on POD 1 to rediscuss inclusion.

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason, including ineligibility, significant protocol deviation, significant non-compliance with treatment regimen or study requirements, loss of participant's capacity to provide ongoing consent during the study, consent withdrawn, or loss to follow-up.

Participants who wish to withdraw consent for the study or whose participation from the study is discontinued will have anonymized data collected up to the point of that withdrawal of consent included in the analyses, unless the participant specifically asks for all data collected to be destroyed. No additional data will be collected from the participant. The primary reason for withdrawal will be documented in the participant's case report form if possible.

Co-enrolment will be permitted if in accordance with the Academic and Clinical Central Office for Research and Development (ACCORD) Co-enrolment Policy (POL008 Co-enrolment Policy)[41] and agreement of relevant Chief Investigators. Careful consideration will be given to minimize the burden on participants and their families, as will the possibility of any positive or deleterious impact on the results for both studies.

Study assessments

The primary goal of hip fracture surgery is to restore function and reduce pain – the outcome measures have been chosen to reflect these factors.

As mentioned earlier, the primary outcome will be measuring ability to mobilize on POD 1 and POD 2. Pain will be assessed at rest and on passive hip flexion, using the VAS for pain. Patients who report a score of 5/10 or higher at rest or on passive hip flexion are currently provided with the analgesia, either oral oxycodone or subcutaneous alfentanil. The physiotherapy team will aim to assess all patients within thirty minutes of analgesia administration to reduce confounding variables. Should this not be achievable for a patient for any reason, this patient will have their pain reassessed at rest and on passive hip flexion. If a score of 5/10 or higher is again found, further analgesia will be provided. It is at the discretion of the medical and physiotherapy team, and patient preference, which medication they receive. Which group the patient will be allocated to will depend on which drug the patient receives. The analgesia the patient receives on POD 1 and POD 2 will be the same.

POD 1 and POD 2 were chosen since the standardized care in the study centre is for all patients to receive physiotherapy input on POD 1 and POD 2 post hip fracture surgery, regardless of age, sex, surgical procedure, or postoperative condition. Further physiotherapy after this is dependent on the prioritization of patients who are likely to make a quicker recovery. As such, uniform data collection across all patients can only be conducted on POD 1 and POD 2. Mobilization has been classified into three different levels, each with increasing independence and complexity:

- Physiotherapy (PT) level 1, standing transfer: ability to weightbear on both legs, and transferring from bed to chair without stepping. Equipment will be used to help the

patient swing round from bed to chair (Sara Stedy/Samhall Turner (Etac, UK))
- PT level 2, stepping transfer: ability to weightbear on both legs, and transferring from bed to chair with stepping. Equipment will be used to help support the patient when stepping (gutter frame/Zimmer frame)
- PT level 3 A, mobilizing to the toilet with assistance of two people
- PT level 3B, mobilizing to the toilet with assistance of one person
- PT level 3 C, mobilizing to the toilet without assistance

Rate of mobilization was chosen as the primary outcome measure as it is thought to assess not only pain relief but also the speed on onset and the potential side effects of oxycodone. To simply use level of pain at rest is dependent on the time of assessment and may not account for the individual's ability to mobilize due to the potential side effects of oxycodone.

The secondary outcome measures of pain on POD 1 and POD 2 will be assessed as mentioned above, prior to physiotherapy, using the VAS. VAS pain scores will also be assessed immediately after physiotherapy.

To measure HRQoL, the National Institute for Health and Care Excellence (NICE) currently recommends the use of the EuroQol five-dimension (EQ-5D) questionnaire when conducting cost-effectiveness analyses and reference case analyses.[42] There are two versions of the EQ-5D: three-level (3L) and five-level (5L), which represent options of three or five levels of severity, respectively. The latter version of the EQ-5D-5L is newer and intended to be more sensitive than the previous iteration. There is strong evidence suggesting that, compared to the EQ-5D-3L, the EQ-5D-5L reduces the ceiling score and improves validity.[43,44] NICE recommends use of the EQ-5D-5L descriptive system to collect data on quality of life in prospective clinical studies.[42] The investigators have thus decided to use EQ-5D-5L as the PROM.

