Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

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The intraoperative effect of ketamine and magnesium sulphate on patients undergoing total knee arthroplasty in spinal anaesthesia

Master's thesis in Clinical Nursing
Supervisor: Strand, Linn Beate
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Sammendrag

Bakgrunn

I 2020 ble en kombinasjon av ketamin og magnesiumsulfat inkludert i fast-track regimet for kneproteseoperasjoner ved St. Olavs Hospital, Trondheim Universitetssykehus. Hensikten med denne studien var å undersøke den intraoperative effekten av ketamin og magnesiumsulfat på mengde propofol administrert og hemodynamisk stabilitet.

Metode

En ikke-randomisert klinisk studie med 249 pasienter som gjennomgikk kneprotesekirurgi i spinalbedøvelse. Pasienter operert i 2020 dannet intervensjonsgruppen, og fikk en intraoperativ infusjon med ketamin og magnesiumsulfat. Forholdet mellom infusjonen og administrert mengde propofol og hemodynamikk ble analysert ved hjelp av lineær- og logistisk regresjon.

Resultat

Det var ingen sammenheng mellom ketamin og magnesium og mengde propofol administrert intraoperativt (B 10.074, 95% CI -99.216-119.365, p=0.856). Risikoen for systolisk hypotensjon var 48% lavere i intervensjonsgruppen (OR 0.52, 95% CI 0.288-0.940, p=0,03) sammenlignet med kontrollgruppen. Risikoen for lavere MAP var også redusert, men dette funnet var ikke-signifikant (OR 0.711, 95% CI 0.378-1.336, p=0.289), muligens på grunn av mangel på styrke. Det var ingen sammenheng mellom ketamin og magnesium og bruk av pressor (OR 0.981, 95% CI 0.544-1.770, p=0.95). Det var 35% lavere risiko for en eller flere episoder med bradykardi, men resultatet nådde ikke statistisk signifikans (OR 0.655, 95% CI 0.265-1.617, p=0.359).

Konklusjon

Den intraoperative infusjonen med ketamin og magnesium ser ut til å bidra til bedre hemodynamisk stabilitet blant pasientene som gjennomgår kneprotesekirurgi i spinalbedøvelse.

Abstract

Background

In 2020 a combination of ketamine and magnesium was added to the fast-track regime for patients undergoing total knee arthroplasty (TKA) at St. Olavs Hospital, Trondheim University Hospital. The aim of this study was to investigate the intraoperative effect on the amount of propofol administered and hemodynamic stability.

Methods

A non-randomized clinical study including 249 patients undergoing total knee arthroplasty in spinal anaesthesia. The intervention group received an intraoperative infusion of ketamine and magnesium sulphate. The relationship between the infusion and amount of propofol administered and hemodynamics was analysed by linear and logistic regression.

Results

There was no association between the use of ketamine and magnesium sulphate on the amount of propofol administered intraoperatively (B 10.074, 95% CI -99.216-119.365, p=0.856). Patients receiving ketamine and magnesium sulphate had 48% lower risk of systolic hypotension (OR 0.520, 95% CI 0.288-0.94, p=0.03) compared to the control group. There was also a trend towards fewer episodes of low mean arterial pressure (OR 0.711, 95% CI 0.378-1.336, p=0.289), although not statistically significant, possibly due to lack of power. There was no association between ketamine and magnesium and the use of vasopressors (OR 0.981, 95% CI 0.544-1.770, p=0.95). There was a 35% decrease in risk of episodes of bradycardia, neither statistically significant (OR 0.655, 95% CI 0.265-1.617, p=0.359).

Conclusion

The combination of ketamine and magnesium sulphate seems to contribute to better hemodynamic stability among patients undergoing total knee arthroplasty in spinal anaesthesia.

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PART TWO - THE ARTICLE

1. Introduction

Total joint arthroplasty has become one of the most performed surgical procedures in the world (1,2). In 2019 and 2020 there were approximately 418 patients who within a fast-track-regime underwent total knee arthroplasty (TKA) at St. Olavs Hospital, Trondheim University Hospital (Appendix 1, Figure 1). TKA is often the last resort for patients with osteoarthritis or rheumatoid arthritis and is done as an attempt to alleviate pain and improve quality of life (3). Despite the fact that many patients experience improvement long term, the surgery is associated with a moderate risk for complications and moderate to severe postoperative pain (1,3–5).

The last few years all the patients undergoing TKA at St. Olavs Hospital, Trondheim University Hospital have been enrolled in a fast-track regime. It is a standardised and well-prepared patient course that includes a precise management of the whole perioperative period. This includes, such as, patient information at the outpatient clinic, multimodal pain control, focus on minimising bleeding and surgery time and early mobilisation (4). Spinal anaesthesia is commonly preferred for TKA patients and is the standard anaesthetic for the fast-track patients (1).

At the start of 2020 an intraoperative administration of an intravenous infusion of ketamine and magnesium was added to the fast-track regime with the goal of minimising postoperative pain. Since the combination is administered during surgery it is reasonable to investigate the intraoperative effects.

1.1 Spinal anaesthesia

The choice of anaesthesia for the patients undergoing TKA may influence the intraoperative and postoperative phase (1). The international consensus for the recommendation is weak, but since there are few contraindications, spinal anaesthesia is preferred (1). It reduces surgical stress response and blood loss due to decrease in central venous pressure while it reduces postoperative pain and opioid consumption (1,6). Although spinal anaesthesia is beneficial for TKA surgeries, it is associated with several side effects.

1.1.1 Spinal anaesthesia induced hypotension and bradycardia

The most common side effects of spinal anaesthesia is hypotension and bradycardia. Studies suggest a definition of hypotension as a decrease of 20% from baseline measurements (7,8). Hypotension occurs in 10-40% of all patients receiving spinal anaesthesia, and the older the age the greater the likelihood. Hypotension is a direct consequence of the sympathetic blockade leading to arterial and arteriolar vasodilation causing a decrease in systemic vascular resistance and pooling of blood in the lower regions (6,9). After placing spinal anaesthesia 20% of the patients experience nausea and vomiting, which can be interpreted as a warning sign for hypotension (6).

Bradycardia can be defined by a heart rate (HR) lower than 45 beats/min (6,7,9). Approximately 13% of patients experience spinal anaesthesia induced bradycardia as a result of a sympathovagal imbalance in favour of the parasympathetic (9). If spinal anaesthesia induced bradycardia occurs, it must be considered a sign of forthcoming hemodynamic collapse (9).

If there is a need for pharmacological interventions for treating hypotension, vasopressors such as ephedrine and phenylephrine are the best options. If the patient is both hypotensive and bradycardic ephedrine will have both a vasoconstrictive and chronotropic effect while phenylephrine increases peripheral vascular resistance (6,9). When administering phenylephrine reflex bradycardia may occur when increasing the blood pressure (BP) (6,9). Atropine is an effective anticholinergic drug for treatment of vagal stimulation and bradycardia (8,10,11).

1.2 Propofol as a sedative agent

TKA patients often want sedatives during the intraoperative phase, and propofol is often the drug of choice. Propofol is a commonly used and a well-suited agent with early onset and short half-life, and therefore a controllable agent to administer when sedating patients (6,7,12). Some patients receive Midazolam in addition. Despite several positive effects, there are several challenging side effects in case of overdosage. Administration of propofol leads to reduction in systemic vascular resistance, cardiac contractility and preload which further leads to hypotension and bradycardia. Additionally, respiratory depression may occur (7,12–15). Spinal anaesthesia induced hypotension can increase when simultaneously administering sedatives (9).

1.3 Ketamine

Ketamine is known as a dissociative agent with an analgesic effect in subanaesthetic doses (12,14,15). It is short acting, and unlike propofol it maintains the airway reflexes and ensures cardiovascular stability (16). Ketamine increases the heart rate, arterial blood pressure and cardiac outflow (13). It induces release of catecholamines which increases

vascular tone which again decreases blood pressure variability (17). Ketamine works on the N-methyl-D-aspartate-receptor (NMDA) which is located in the cell membrane of neurons and plays an important part when it comes to central sensation. Ketamine can decrease postoperative pain and postoperative opioid consumption (18). The downside of ketamine is side effects such as hallucinations, agitation and nausea (12,14,15).

1.4 Magnesium sulphate

Magnesium is a non-competitive agonist of NMDA-receptor. It works by preventing calcium influx into cells and therefore preventing transmission of pain impulses which further improves perioperative and postoperative analgesia (19). The prevention of calcium influx also has a direct effect on depolarization and repolarization of the heart as well as blocking the release of catecholamines and stress response to surgery (19,20). Ketamine and magnesium both work on the NMDA-receptors and are proven to have antinociceptive effects with the potential to treat and prevent pain (8,10,21). Nausea, shivering and flushing are reported side effects of magnesium (8,19).

1.5 Previous research

When sedating patients, the goal is great patient satisfaction while securing the airways and respiration, keeping a stable BP and HR, and minimising side effects (16). Earlier studies show that combining propofol, ketamine and magnesium can have favourable effects during surgery. Atashkhoyi et al. (14) and Tuncali et al. (16) found that combining propofol and ketamine led to a decrease in the amount of propofol administered in the ketamine group compared to the control group as well as it led to a deeper sedation (12,15). In studies of Sanatkar et al. (15) and Tuncali et al. (16) none of the patients receiving ketamine

experienced hallucinations, but in a study of Fligou (12) both hallucinations and nausea were observed side effects.

Studies suggest that magnesium can have an additive effect and lower the requirement of propofol (20,21). Shah & Dhengle (10) investigated the effect of magnesium sulphate, but did however not find a significant difference in the amount of sedation given (10). A previous study found that only 3 out of 108 patients experienced flushing, while another study found no side effects when administering magnesium (10).

Both spinal anaesthesia and propofol may be a potential source for hypotension and bradycardia (6,7,9,12,14,15). By using ketamine in addition to propofol you can counteract the cardio depressive effects of propofol and spinal anaesthesia, making the patients seem more stable during surgery (12,13). Studies also show that patients receiving ketamine need less vasopressors (13). Regarding the effect of magnesium on hemodynamics, studies report differently. When adding magnesium, studies present no significant difference in hemodynamic variables compared to control groups (8,10,21). However, Forget & Cata (17) found in their meta-analysis that both ketamine and magnesium reduced hemodynamic variability during surgery. Ketamine gave blood pressure stability while magnesium provided stability in heart rate. Atashkhoyi et al. (14) found a decrease in MAP of 7% in the ketamine group compared to 37% in the control group. Mortero et al. (22) did not find a difference in mean BP or HR between patients that got both ketamine and propofol (22). The results from previous studies differ, however, the tendency is less hemodynamic changes in patients receiving ketamine and magnesium, compared to patients that do not (7,15,17).

1.7 The aim of the study and research question

The aim of the study was to investigate the impact of adding an intraoperative infusion of ketamine and magnesium in TKA patients receiving spinal anaesthesia. Based on previous studies we hypothesised that patients that received ketamine and magnesium required a lower amount of propofol intraoperatively and displayed a more stable hemodynamic with less need for vasopressors.

Research questions:

1. Do patients that receive the combination of ketamine and magnesium need less propofol intraoperative compared to patients not receiving this combination?
2. Is there a difference in intraoperative hemodynamic stability between patients receiving ketamine and magnesium and patients who do not?

2. Method

2.1 Study design

This study is a non-randomized clinical study of an already implemented practice at St. Olavs Hospital, Trondheim University Hospital. It is structured the same way as a randomised control study, but due to the use of historical controls; without the randomization. The intervention group is compared to a control group who got another treatment earlier on (23).

2.2 Participants

The sample in this study is based on all patients who underwent TKA in the period 1. January 2019 to 31. December 2020. They were divided in a control group (surgery performed between 1. January 2019 and 31. December 2019) and in an intervention group (surgery performed between 1. January 2020 and 31. December 2020). The sample size was decided by how many patients who met the criteria of inclusion and exclusion.

2.2.1 Inclusion and exclusion criteria

Inclusion was based on the criteria for the fast-track regime at St. Olavs Hospital, Trondheim University Hospital (Appendix 1). This included patients between the age of 18-80 years with American Society of Anesthesiologists (ASA) physical classification I-III, who underwent TKA in spinal anaesthesia. The ASA-classification system is a tool to help predict operative risk, based on a patient's previous medical history and functional ability (24).

It was a requirement that all patients had received the same standard premedication consisting of paracetamol 1.5/2 grams (g), dexamethasone 16/20 milligrams (mg), tapentadol 50 mg and Vimovo (esomeprazole 20 mg/naproxen 500 mg). In addition, all included patients in the intervention group must have received the intraoperative infusion of ketamine and magnesium. The selection process is shown in detail in Figure 1 and Figure 2.

Figure 1. Flow chart of the selection process

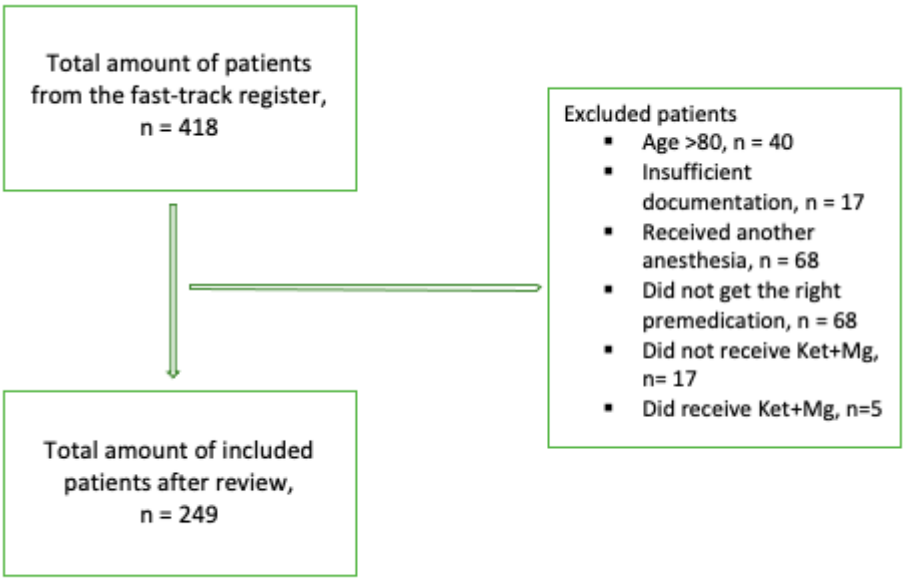
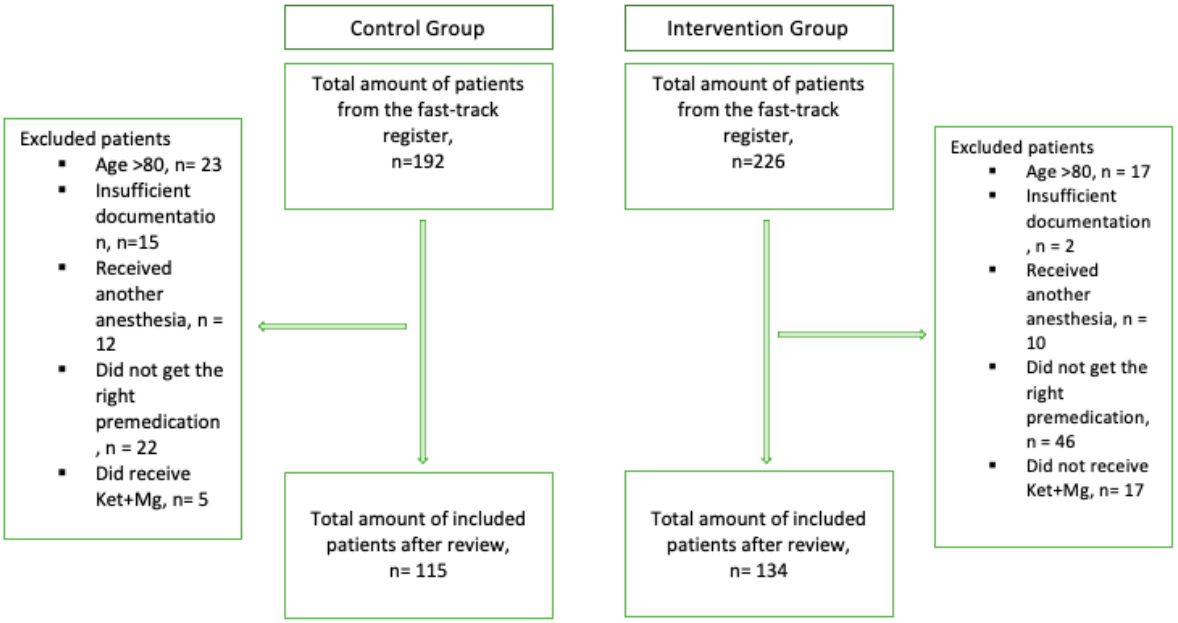


Figure 2. Flow chart of the selection process, in groups



2.3 Exposure

The patients in the intervention group were exposed to an intraoperative infusion of ketamine and magnesium. The dose ratio was ketamine 10 mg and magnesium sulphate 10 mmol (2460mg) diluted in sodium chloride 0.9% 100 millilitres.

Preparations of the TKA patients within the fast-track regime were done outside of the operating room. The patients in both groups were monitored with a three-lead electrocardiogram, pulse oximeter and non-invasive or invasive BP decided by ASA-classification and underlying diseases. If possible, the spinal anaesthesia was placed in a lateral position. The ketamine and magnesium infusion was administered after entering the operating room, continued throughout the surgery and terminated before leaving the operating room.

2.4 Outcomes

If the patients wished for sedation during surgery, propofol was administered as either a bolus or as target controlled infusion. The total amount of propofol was measured in milligrams (mg). Only the amount given in the operating room, the same period as the infusion of ketamine and magnesium, was included in our study.

Hemodynamic stability was measured in BP, HR and use of vasopressors. The first measured BP was registered as baseline systolic BP and baseline mean arterial pressure (MAP). The same goes for HR. BP and HR were measured with frequencies based on the condition of the patient, however, all the measurements were extracted. A decrease of 20% in mean BP from baseline BP was defined as hypotension SBP and hypotension MAP. Bradycardia was

defined as a HR <45 beats/min. The need for vasopressors was recorded as a dichotomous variable, depending on whether or not ephedrine and/or phenylephrine was in use.