The EQ-5D-5L consists of questions in five domains of mobility, self-care, usual activities of daily living, pain/discomfort, and anxiety/depression.[40] There are five options for marking severity for each domain. There is also a VAS rating how the patient perceives HRQoL from 0 (worst) to 100 (best).

POD 1 and POD 2 have been selected as this is when all patients will have received physiotherapy input. Questionnaires will be conducted after the participants have received physiotherapy in order to standardize answers. This will be conducted for all included patients, regardless of what analgesia they receive and how they manage physiotherapy. POD 7 and POD 30 have been selected since these are reasonable times after surgery for function and pain to improve. Should patients be discharged prior to POD 7 or POD 30, they will be followed up via a phone call to answer these questions using the validated verbal version of the questionnaire.

In-hospital length of stay and discharge destination

In-hospital LOS will be calculated as the number of days in hospital, from the date of admission to the day of discharge. The discharge destination will also be sought, and compared with pre-admission place of domicile, to determine if analgesic modality affects discharge destination. Two LOS will be assessed: total time in hospital (admission to discharge home), and time on the acute orthopaedic ward (admission to either discharge home or to discharge to rehabilitation unit).

Total use of analgesia over POD 1 and POD 2

This outcome will be assessed to determine if early mobilization helps reduce overall postoperative pain during in-hospital admission and see if differing analgesic methods have any effect on this. Studies have previously shown that early postoperative mobilization does not worsen postoperative pain in hip fracture surgery patients,[20] and may actually lead to a reduction in overall pain.[17,45]

Patients at the study centre receive both regular and additional-as-required analgesia, in the form of oxycodone. This is standardized across all Trauma & Orthopaedic (T&O) patients according to age (Table I).

In addition, all patients receive paracetamol, according to their weight. The total amount of regular and as-required analgesia will be calculated. Pre-existing analgesia will be included in the pre-injury comparison assessment between the groups.

Complication and mortality rates

Each patient will be followed up, via their internal electronic medical (TRAKcare) patient notes to determine 30-day mortality. Complication rates will be assessed at POD 1, 2, and 7 alongside the EQ-5D-5L questionnaire. They will also be followed up at 30 days to assess any further complications. The following complications will be assessed: any complication, postoperative delirium (clinical diagnosis or a 4AT of four or more), constipation (requiring laxative), surgical site infection, wound dehiscence, pneumonia, pulmonary embolism, acute kidney injury, urinary tract infection, cerebrovascular accident, cardiac arrest, myocardial infarction, deep vein thrombosis, delirium, sepsis, mortality, dislocation, reoperation (and reason for this), and readmission (and reason(s) for this).

Data management

Data will be collected at baseline, and at POD 1, 2, 7, and 30. The following personal data will be collected as part of the baseline characteristics: age, sex, weight, height, phone number, comorbidities, location prior to admission (i.e. home, care home, sheltered housing), functional status prior to admission/injury and cognition (4AT), and clinical frailty score (Rockwood).[46] A standardized PROM with be used – EQ-5D-5L, which will be conducted with the patient at POD 1, 2, 7, and 30. Patients who have been discharged prior to POD 7 and 30 will be followed up by telephone to allow for completion. The patient contact schedule over the study period is outlined in Table II.

All study data will be entered on to paper case report forms (CRFs) and subsequently inputted into the study database by the research team. This will be conducted on NHS Lothian computers on site at the study centre. The participants will be identified only by an ID number on the CRF and any electronic database. Participant-identifiable data will be stored separately from trial data and in accordance with standard operating procedures (SOP). The name, and any other identifying details, will not be included in any trial data electronic file. All documents will be stored securely and only accessible by trial staff and authorized personnel. The study will comply with the Data Protection Act 1998, General data

Table I. Oxycodone dosages according to patient group.