2.5 Data collection

The Orthopaedic Science Centre contributed a list of all TKA patients operated in 2019 and 2020 from the quality register at St. Olavs Hospital, Trondheim University Hospital. The data was collected by nurses and physiotherapists and arranged for science purposes. Either of the mentioned is not responsible for the analysis or the interpretation of data in this study (Appendix 2).

The selection process required entering the patient's medical record, and controlling the patient's charts, their anaesthesia journal from the day of surgery, and the journal from the post-anaesthetic care unit. All patients were controlled twice according to the exclusion criteria, and if in doubt the patients were controlled a third time by both authors.

After exclusion the patient data was extracted from Picis, the Patient Surgery Management Software, which is the software in use for intraoperative and postoperative documentation. The extracted information was demographic data, time of surgery, time of anaesthesia, BP and HR measurements, use of tourniquet, intraoperative notes, comments on progress or problems during the anaesthesia and the total quantity of all medications given in the intraoperative period.

After all necessary data was collected in an Excel-file there was detected random errors in the extracted demographics, such as wrong sex and several missing values regarding

ASA-classification, height and weight. All the included patients were reviewed one more time and the missing values were collected manually from the anaesthesia records, the surgery planner or in the patients' charts.

2.6 Data analysis

Visual inspection of both histograms and q-q plots as well as the Kolomogorov-Smirnov tests of normality was used to determine whether the data were normally distributed or skewed. The normally distributed continuous variables were analysed with an Independent-Samples T-test, while the skewed data were analysed using the Independent-Samples Mann-Whitney U test. Categorical variables were analysed with the Pearson Chi-Square test or Fisher's Exact Test if expected count less than 5.

The amount of propofol is presented as a continuous variable and analysed with multiple linear regression to adjust for confounding factors such as age, sex, BMI, duration of surgery, ASA-classification and use of tourniquet. Scatterplot, histogram and normal P-P plot were controlled and the assumptions of normal distribution and independent residuals were fulfilled. Results are presented as beta-coefficient and 95% confidence interval (CI).

Logistic regression was used for analysing the association between the addition of ketamine and magnesium, and the categorical variables. Potential confounders adjusted for was age, sex, BMI, ASA-classification, use of tourniquet, atropine and vasopressors. Results are presented as odds ratios (OR) and 95% CIs. In line with standards in research, a *p*-value of less than 0.05 was considered statistically significant (25). Data were analysed by using IBM SPSS Statistics Version 27.

2.7 Ethical considerations

The ethical considerations in this study are based on the general guidelines and the four principles; respect, good consequences, justice and integrity, made by The National Committee of Research Ethics (26). Since this is medical research including human subjects, the principles from The Declaration of Helsinki developed by the World Medical Association are followed (27).

The study was approved by the Regional committee for Medical and Health Research Ethics, Central Norway (REK), approval reference ID 427044 at 05.04.2022 (Appendix 3). Subject to approval from REK, the study was also approved by the Orthopaedic Science Centre at Trondheim University Hospital at 04.07.2022 (Appendix 2).

A Data Protection Impact Assessment was formed by the project initiator before data collection. The data was handled after the guidelines “Collection of Personal data for research projects” from the Norwegian University of Science and Technology (NTNU)(28). The data was treated confidentially according to the health personnel act chapter 5, the duty of confidentiality and the right of disclosure (29). The data was stored securely in the hospitals database where only the authors and the project initiator were granted access. All data taken out of the secure database was encrypted and anonymised.

All patients received a brochure before surgery, informing that the department wished to collect their data into the quality register, and that data could be used for research. Participating was voluntary, and the consent could be withdrawn at any time. Information was repeated orally before surgery and the patient signed a consent form (Appendix 4).

It was assumed that this study would not inflict any inconvenience to the patients included. All data was collected in the aftermath. There was not predicted to be any great risks or burden to the patients by administering the infusion of ketamine and magnesium. The potential benefits were assessed to outweigh eventual risks. The control group was not subject to additional risk or harm as a result of not receiving the combination.

Due to the researcher's duty to make the results of research on human subjects accessible to the public, this study will be made publicly available no matter the results (27). The authors declare no conflicts of interest.

3. Results

3.1 Descriptive statistics

A total of 418 patients were reviewed for inclusion, and 249 patients were included. The intervention group consisted of 134 patients and the control group of 115 patients (Figure 1, 2). The demographic and descriptive data are presented in table 1. Continuous variables are presented as mean and standard deviation (SD), and categorical variables are presented as percentages (%) and proportions. Except for the duration of anaesthesia (178.69 ± 22.17 vs 173.22 ± 22.98), and the number of patients who received atropine (1.7% vs 1.5%), all patient characteristics were comparable across the two groups (Table 1).

Table 1. Demographic data

		Control group (2019) (*n*=115)	**Intervention group (2020) (*n*=134)**	
Continuous variables		**Mean ± SD**	**Mean ± SD**	***p*-value**
Age (years)		67.27 ± 8.74	65.10 ± 9.39	0.060
BMI (kg/m2)		29.28 ± 5.37	29.62 ± 4.56	0.472
Duration of anaesthesia (min)		178.69 ± 22.17	173.22 ± 22.98	0.026
Duration of surgery (min)		85.95 ± 18.52	85.77 ± 22.84	0.428
Baseline SBP (mmHg)		140.83 ± 22.62	135.87 ± 21.74	0.064
Baseline MAP (mmHg)		94.56 ± 14.85	93.83 ± 16.82	0.718
Mean SBP (mmHg)		119.76 ± 15.28	119.13 ± 12.82	0.713
Mean MAP (mmHg)		82.93 ± 7.96	84.13 ± 7.96	0.237
Baseline HR (beats/min)		72.49 ± 12.18	72.07 ± 13.0	0.682
Mean HR (beats/min)		68.43 ± 9.84	70.44 ± 10.06	0.114
Categorical variables		***n* (%)**	***n* (%)**	***p*-value**
Sex	Female Male	68 (59.1%) 47 (40.9%)	90 (67.2%) 44 (32.8%)	0.189
ASA	I 2 3	11 (9.6%) 84 (73.0%) 20 (17.4%)	26 (19.4%) 89 (66.4%) 19 (14.2%)	0.089
Tourniquet	Yes	63 (54.8%)	86 (64.2%)	0.132
Atropine	Yes	2 (1.7%)	2 (1.5%)	0.024
Midazolam	Yes	3 (2.6%)	6 (4.5%)	0.512
Nausea intraoperative	Yes	4 (3.5%)	12 (9.0%)	0.079
Nausea postoperative	Yes	0 (0%)	2 (1.5%)	0.188
Hallucinations	Yes	1 (0.9%)	0 (0%)	0.279

Data is presented as mean (SD) or n (%), and *p* value.
BMI = Body Mass Index
SBP = Systolic blood pressure
MAP = Mean arterial pressure
HR = Heart rate
ASA = American Society of Anesthesiologist

3.2 The amount of propofol administered

There was no association between the addition of ketamine and magnesium sulphate and the amount of propofol administered (B 10.074, 95% CI -99.216-119.365, *p*=0.856) (Table 2).

3.3 Hemodynamic stability

Patients receiving ketamine and magnesium sulphate had a 48% statistically significant (*p*=0.03) lower risk of hypotension in SBP during surgery (OR 0.520, 95% CI 0.288-0.940) compared to those not receiving this combination (Table 2).

There was a trend towards lower risk of a decrease in MAP in the intervention group (OR 0.711, 95% CI 0.378-1.336, *p*=0.289) compared to the control group (Table 2). The finding was not statistically significant, possibly due to lack of power. For bradycardia, the patients in the intervention group had a statistical non-significant 35% less risk of one or more incidences compared to the control group (OR 0.655, 95% CI 0.265-1.617, *p*=0.359) (Table 2). There was neither any association between the intervention and whether the patients received vasopressors intraoperatively (OR 0.981, 95% CI 0.544-1.770, *p*=0.95) (Table 2).

Table 2. Linear regression of propofol and logistic regression of hemodynamics

	Model 1			Model 2		
	B	**95% CI**	***p*-value**	**B**	**95% CI**	***p*-value**
Propofol	19.244	-88.838-127.325	0.726	10.074	-99.216-119.365	0.856
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Hypotension SBP	0.521	0.293-0.929	0.027	0.520	0.288-0.940	0.03
Hypotension MAP	0.708	0.382-1.314	0.274	0.711	0.378-1.336	0.289
Vasopressors	1.019	0.582-1.786	0.946	0.981	0.544-1.770	0.950
Bradycardia	0.590	0.248-1.403	0.233	0.655	0.265-1.617	0.359

Model 1: adjusted for age, sex.
Model 2: Propofol adjusted for age, sex, ASA, BMI, use of tourniquet, duration of surgery, midazolam.
Hypotension/Bradycardia adjusted for age, sex, ASA, BMI, use of tourniquet, vasopressor, atropine, duration of anaesthesia.
Vasopressors adjusted for age, sex, ASA, BMI, use of tourniquet, atropine, duration of anaesthesia
Hypotension SBT = Mean systolic blood pressure decrease with >20% from baseline
Hypotension MAP = Mean of mean arterial pressure decrease with >20% from baseline
Vasopressors = Ephedrine and Phenylephrine
Bradycardia = Heart rate <45 beats/min

4. Discussion

4.1 Key findings

This study compared TKA patients who received an infusion of ketamine and magnesium sulphate to a control group. There was a lower risk of hypotension SBP in the intervention group compared to the control group resulting in a more stable hemodynamic. Despite this, there was no difference in the number of patients receiving vasopressors. There was not a statistically significant lower risk for one or more incidences of bradycardia among patients

in the intervention group than in the control group, and no association between ketamine and magnesium sulphate and the amount of propofol administered intraoperatively.

4.2 Comparison with previous studies

4.2.1 The combination of ketamine and magnesium on propofol amount

Our result regarding propofol contradicts findings from previous studies. There are few studies that compare the effect of both ketamine and magnesium together with propofol; the majority of the studies investigates the effect of only ketamine. Studies on patients in spinal anaesthesia are lacking as well. Contrary to our study, previous research from Iran and Belgium, found a significant reduction in the amount of propofol administered when simultaneously administering ketamine, compared to not adding ketamine (14,16). There are, however, two important differences that must be considered when comparing our research to the mentioned studies. One of the studies investigated only women in general anaesthesia, with a lower age average (32.7 ± 3.4 and 34.3 ± 5.4) and ASA-classification (I-II) (14). While the other study showed a great difference in duration of surgery with only 13 minutes (13.8 ± 5.2 and 13.4 ± 4.7) in comparison to 86 minutes (85.95 ± 18.52 and 85.77 ± 22.84) in our study (16). The addition of magnesium has in studies from Egypt and Turkey been shown to reduce the needs of propofol during general anaesthesia compared to a control group not receiving magnesium (20,21). Choice of anaesthesia may result in rather different doses of propofol, due to the importance of deep enough anaesthesia, and respiratory depression is an expected and manageable consequence in general anaesthesia (14,20,21). This compared to our study where propofol was given until patient satisfaction or adjusted after clinical effect. Another effect not considered in our study, is the effect on respiration which can be decisive for whether a patient can tolerate a deeper sedation or not. The levels of SpO2 have been shown to be higher among patients who received ketamine in addition to propofol, compared

to those only receiving propofol. A possible explanation might be ketamine's ability to ensure airway reflexes (16). This can have important implications for the administration of propofol in our study.

4.2.2 The combination of ketamine and magnesium on hemodynamic stability

The tendency of lower risk of episodes of hypotension is supported by previous research. A meta-analysis published in Belgium, investigated the hemodynamic effect of both ketamine versus placebo and magnesium versus placebo (17). Ketamine significantly reduced blood pressure variability without any significant effect on heart rate. Magnesium did not contribute with a significant effect on blood pressure variability, but it significantly reduced variability of heart rate (17). Even though the meta-analysis contains several RCTs and a sufficient sample size the authors question the study´s clinical relevance due to a modest magnitude of the effect (17). As previously mentioned, not many studies have investigated the combined effect of ketamine and magnesium and especially not on patients in spinal anaesthesia. Studies from respectively Turkey and Iran, investigated the effect of ketamine on propofol during different surgeries, and found a lower decrease of SBP and MAP in the ketamine group compared to the control group (7,15,16). However, in a study from Saudi Arabia they did not find a difference in MAP between the groups, but the sample size was small with only 27 patients, which may have caused a lack of statistical power (12). The definition of hypotension varies. A 20% decrease from baseline is most used, but some studies operate with a 30% decrease or SBP <80 mmHg or <90 mmHg (7–10,13,15,16,19). This can presumably lead to a mismatch in relation to when hypotension is detected. Hypotension can contribute to increased morbidity and mortality. Using a 20% decrease as definition instead of 30% may be beneficial for a better patient outcome (9).

Even though the patients in the mentioned studies are being sedated with propofol, it is important to highlight that the patients in our study are affected by the physiological changes due to spinal anaesthesia as well. The physiological effects of spinal anaesthesia can draw parallels to the effect of propofol based general anaesthesia, which can lead to both hypotension and bradycardia (7,12–15). Studies on the effect of adding ketamine to propofol induced anaesthesia has shown an increase of hemodynamic parameters, meaning higher mean SBP compared to the control groups (14,20). The mean age was lower than in our study, and as the likelihood of hypotension increases with age, it is reasonable to think that younger patients compensate better and maintain their blood pressure better than the older and somewhat more frail patients (14,20). Despite the differences in patient characteristics, the results are in line with the tendencies in our study. However, unlike our study, a study from Turkey additionally found a lower need for vasopressors in the group who received ketamine compared to those who did not (13).

Studies from India, Korea and Egypt investigating the hemodynamic effect of magnesium on patients in spinal anaesthesia, did not present significant results (8,10,19). One of these studies was conducted with patients undergoing total hip replacement and is probably the surgery most similar to ours. However, the demographics are different, with younger patients and lower ASA-classification (8). In another study we did not only see these demographic differences, but in addition, the surgeries varied, and they defined hypotension differently (10). This might influence the results, and the studies will not be completely comparable to ours. Neither when investigating patients in general anaesthesia it was demonstrated any hemodynamic effects of only magnesium (21). Since several previous studies of magnesium

report no effect on hemodynamic stability, it may be discussed whether the findings in our study is associated with magnesium, or in fact ketamine (8,10,19,21).

In our study bradycardia was defined as a HR <45 beats/min, as most frequently used in previous research (7,8,13). However, definitions of <40 beats/min, <50 beats/min and <55 beats/min are also presented (10,16,20). Our results regarding bradycardia were non-significant, and results from previous research differ. Several studies presented a higher HR in groups that received ketamine, compared to those who did not, while other studies demonstrated no significant difference (7,10,12–14,16,21). Here as well, different definitions can contribute to the results being difficult to compare and incidences of bradycardia not being detected.

When reviewing previous research, the results vary and the fact that studies originate from different countries and different health care systems may be an important factor. However, the trend represents a greater hemodynamic effect of ketamine than magnesium. If seeing it against our study the hemodynamic effect of both ketamine and magnesium might have something to do with the synergistic effect due to the competitive blocking actions on the NMDA-receptor and could be complementary to stable hemodynamics (17).

4.3 Methodological strengths and limitations

4.3.1 Methodological strengths

Using historical controls gave the ability to conduct the research with a large sample size without having to recruit the patients. The efficacy of this method was advantageous, and it ensured that all patients received all available treatment at that given time. Patients were not

deprived of any treatment that could have improved patient outcomes. The benefits of investigating patients enrolled in the fast-track regime is the fact that even though the study is non-randomized, the procedures are the same regardless.

4.3.2 Internal and external validity

This non-randomised clinical study of already conducted practice, used historical controls and data that already was assembled. Therefore, there was no possibility to influence which data that was collected and how. Even though there are not proven big differences between the groups there might be some consequences of this study being non-randomised. When participants are not randomly allocated into groups one risks a skewed distribution of external factors that might influence the outcome. This may result in unequal groups and have significance for the study's internal validity. Even though the study is based on a standardised fast-track regime that minimises the risk of confounders, there is still a risk for residual confounding. Some factors were difficult to adjust for, such as infusion rate of ketamine and magnesium, invasive versus non-invasive BP measurement, no existing guideline for when to administer vasopressors, not taking the respiratory effects into account and whether propofol was administered as boluses or an infusion. We did, however, adjust for several important confounding factors that may have influenced the association between the exposure and the outcome (Table 2).

Despite a relatively large sample size, we did not have enough power to detect a statistically significant lower risk of low MAP or bradycardia (Table 2). When experiencing such results, one must be aware of Type-II-errors which means not rejecting the null-hypothesis, when in fact it is false. Despite a non-significant difference, the difference might still exist. This can be important for the study's external validity. Seeing our non-significant decrease of risk of

low MAP in the intervention group, in context with the risk of low SBP, the trend is similar and due to the considerable effect size, it may still provide clinical significance. Regarding the risk of bradycardia, the 95% CI just crosses the null. But again, due to the large effect size and the 95% CI mainly consisting of values showing lower risks, these results could still be useful when considering magnesium and ketamine in the clinic. Future studies should be undertaken on larger samples to ensure enough statistical power to detect the difference between the intervention group and the control group.

4.3.3 Generalizability

This study consists of a large number of the TKA patients in spinal anaesthesia at St. Olavs Hospital, Trondheim University Hospital over a two-year period. Therefore, the generalisability of the study is likely to be high. Nevertheless, it is important to note that the health care system in Norway is different compared to other countries and the findings can not necessarily be generalised across countries with different healthcare systems.

4.4 Implications for clinical practice

Based on our results there is indication to continue the intraoperative administration of ketamine and magnesium as it can contribute to avoiding hypotension.

There is a lack of studies on the synergetic effect of ketamine and magnesium, especially in patients receiving spinal anaesthesia and sedation. We believe this study to be the first to investigate these elements in TKA patients and consider it a useful contribution to the professional field. Results from our study may be beneficial for treatment of patients as well as further investigations.

5. Conclusion

The combination of ketamine and magnesium sulphate can contribute to increased hemodynamic stability in patients undergoing total knee arthroplasty in spinal anaesthesia.

Future studies should aim to randomise the participants by doing an RCT, to better account for potential confounders. Although prior studies have investigated the effect on respiration of ketamine and magnesium separately, the synergetic effect on respiratory aspects of TKA patients in spinal anaesthesia is not yet examined. Furthermore, future studies should consider increasing the doses of ketamine and magnesium sulphate, as the tendency from prior studies shows higher doses than in our study.