Patient group	Analgesia dosage
Aged < 65 yrs	Regular oxycodone MR 5 mg BD 8am and 8pm
	PRN oxycodone IR 5 mg, max hourly
Aged 65 to 85 yrs	Regular oxycodone 3 mg IR QDS
	PRN oxycodone 4 mg IR, max hourly
Aged > 85 yrs	Regular oxycodone 2 mg IR QDS
	PRN oxycodone 3 mg IR, max hourly
< 50 kg or particularly frail	Regular oxycodone 1 mg IR QDS
	PRN oxycodone 2 mg IR, max hourly

BD, twice daily; IR, immediate release; MR, modified release; PRN, as required; QDS, four times per day.

Protection Regulation (GDPR), and the Freedom of Information Act, which require data to be anonymized as soon as it is practical to do so and stored securely.

In accordance with the ICH GCP (Section 5.5),[47] electronic data entry systems will be validated and SOPs for data entry will be maintained. All files will be password-protected, and only members of the research team will have access to this.

This single-site study is within an NHS hospital (RIE) and will adhere to the NHS Code of Confidentiality. Personal data will be physically stored by the research team in secure lockable cabinets at the study centre. All physical copies of personal data will be stored in confidential locked cabinets in a locked room in the department. Consent forms and other participant information will be stored separately.

All electronic data collected during the study will be stored in a database on secure NHS Lothian servers. This database will be held on an NHS Lothian shared hard drive (S: drive), with access limited to the research team only. Only computers that are part of the NHS server will be accessed at any given time to input these data. Access will be restricted, allowing only members of the research team to access these data. A participant's personal data will only be accessed once consent is obtained.

A data controller is an organization that determines the purposes for which, and the manner in which, any personal data are processed. NHS Lothian is the joint data controller, along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

Any data breaches will be reported to the NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) data protection officers, who will report to the relevant authority according to the appropriate timelines if required.

Statistics and data analysis

A power calculation was performed using the data from the quality improvement audit assessing the rate of POD 1 mobilization (primary outcome) using alfentanil versus oxycodone. Using an α of 0.05 and a power of 0.80, a sample size of 34 patients is required for a two-tailed study. A minimum of 17 patients is required in the oral oxycodone cohort and 17 in the subcutaneous/sublingual alfentanil cohort; a presumed 10% drop-out rate is anticipated in each cohort and would require 38 patients to be included: 19 in the oral oxycodone cohort and 19 in the subcutaneous/sublingual alfentanil cohort. Furthermore, only 22/36 patients (61.1%) in the quality improvement audit required analgesia. As such, considering that approximately only 60% of the patients included in the study may require analgesia, 64 patients would be required. Therefore, 32 participants will be included in each cohort.

Statistical analysis will be performed using Statistical Package for Social Sciences v. 17.0 (SPSS, USA). Parametric and non-parametric tests will be used as appropriate to assess continuous variables for significant differences between groups.

Unadjusted statistical tests will be conducted to determine differences between the two analgesic groups, in baseline characteristics such as smoking, premobilization status, type of surgery, and comorbidities. According to the distribution of data, independent-samples *t*-tests, variance analysis, and Mann-Whitney U tests will be used. An α value of 0.05 will be used to power the study for the outcomes measured at POD 1, 2, 7, and 30. Therefore, should a significant result be found we are 95% confident it is real. Bonferroni correction will be performed for other outcome measures assessed at the different timepoints to account for multiple testing of data.

No adverse effects for participants enrolled in this study are expected, since the treatment provided is part of standard care. Should patients not tolerate the side effects of the given analgesia, or these cannot be managed with medications, the patient will receive the other analgesia, as per standard ward practice. These patients will be placed in a sub-cohort and will be followed up to completion.

Oversight arrangements

Investigators and institutions involved in the study will permit study-related monitoring and audits on behalf of the sponsor, research ethics committee review, and regulatory inspection(s). In the event of audit or monitoring, the investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the investigator agrees to allow inspectors direct access to all study records and source documentation.

The ACCORD sponsor representative will assess the study to determine if a study-specific risk assessment is required. Such an assessment will be performed by sponsor representatives, ACCORD monitors, and the quality assurance (QA) group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. If considered necessary, ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits,

Table II. Patient assessment timepoints.

Variable	ED/admission to orthopaedic ward	Orthopaedic ward prior to surgery	Day of surgery	POD 1	POD 2	POD 7	POD 30
Screening and first approach	x						
Information provision	x						
Confirm if patient would like to participate		x					
Written informed consent		x					
Surgical intervention and data collection			x	x			
PROM				x	x	x	x
Pre-mobilization pain scores and mobilization status				x	x		
Total analgesia use				x	x		
Complications and mortality				x	x	x	x
In-hospital length of stay							x

ED, emergency department; POD, postoperative day; PROM, patient-reported outcome measure.

study management audits, and facility (including third parties) audits as necessary.

Good clinical practice

The study will be conducted in accordance with the principles of the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP) [48] . Before the study can commence, all necessary approvals will be obtained, and any conditions of approvals will be met.

The investigator is responsible for the overall conduct of the study at the site, and compliance with the protocol and any protocol amendments. In accordance with the ICH GCP principles, the following areas listed in this section are also the investigator's responsibility. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a delegation log and signed by all those named on the list prior to undertaking applicable study-related procedures.

The investigator is responsible for ensuring informed consent is obtained before any study-specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved. Participants must receive adequate oral and written information – appropriate PIL and informed consent forms will be provided. The oral explanation to the participant will be performed by the investigator or qualified delegated person, and will cover all the elements specified in the PIL and consent form. The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant will be given sufficient time to consider the information provided. It will be emphasized that the participant could withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. The participant will be informed and consent will be sought to allow their medical records to be inspected by regulatory authorities and sponsor representatives. The investigator or delegated member of the study team and the participant will sign and date the informed consent form to confirm that consent has been obtained. The original will be signed in the investigator site file (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

The investigator will be familiar with the protocol and the study requirements. It is the investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study-related duties. The Principal Investigator is responsible for the quality of the data recorded in the CRF at each investigator site. The Principal Investigator will ensure that the required documentation is available in ISFs. For non-CTIMP (i.e. non-drug) studies, all researchers are encouraged to undertake GCP training to understand the principles of GCP. This is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

Clinical information will not be released without the written permission of the participant. The investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained

for the disclosure of any said confidential information to other parties.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory information governance IT Security training through LearnPro (UK). Non-NHS Lothian staff who have access to NHS Lothian systems will familiarize themselves and abide by all NHS Lothian IT policies, as well as employer policies.

All investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the GDPR and Data Protection Act) with regard to the collection, storage, processing, and disclosure of personal information. Computers used to collate the data will have limited access measures via usernames and passwords. Published results will not contain any personal data that could allow identification of individual participants.

Study conduct responsibilities

This protocol and the template informed consent forms contained in the Supplementary Material have been reviewed and approved by the sponsor and the research ethics committee (REC reference 23/EM/0262) with regard to scientific content and compliance with applicable research and human subjects regulations.

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator. Proposed amendments will be submitted to the sponsor for classification, review, and authorization. Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D office for approval prior to implementation and prior to participants being enrolled into the amended protocol.

Prospective protocol deviations (i.e. protocol waivers) will not be approved by the sponsors and therefore will not be implemented except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

A serious breach is a breach which is likely to significantly affect the safety or physical or mental integrity of the study participants, or the scientific value of the study. If a potential serious breach is identified by the Chief Investigator, Principal Investigator, or delegates, the sponsor (qa@accord.scot) must be notified within 24 hours. It is the responsibility of the sponsor to assess the impact of the breach on the scientific value of the study, to determine whether the incident constitutes a serious breach, and report to research ethics committees as necessary.

All study documentation will be kept for a minimum of three years from the protocol-defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the sponsor. The end of study is the date of the 30-day follow-up of the last participant. The investigators and/or the sponsor have the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the REC, R&D office, and sponsor within 90 days, or 15 days if the study is terminated prematurely. The investigators will inform participants of the premature study closure and ensure that the appropriate follow-up is arranged for all participants involved. End-of-study notification will be reported to the sponsor via email to researchgovernance@ed.ac.uk.