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8. Appendices

Appendix 1. Total knee arthroplasty, fast-track regime

Fasttrack kneprotese – Ortopedi – Anestesi

Retningslinje for St Olavs Hospital, Anestesiavdelingen. Gjelder fra 14.05.2014 – utgår 14.05.2019.

Forfatter: Overlege Shawn Davis

Hensikt/omfang

Retningslinjen skal sikre at pasienter som får anestesi ved Fasttrack kneproteser får sikker behandling og et godt postoperativt resultat. Retningslinjen gjelder pasienter som får anestesi ved Fasttrack kneproteser.

Retningslinjen er godkjent på medisinsk faglig grunnlag av avd.overlege Sigurd Fasting, Anestesiavdelingen.

Grunnlagsinformasjon

Kneprotese er aktuelt ved gonartrose, RA (revmatoid artritt), feilstilling.

Ved Fasttrack protesekirurgi er hovedmål en pasient som kan mobiliseres, dvs pasienter skal ut av sengen og stå på operert bena helst på overvåkningen.

Operasjonen gjøres med pasienten i ryggleie. Tilgang gjennom midtlinjesnitt, åpner leddet på medialsiden og lukserer patella lateralt. Evt. synovectomi og evt. subperiostal løsning for å rette ut feilstillinger i kneet før saging og tilpassing av tibia- og femurkomponenten. Når protesen er tilpasset, skylles kneleddet og protesen støpes fast i en seanse. Inngrepet gjøres i blodtomhet. Dette medfører minimal/ingen blødning peroperativt, men det kan blø betydelig v/oppslipping av blodtomheten og senere postoperativt. Forberedelse av pasienten, bedøvelse og leiring foregår vanligvis på innledningsrom.

Operasjonstid: 1,5-2 timer

Arbeidsbeskrivelse

Ansvar

Sykepleiere og leger v/anestesi og overvåking.

Fremgangsmåte

Preoperativt

- Pasienten tilsees av anestesilege på onsdag 1 uke før. De fleste pasienter er ASA I/II med god allmentilstand. ASA III som har optimalisert behandling av grunnsykdom kan også tas. Det må ikke være behov for avansert behandling som arteriekran, vasopressor, post-op respirator. Komplekse kroniske smertepasienter som LAR pasient skal unngås.
- Tromboseprofylakse og preoperativ antibiotika forordnes av ortoped etter gjeldende retningslinjer.
- Premedikasjon: Paracetamol 1.5/2 g, Dexametason 16/20 mg, Vimovo 1tabl og Palexia depot 50mg po gis rutinemessig etter gjeldende retningslinjer

såfremt det ikke foreligger **sterke** kontraindikasjoner. Benzodiazepiner gis ikke.
- Blod: Blod bestilles ikke på disse pasienter på forhånd
- Utstyr/monitorering: Minimum 2 gode innganger, O2 på nesekateter, EKG-monitorering, pulsoxymetri, non-invasiv BT-måling, Urinkateter.

Peroperativt
- Anestesimetode: Som hovedregel velges regionalanestesi. Spinal er førstevalget. Settes av erfaren anestesilege. Spinalbedøvelsen settes med pasienten liggende i sideleie med operasjonsside oppe. 2.5 ml Marcain (bupivacaine) 0.5% plain
- Ca 10 min før blodtomheten slippes opp gis Cyklokapron (fibrinolysehemmer)15 mg/kg såfremt det ikke foreligger kontraindikasjoner.
- Under lukning av kneet setter ortopeden Naropin (ropivacain) 0.2% (maks 100ml) intra/peri-articulært. Dette utgjør en viktig del av den postoperative smertebehandlingen.
- Beredskapsmedikamenter: Thiopenton, Atropin, Curacit, Fenylefrin, Efedrin, antiemetika.

Postoperativt
- Væske: Rest Ringer/NaCl/kolloid og Glucose 5%. Evt. ytterligere volumbehov og evt. behov for SAG vurderes i hvert enkelt tilfelle.
- Standard smertelindring: Paracet 1/1,5g x4 po, Vimovo 1tabl x2 po, Palexia Depot 50mg x2 po. Morfin iv. v/behov. Oxynorm 5 mg vb på sengepost.
    - Dette er smertebehandling som vil fungere utmerket for over 90% av pasienter. For pasienter som ikke kan få NSAIDS eller som har stor, uforventet smerte vil andre løsninger, som for eksempel nervblokkade, epidural, PCA pumpe eller andre opioider være indisert.
- Prøver: Hb-ktr. Evt. andre prøver vurderes i hvert enkelt tilfelle.

Dokumentasjon

Dokumentasjonskilder som er benyttet: Avdelingens praksis, Metodebok for ort. operasjonsavdeling, Miller (kap 61; Anesthesia for Orthopedic Surgery).

Appendix 2. Approval Orthopaedic Science Centre

Søknad om data/resultater fra kvalitetsregistrene

Det er mulig å søke om data eller resultater fra kvalitetsregistrene ved Ortopedisk forskningssenter ved å fylle ut følgende søknadsskjema og signere vilkår for bruk av data/resultater. Dette sendes pr. e-post til leder for kvalitetsregistrene ved Ortopedisk forskningssenter Universitetssykehuset i Trondheim. Søknaden vil bli vurdert av styringsgruppen for kvalitetsregistrene og tilbakemelding gitt pr. e-post til søker.

Søknadsskjema

Bestilling av data/resultater fra Kvalitetsregister for

☑ Leddproteser

☐ Pasienter med hoftebrudd

☐ Pasienter som gjennomgår underekstremitets-amputasjon

Jeg søker om ☑ data ☐ resultater

1. Kontaktinformasjon

1.1 Sted og dato	Trondheim 300322
1.2 Søkers navn	Torbjørn Rian
1.3 Stilling/akademisk grad	Overlege/phd sipendiat
1.4 Telefon/e-post	torbjorn.rian@ntnu.no

2. Prosjektinformasjon

2.1 Gi en kort beskrivelse av prosjektet:
(Dersom det søkes om utlevering av data vedlegges utfyllende prosjektbeskrivelse)

Se vedlagt prosjektbeskrivelse

3. Formål

3.1 Hva skal data/resultater brukes til? *(forskning, kvalitetssikring, presentasjon etc.)*

Forskning.
Evaluering av effekt av endret standard smertelindring

3.3 Hvor, når og hvem skal presentere resultatene?

Hvor: Peer-reviewed tidsskrift
Når: 2023
Hvem: Emilie Fremo Lefdal, Silje Emilie Antonsen, Torbjørn Rian

3.2 Dersom data skal brukes til forskning; er godkjenning fra REK innhentet?

(oppgi REK-nummer)

427044

4. Utlevering av data/resultater

4.1 Hvordan ønskes data utlevert? Begrunn
(Personidentifiserbar, avidentifisert, anonymisert)

Første fase: Personidentifiserbar
Oversikt over primære kneproteser i prosjektperioden må kontrolleres opp mot pasientjournal for å se om pasienten har fått standard smertebehandling eller ikke
Andre fase: Avidentifisert
Etter kontroll av inkluderbarhet kan data være avidentifisert

4.2 Hvilke data/resultater søkes det om? Dersom det søkes om resultater; hvordan ønskes de presentert? *(kjønn, operasjonstid, smerte/ gjennomsnitt, SD etc.)*

Data:
Primære totale kneproteser
Smertescore NRS, forbruk oxynorm, liggetid
Demografi: Kjønn, alder, ASA gruppe, vekt evt BMI

4.3 Hvilket tidsrom søkes det data fra?
(for eksempel smerte dag 1 og 2 i august eller komplikasjoner registrert på 1. etterkontroll i september)

Smerte dag 1 (trolig manglende data for smerte dag 2 grunnet kort liggetid).
Oxynormforbruk første døgn.

4.4 Hvilke pasienter søkes det om data/resultater fra?

Primære kneproteser

4.5 Hvordan og hvor skal dataene oppbevares? Spesifiser
(filområde hos hemit, datamaskin uten internettforbindelse etc.)

Filområde hos Hemit

4.6 Hvordan skal resultatene fremstilles? Spesifiser
(For eksempel primæroperasjoner vs. reoperasjoner)

Standard smertelindring 2019 vs standard smertelindring fra 01012020. Peroperativ bruk av magnesium og ketamin ble innført som standardbehandling fra 01012020.

4.6 Hvordan skal dataene håndteres etter prosjektslutt? Spesifiser
(Slettes, avidentifiseres, anonymiseres)

Oppbevaring er avindentifisert
Slettes etter 5 år (jfr REK godkjenning)

5. Resultater

5.1 Hvordan skal data/resultater presenteres *(artikkel, presentasjon etc.)*

To artikler planlegges, se vedlagte forskningsprotokoll

5.2 Hvordan vil Ortopedisk forskningssenter bli referert *(medforfatterskap, referanse etc.)*

Etter avtale

Avtale om bruk av data/resultater

Data blir lånt ut bare til personlig bruk, og kan ikke bli overført til andre.

Alle forskningsprosjekter må godkjennes/vurderes av Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK) før data kan utleveres. En forutsetning for bruk av data fra registeret er at følgende blir tatt med i forord, fotnote eller lignende i eventuelle publikasjoner;

> "(En del av) De data som er benyttet her er hentet fra kvalitetsregisteret, Ortopedisk forskningssenter ved Universitetssykehuset i Trondheim. Data ble samlet inn av sykepleiere/fysioterapeuter og tilrettelagt for forskningsformål ved Ortopedisk forskningssenter. Ingen av de ovennevnte er ansvarlige for analysen eller tolkningen av data som er gjort her:"

Videre skal Ortopedisk forskningssenter inviteres til medforfatterskap dersom data blir publisert i vitenskapelige tidsskrift. Medforfatter forplikter seg gjennom dette til å bidra i publikasjonsprosessen ihht gjeldende lover og regler.

En annen forutsetning for bruk av data er at Ortopedisk forskningssenter får tilsendt ett eksemplar av rapporter, artikler eller andre publikasjoner, dette for å sikre informasjon om Ortopedisk forskningssenter sine ulike brukere.

Data skal returneres til Ortopedisk forskningssenter etter bruk.

Med vennlig hilsen

Ortopedisk forskningssenter

Universitetssykehuset i Trondheim

Jeg har lest og aksepterer forutsetningene for bruk av data/resultater fra Ortopedisk forskningssenter

30032022	Torbjørn Rian	*Godkjent 04.07.2022*
Sted, dato	Signatur	*Siri B Winther* *Leder kvalitetsregistre* *Ortopedisk forskningssenter* *St.Olavs hospital*

Appendix 3. Approval Regional Ethics Committee

REK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Hilde Eikemo	73597508	06.04.2022	427044

Linn Beate Strand

Prosjektsøknad: Effekten av magnesium og ketamin på postoperative smerter etter kneprotesekirurgi. En ikke-randomisert klinisk studie.
Søknadsnummer: 427044
Forskningsansvarlig institusjon: Norges teknisk-naturvitenskapelige universitet
Samarbeidende forskningsansvarlige institusjoner: St. Olavs Hospital HF

Prosjektsøknad: Endring godkjennes

Søkers beskrivelse

Smertelindring til kneprotesepaseinter er svært utfordrende og 80% av disse pasientene opplever moderate postoperative smerter. Det er derfor viktig å evaluere smertelindringsregimer hos denne pasientgruppen. Ved St. Olavs hospital følger de fleste kneprotesepasientene et standardisert pasientforløp (fast-track) som sikrer at pasientene får en sikker og effektiv behandling og et godt postoperativt resultat. Disse pasientene får spinalbedøvelse, samt en standard smertestillende pakke. Siden januar 2020 har det i tillegg blitt tatt i bruk en kombinasjon av magnesium og ketamin. Dette kombinasjonspreparatet har i denne sammenhengen blitt omtalt som St. Patricks Pain Package Regional. Hensikten med denne studien er å undersøke om St. Patricks Pain Package Regional har en postoperativ smertelindrende effekt etter kneproteseoperasjoner. Studien baserer seg på alle fast-track kneprotesepasienter som er tilgjengelig fra 1. januar 2019 til dags dato. Pasientene deles inn i en kontrollgruppe og en intervensjonsgruppe. Deltakerne i kontrollgruppen samles fra 1. januar 2019 til 1. november 2019. VI vil ved hjelp av statistiske analyser sammenligne disse to gruppene for å se om de som har fått St. Patricks Pain Package Regional har mindre postoperative smerter enn de som ikke fikk det.

Vi viser til søknad om prosjektendring mottatt 31.03.2022 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge (REK midt) på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Du har søkt om følgende endringer:

1) å endre sluttdato fra 31.01.2023 til 31.01.2025

2) endringer i protokoll

Deltakelse i studien er basert på et bredt samtykke. Endringene i protokoll er hovedsaklig presiseringer. Ingen av endringene påvirker vår tidligere vurdering av avgitt samtykke som dekkende for omsøkte bruk. Vi tar endringene til orientering uten innvendinger.

Vedtak

Godkjent

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Hilde Eikemo

Sekretariatsleder, ph.d.

REK midt

Kopi til:

Appendix 4. Consent form

Samtykkeerklæring

Til deg som skal opereres for leddprotese
Ortopedisk avdeling ved St. Olavs hospital ønsker å kunne bruke informasjonen vi får om deg i forbindelse med behandlingsforløpet til å i framtiden kunne forske på helsehjelp til pasienter med muskel- og skjelettlidelser. På denne måten kan vi undersøke hva som har betydning for resultatet av en slik operasjon, hvilken betydning behandlingen har i relasjon til trygde-, og sosialmedisinske forhold og i forhold til helseøkonomi.

Hvilke opplysninger registreres?
De opplysningene som registreres er informasjon om diagnose, sykehistorie, røntgenfunn og opplysninger knyttet til behandlingen, blant annet hvilken form for leddprotese du er operert for og resultatene fra undersøkelser i forbindelse med kontroller. Vi ønsker også at du gir tilbakemelding på hvor tilfreds du er med behandlingen vi har gitt. Denne tilfredshetsundersøkelsen er anonym og vil ikke være knyttet til deg i etterkant av behandlingen.

For spesielle forskningsprosjekter kan det være aktuelt å sammenstille informasjon vi nå samler inn med andre offentlige registre (se oversikt på baksiden av dette arket). Dersom du godtar at dine opplysninger kan brukes til forskning, samtykker du også til at du kan kontaktes på nytt utenom ordinær kontroll, eventuelt mange år fram i tid. De enkelte forskningsprosjektene og eventuelle koblinger til andre registre vil måtte vurderes av Personvernombudet, og om nødvendig, godkjennes av datatilsynet. Forskningsresultatene kan komme framtidlige pasienter til nytte og vil bli publisert i medisinske tidsskrifter i inn- og utland.

Hvordan samles opplysningene inn?
Opplysningene samles inn både før, under og etter operasjonen. Dette gjelder ulike spørreskjema samt opplysninger fra leger, fysioterapeuter og sykepleiere som behandler deg. Opplysninger fra undersøkelser i forbindelse med kontrollene etter operasjonen vil også bli registrert, og du vil bli bedt om å fylle ut de samme spørreskjemaene ved etterkontrollene som du gjorde før operasjonen.

Hvem kan få tilgang til opplysningene?
Det er kun de som har behandlet deg og de ansvarlige for kvalitetsregisteret for leddproteser ved St. Olavs hospital som får tilgang til dine personidentifiserbare opplysninger. Opplysningene behandles konfidensielt og de som har tilgang til dem har taushetsplikt.

Lagring av data og dine rettigheter
Opplysningene som er samlet inn fra ditt behandlingsforløp lagres elektronisk og oppbevares i et arkiv ved sykehuset på en trygg måte som ivaretar personvernet. De vil bli lagret i flere tiår framover. Det er frivillig om du vil tillate at de opplysningene som samles inn i forbindelse med behandlingsforløpet kan brukes til eventuelle forskningsformål, og du har alltid rett til å si nei. Selv om du har sagt ja, kan du på ethvert tidspunkt trekke ditt samtykke.

Med vennlig hilsen
Ortopedisk avdeling, St. Olavs Hospital

☐ Jeg samtykker til at opplysningene kan brukes til forskning på helsehjelp til pasienter med muskel- og skjelettlidelser.

Sted:_____ Dato:_____ Underskrift:_____

PART TWO - THE ARTICLE

The intraoperative effect of ketamine and magnesium sulphate on patients undergoing total knee arthroplasty in spinal anaesthesia

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2: Clinic of Anaesthesia and Intensive Care Medicine, St. Olavs hospital, Trondheim University Hospital, Norway.

The article is based on guidelines from the British Journal Of Anaesthesia (Appendix 1).

Abstract

Background

In 2020 ketamine and magnesium sulphate was added to the standardised regime for total knee arthroplasty (TKA) patients at St. Olavs Hospital, Trondheim University Hospital. The aim of the study was to assess the intraoperative effect of ketamine and magnesium on the amount of propofol administered and hemodynamic stability.

Methods

A non-randomised clinical study including 249 patients undergoing TKA in spinal anaesthesia. Patients operated in 2020 formed the intervention group, they received an intraoperative infusion of ketamine and magnesium sulphate. The relationship between this infusion and propofol and hemodynamic stability was explored with linear and logistic regression.

Results

There was no association between the use of ketamine and magnesium sulphate on the amount of propofol administered intraoperatively (B 10.074, 95% CI -99.216-119.365, *P*=0.856), neither in use of vasopressors (OR 0.981, 95% CI 0.544-1.770, *P*=0.95). Patients receiving the infusion had 48% lower risk of systolic hypotension (OR 0.520, 95% CI 0.288-0.940, *P*=0.03) compared to the control group. There was a trend towards lower risk of mean arterial pressure (OR 0.711, 95% CI 0.378-1.336 , *P*=0.289), although non-significant, possibly due to lack of power. There was a 35% decrease in risk of episodes of bradycardia, neither statistically significant (OR 0.655, 95% CI 0.265-1.617, *P*=0.359).

Conclusions

The combination of ketamine and magnesium sulphate can contribute to better hemodynamic stability among patients undergoing TKA in spinal anaesthesia.

Keywords

Ketamine●Magnesium sulphate●Spinal anaesthesia●Total knee arthroplasty●Sedation●Propofol●Hemodynamics

Introduction

Total joint arthroplasty is one of the most performed surgical procedures in the world. Further, total knee arthroplasty (TKA) is the last resort for patients with osteoarthritis or rheumatoid arthritis and is done as an attempt to alleviate pain and improve quality of life (1–3). The surgery is associated with a moderate risk for complication and moderate to severe postoperative pain (1,3–5). Spinal anaesthesia is commonly preferred for TKA patients, also at St. Olavs Hospital, Trondheim University Hospital (1)(Appendix 2).