Continuation of treatment following the end of the study

After the end of the study, the data collected will be analyzed and a report will be compiled and published in a peer-reviewed journal. A summary report of the study will also be provided to the REC within one year of the end of the study. Both oral oxycodone and subcutaneous alfentanil are already part of routine use in T&O surgical wards. Should evidence show that alfentanil provides superior analgesic effects to oxycodone, this will be disseminated across the multidisciplinary team in T&O surgery. Furthermore, should sublingual alfentanil provide the same or greater benefit than subcutaneous oxycodone, this may be introduced to routine T&O surgery practice.

Insurance and indemnity

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff. The following arrangements are in place to fulfil the sponsor's responsibilities: 1) sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study, and covered by the duty of care owed to them by the sites concerned. The sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. 2) Sites which are part of the UK's NHS will have the benefit of NHS Indemnity.

Reporting, publications, and notification of results

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases, and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Discussion

Early mobilization is associated with several improved postoperative outcomes. These include lower 30-day mortality and complication rates, and shorter hospital LOS.[15–18,20,21,23,49] The most common barrier to early mobilization is pain.[21,45,50] Thus, a standardized strategy to tackle postoperative pain prior to physiotherapy is needed.

Studies have previously recommended that early ambulation could improve both postoperative pain and lower delirium rates.[51,52] On the other hand, both pain and delirium may hinder attempts at early mobilization. Early improvements in pain analgesia, especially during and after mobilization, could reduce postoperative pain and delirium rates.

Oral oxycodone has a long mechanism of action and half-life.[27,28,31] As such, patients may not be receiving adequate analgesia prior to and during physiotherapy sessions, thereby limiting progress. Furthermore, the longer half-life increases the risk of opioid toxicity and potential delirium. By contrast, alfentanil has a faster mechanism of action and shorter half-life.[32–36] Given its properties, this medication is usually reserved for frailer patients with renal impairment

and for those in a palliative care setting.[32,37,38] Its property of fast-acting mechanism of action is ideal when given prior to physiotherapy sessions. A short half-life reduces the risk of opioid toxicity, which is especially important in the frail elderly population.

Alongside assessing the efficacy of these analgesic methods, this study may provide further insight into barriers for early mobilization in this patient cohort. Leal et al[14] conducted a scoping review to elucidate the factors which affect early mobilization after hip fracture surgery; they highlighted that patients who were admitted towards the end of the week were more likely to suffer from inequalities in physiotherapy assessment and orthogeriatric assessment over the weekend. This study will assess if such inequalities are present at this centre and, if so, will determine the impact of such inequalities.

There are limitations to this study. The size of the proposed cohorts is a limiting factor when assessing analgesia efficacy. However, after careful consideration of the financial implications, it is not possible to assess a larger cohort without significant financial cost. Similarly, this study hypothesis would benefit from a randomized controlled trial. However, the study would then fall into the Clinical Trial of an Investigational Medicinal Product (CTIMP) category. Due to costs associated with such a study, the authors considered this impractical without pilot data assessing the potential benefits. There is also a short follow-up of only 30 days. However, this is comparable to other studies in the literature which have assessed outcomes in early versus delayed mobilization [21–23,49]. The aims of this study are to assess the efficacy of oral oxycodone and subcutaneous alfentanil. Given that the clinical team (rather than the researchers) assesses who receives which medications, in line with daily practice, there could be some unintentional selection bias regarding who receives which medication. This will be assessed and reported on during the study.

Furthermore, another limitation is that patients with incapacity to consent are not included in this study. Though this patient population comprise a small proportion of patients with hip fractures, the researchers believe the burden of this study on such vulnerable patients would not be in their best interest. Furthermore, patients with cognitive impairment usually have poorer compliance with physiotherapy. Therefore, the researchers did not want to skew the data with their inclusion.

Supplementary material

Consent form, physiotherapy forms, and patient information leaflet.

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Data sharing

The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

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