Spinal anaesthesia for patients undergoing TKA is known to reduce surgical stress response and blood loss due to a decrease in central venous pressure while it reduces postoperative pain and opioid consumption (1,6). However, when receiving spinal anaesthesia 10-40% experience hypotension, 13% experience bradycardia and 20% experience nausea and vomiting, whereas nausea often is a warning sign for hypotension (6,7). Intraoperative hemodynamic instability can lead to increased postoperative morbidity and mortality (7).

The majority of TKA patients at St. Olavs Hospital, Trondheim University Hospital, receives propofol as a sedating agent during surgery because it is well-suited with early onset and short half-life. Nevertheless, a common side effect of propofol is hypotension, bradycardia and respiratory depression (8–12). Additionally, in 2020 an intraoperative infusion of ketamine and magnesium sulphate was implemented for TKA patients at St. Olavs Hospital, Trondheim University Hospital. This with a goal of preventing postoperative pain and opioid consumption. However, both ketamine and magnesium have been investigated for its influence on hemodynamic parameters(13). Nevertheless, there is a knowledge gap on the synergistic effect and especially regarding patients in spinal anaesthesia Ketamine increases the heart rate (HR), arterial blood pressure (BP) and cardiac outflow while release of

catecholamines increases vascular tone and decreases BP variability (8,13). Magnesium ensures prevention of calcium influx into cells and has a direct effect on depolarization and repolarization of the heart as well as blocking the release of catecholamines and stress response to surgery (14,15). Previous studies found that combining propofol, ketamine and magnesium can lead to several favourable intraoperative effects (11,12,16). Combining ketamine and propofol can provide a deeper sedation with a lower amount of propofol administered (11,12,16). Others found that magnesium can have an additive effect and lower the requirement of several anaesthetics, but the results were inconclusive (15,17).

As mentioned, both spinal anaesthesia and propofol is known to be a potential source for hypotension and bradycardia (6–12). Additionally, administering ketamine and magnesium sulphate can counteract the cardio depressive effects, and the patient may seem more stable during surgery (6,7,9–12). Ketamine is proven to give BP stability while magnesium is found to ensure HR stability (13). A decrease of 7% in mean arterial pressure (MAP) after induction is shown in patients receiving ketamine, compared to 37% in patients not receiving ketamine (11).

The aim of this study was to investigate what impact the combination of ketamine and magnesium sulphate have on the intraoperative phase of TKA patients in spinal anaesthesia. Specifically, we investigated whether administration of ketamine and magnesium sulphate can lead to lower doses of propofol and a more stable hemodynamic by investigating incidences of hypotension, bradycardia and use of vasopressors.

Methods

Study design

This is a non-randomized clinical study of an already implemented practice at St. Olavs Hospital, Trondheim University Hospital. The intervention group, patients who had received the infusion of ketamine and magnesium, was compared to a control group who had not received the infusion. The study was approved by the Regional committee for Medical and Health Research Ethics (REK), Central Norway, approval reference ID 427044 at 05.04.2020. Subject to approval from REK, the study was approved by the Orthopaedic Science Centre at St. Olavs Hospital, Trondheim University Hospital on 04.07.2022 (Appendix 3).

Participants

All patients who underwent total knee arthroplasty in 2019 and 2020 were included for review and divided in a control group (surgery performed between 1. January 2019 and 31.December 2019) and an intervention group (surgery performed between 1. January 2020 and 31. December 2020). Inclusion in the study was based on the same criteria as for the standardised TKA regime; age between 18-80 years with American Society of Anesthesiologists (ASA) physical classification 1-3, who underwent TKA in spinal anaesthesia (Appendix 1). It was a requirement that all participants had received the same premedication consisting of paracetamol 1.5-2 g, dexamethasone 16-20mg, tapentadol 50 mg and naproxen 500 mg/esomeprazole 20 mg (Vimovo, Grünenthal GmbH, Germany). In addition, the intervention group received an intraoperative infusion, prepared and administered by the nurse anaesthetist, consisting of ketamine 10 mg and magnesium sulphate 10 mmol (2460 mg) diluted in sodium chloride 0.9% 100 ml. The infusion was administered

after entering the operating room, continued throughout the surgery and terminated before leaving the operation room. The selection process and sample size are shown in detail in Figure 1.

Data collection

The Orthopaedic Science Centre contributed a list of all patients included in the quality register at St. Olavs Hospital, Trondheim University Hospital. Demographic and descriptive data such as age, sex, height, weight, BMI, ASA-classification, duration of surgery and anaesthesia, use of tourniquet, medications given at the operating room , vital parametres and symptoms/problems, was extracted from the patient's electronic journal. Further, HR and BP were measured at the start of anaesthesia in the preoperative preparation room and every 2-10 minutes during surgery until arriving at the recovery ward.

Measurements

Firstly, propofol was measured in mg. Secondly, hemodynamic stability was measured by systolic BP (SBP), MAP, use of vasopressors (ephedrine and phenylephrine) and HR. A decrease of 20% in mean BP from baseline was defined as hypotension SBP and hypotension MAP. Bradycardia was defined as one or more episodes of HR with <45 pulse min^{-1}.

Sample size and statistical analysis

Sample size was dependent on the criteria of inclusion and exclusion mentioned previously. The authors reviewed all data to verify its accuracy. Descriptive data are presented as mean and standard deviation (SD) for continuous variables and *n* (%) for categorical variables.

Comparison of continuous variables between the groups were analysed using independent samples *t*-test or Mann-Whitney U test, as applicable. Comparison of categorical variables between the groups were analysed using ^{2}-test or Fisher's Exact Test if expected count less than 5 (Table 1). Multiple linear regression was used for analysing the relationship between ketamine and magnesium and amount of propofol administered during surgery (Table 2). For investigating the association of ketamine and magnesium and SBP, MAP, use of vasopressors and bradycardia, logistic regression was used. Covariates adjusted for was ASA, age, BMI, sex, use of tourniquet, vasopressors, atropine and duration of surgery (Table 2). In line with standards in research, values of $P< 0.05$ were considered statistically significant (18). The extracted data were recorded using Microsoft Excel 2016 (Microsoft Corp, Redmond WA, USA). Data were analysed using IBM SPSS Statistics 27.0 (IBM Corp, Armonk, NY).

Results

In total, 249 patients met the inclusion criteria, with 134 patients in the intervention group and 115 in the control group (Figure1). Except for the duration of anaesthesia (178.69 ± 22.17 vs 173.22 ± 22.98) and the number of patients who received atropine (1.7% vs 1.5%), all patient characteristics were comparable across the two groups (Table 1).

There was no association between the addition of ketamine and magnesium sulphate and the amount of propofol administered (B 10.074, 95% CI -99.216-119.365, *P*=0.856). Patients receiving ketamine and magnesium sulphate had a 48% lower risk of hypotension in SBP during surgery (OR 0.520, 95% CI 0.288-0.940, *P*=0.03) compared to those not receiving this combination (Table 2). There was a trend towards lower risk of a decrease in MAP in the intervention group (OR 0.711, 95% CI 0.378-1.336, *P*=0.289) compared to the control group (Table 2). The finding was not statistically significant, possibly due to lack of power. However, seen in context with decreased risk of low SBP in the intervention group, the trend is similar and due to the considerable effect size, it may still provide clinical significance.

For bradycardia, the patients in the intervention group had 35% lower risk of one or more incidences compared to the control group (OR 0.655, 95% CI 0.265-1.1617, *P*=0.359) (Table 2). These results were also not statistically significant as the 95% CI just crosses the null. But again, due to the large effect size and the 95% CI mainly consisting of values showing lower risk, these results could still be useful when considering magnesium and ketamine in the clinic. There was no association between the intervention and whether the patients received vasopressors intraoperatively (OR 0.981, 95% CI 0.544-1.770, *P*=0.950) (Table 2).

Discussion

This study compared TKA patients who received an infusion of ketamine and magnesium sulphate to a control group. There was a lower risk of hypotension SBP in the intervention group compared to the control group resulting in a more stable hemodynamic. Despite this, there was no association between ketamine and magnesium sulphate and the need for vasopressors, neither with propofol. There was not a statistically significant lower risk of one or more incidences of bradycardia among patients in the intervention group than in the control group.

Our results align with prior research from Turkey and Belgium that suggests ketamine to be associated with less decrease in BP (9,13,16). The decrease in MAP in our study was non-significant, which is similar to another study. Nevertheless, this study from Saudi Arabia contained few participants (27 patients) which may have caused lack of statistical power (10). The definition of hypotension varies. A 20% decrease from baseline is most used, but some studies operate by a 30% decrease or SBP <80 mmHg (7–9,12,14,16,19,20). The same applies for bradycardia, where the definition of pulse min^{-1} <45 is most frequent, though other studies operate with <40, <50 and <55 (8,9,15,16,19,20). Different definitions can lead to a mismatch in relation to when hypotension and bradycardia is detected. Hypotension can contribute to increased morbidity and mortality, using a 20% decrease as definition instead of 30% may be beneficial for a better patient outcome (7).

Magnesium has formerly been identified as a factor for stability in HR (13). We investigated if ketamine and magnesium sulphate could contribute to fewer incidences of bradycardia, therefore, stability in heart rate is not investigated further (Table 2). The mentioned

meta-analysis contains several RCTs and a sufficient sample size, but the authors question the study´s clinical relevance due to a modest magnitude of the effect (13). In view of the fact that other previous studies of magnesium, from respectively Turkey, Korea and India, report no effect in hemodynamic stability, it may be discussed whether the findings in our study is associated with magnesium, or in fact ketamine (17,19,20). When using ketamine in addition to propofol you can counteract cardio depressive effects (8,10). However, combining ketamine and magnesium might be associated with a hemodynamic stability due to the synergistic effect of the two agents, in fact the competitive blocking actions on the NMDA-receptor (13). Contrary to our investigations, previous research from Japan states that a lower number of patients needed vasopressor when receiving ketamine and propofol compared to patients receiving only propofol (8). An important difference compared to our study is the predefined protocol for when to give vasopressors (SBT < 80 mmHg, SBT <90 mmHg or MAP decrease >20% from baseline) (8,19).

Further, several other differences must be considered when comparing our study to previous research. Firstly, different patient characteristics might have an impact on the variation of results. The population in this study consists mainly of older patients (67.27 ± 8.74 vs 65.10 ± 9.39), compared to previous studies (Table 1) (9,11,15,16). With increasing age, the likelihood of hypotension increases. It is reasonable to assume that younger patients compensate better than older patients and that older patients have several comorbidities (6,11,13). A natural consequence of lower age is healthier patients with a lower ASA-classification. This might be an explanation for discrepancy in some results. A study mainly consisting of patients classified as ASA 1, and a mean age of 39-41 (± 2.7-4.5) years, the hemodynamic parameters between ketamine group and control group were almost similar

(15). Another important factor for different results may be the fact that studies originate from different countries and different health care systems.

Secondly, the discrepancy in results might also be related to the difference in dose of administration of ketamine and magnesium sulphate. Consistent in several studies is that ketamine and magnesium is dosed according to the patient's weight in contrast to our study where the dose is standard (9–11,14–17,19). In a study the mean dose of ketamine was 145 mg (± 45.62) compared to 10 mg in our study (10). In a study on hip replacement in spinal anaesthesia the total doses of magnesium, based on mean weight (63.4 ± 1.7) and anaesthetic time (195 ± 41), was approximately 6261mg (50 mg kg $^{-1}$ bolus, and maintenance 15 mg kg^{-1} h^{-1}) in the intervention group compared to 2460mg (10 mmol) in our study (19). The trend from several studies indicates that larger doses of both agents might be needed to affect the propofol amount, exemplified by two studies presenting approximately 22.9mg (0.3 mg kg^{-1}, weight 76.2 ± 10.6) of ketamine and 5477 mg (50 mg kg^{-1} bolus, and maintenance 8 mg kg^{-1}h $^{-1}$, weight 81.5 ± 8.8, duration of surgery 129.3 ± 21.7) of magnesium (15,16).

Patients in some studies can be affected by the physiological changes due to general anaesthesia, which can be similar to when placing spinal anaesthesia. Results can therefore be comparable when it comes to hemodynamics. Choice of anaesthesia may however, result in rather different doses of propofol, due to the importance of deep enough anaesthesia in general anaesthesia, as well as the fact that respiratory depression is an expected and manageable effect (11,15,17). This compared to our study where propofol was given until patient satisfaction or adjusted after clinical effect on hemodynamic. The effect on respiration was however not considered in our study. It can be decisive for whether a patient can tolerate a deeper sedation or not. The levels of SpO2 have been shown to be higher in patients who

received ketamine in addition to propofol compared to those only receiving propofol (16). This can have important implications for the administration of propofol in our study.

Weaknesses and strengths of the study

Our research had several limitations. First, since using historical controls and data already collected, we could not influence which data was collected and how. Due to non-randomization, there is a risk of skewed distribution of external factors that might influence the outcome. This may result in unequal groups and have statistical significance for the study's internal validity. Even though the study is based on a standardised regime that minimises the risk of confounding factors, there is still a risk for residual confounding. These factors can for example be the infusion rate of ketamine and magnesium, invasive versus non-invasive BP measurement, no existing guideline for when to administer vasopressors, not taking the respiratory effects into account and whether propofol was administered as boluses or an infusion. We did, however, adjust for several important confounding factors that may have influenced the association between the exposure and the outcome (Table 2). Future studies should aim to randomise the participants to better account for all potential confounders.

Despite a relatively large sample size compared to other studies, we may not have had enough power to detect a statistically significant lower risk of having episodes with low MAP or bradycardia (Table 2). The smaller samples used in previous studies might have increased the likelihood of encountering their results randomly. Future studies should be undertaken on larger samples to ensure enough statistical power to detect the difference between the intervention group and the control group.

Because our study consists of a large number of the patients undergoing TKA at St. Olavs Hospital, Trondheim University Hospital, over a two-year period, the generalisability is likely to be high. Nevertheless, the health care system in Norway is different compared to other countries and the findings can not necessarily be generalised across countries with different healthcare systems.

Future studies should benefit from doing an RCT, to better account for potential confounding factors. Although prior studies have investigated the effect on respiration of ketamine and magnesium separately, the synergetic effect on respiratory aspects of TKA patients with spinal anaesthesia is not yet examined. Furthermore, future studies should consider increasing the doses of ketamine and magnesium sulphate, as the tendency from prior studies shows higher doses than in our study.

Conclusion

The combination of ketamine and magnesium sulphate can contribute to increased hemodynamic stability in patients undergoing total knee arthroplasty in spinal anaesthesia. In terms of hemodynamic stability, our findings may have clinical relevance beyond total knee arthroplasty. Further research should explore how to optimise the intraoperative effects of ketamine and magnesium sulphate.

Authors' contributions

Study design: EFL, SEA

Data collection, analysis and interpretation: EFL, SEA

Writing the first draft, and revising it: EFL, SEA

All authors revised the manuscript and approved the final version.

Acknowledgements

Supervisor

L.B. Strand, NTNU, Trondheim

Project initiator

T. Rian, NTNU and St.Olavs Hospital, University Hospital, Trondheim

Collected data

Orthopaedic science centre, St. Olavs Hospital, University Hospital, Trondheim

T.E. Rø, ANIN/Picis, St. Olavs Hospital, University Hospital, Trondheim

Critical review of the proposal

L. Høvik, NTNU and St Olavs, University Hospital, Trondheim

L.B. Strand, NTNU, Trondheim

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No funding was obtained for this study.

Declaration of interests

The authors declare no conflict of interest.

Appendices

Appendix 1. Guidelines for authors - British Journal of Anaesthesia

https://www.elsevier.com/journals/british-journal-of-anaesthesia/0007-0912/guide-for-authors

Appendix 2. Standardised procedure for total knee arthroplasty at St. Olavs Hospital, Trondheim

Fasttrack kneprotese – Ortopedi – Anestesi

Retningslinje for St Olavs Hospital, Anestesiavdelingen. Gjelder fra 14.05.2014 – utgår 14.05.2019.

Forfatter: Overlege Shawn Davis

Hensikt/omfang

Retningslinjen skal sikre at pasienter som får anestesi ved Fasttrack kneproteser får sikker behandling og et godt postoperativt resultat. Retningslinjen gjelder pasienter som får anestesi ved Fasttrack kneproteser.

Retningslinjen er godkjent på medisinsk faglig grunnlag av avd.overlege Sigurd Fasting, Anestesiavdelingen.

Grunnlagsinformasjon

Kneprotese er aktuelt ved gonartrose, RA (revmatoid artritt), feilstilling.

Ved Fasttrack protesekirurgi er hovedmål en pasient som kan mobiliseres, dvs pasienter skal ut av sengen og stå på operert bena helst på overvåkningen.

Operasjonen gjøres med pasienten i ryggleie. Tilgang gjennom midtlinjesnitt, åpner leddet på medialsiden og lukserer patella lateralt. Evt. synovectomi og evt. subperiostal løsning for å rette ut feilstillinger i kneet før saging og tilpassing av tibia- og femurkomponenten. Når protesen er tilpasset, skylles kneleddet og protesen støpes fast i en seanse. Inngrepet gjøres i blodtomhet. Dette medfører minimal/ingen blødning peroperativt, men det kan blø betydelig v/oppslipping av blodtomheten og senere postoperativt. Forberedelse av pasienten, bedøvelse og leiring foregår vanligvis på innledningsrom.

Operasjonstid: 1,5-2 timer

Arbeidsbeskrivelse

Ansvar

Sykepleiere og leger v/anestesi og overvåking.

Fremgangsmåte

Preoperativt

- Pasienten tilsees av anestesilege på onsdag 1 uke før. De fleste pasienter er ASA I/II med god allmentilstand. ASA III som har optimalisert behandling av grunnsykdom kan også tas. Det må ikke være behov for avansert behandling som arteriekran, vasopressor, post-op respirator. Komplekse kroniske smertepasienter som LAR pasient skal unngås.
- Tromboseprofylakse og preoperativ antibiotika forordnes av ortoped etter gjeldende retningslinjer.
- Premedikasjon: Paracetamol 1.5/2 g, Dexametason 16/20 mg, Vimovo 1tabl og Palexia depot 50mg po gis rutinemessig etter gjeldende retningslinjer

såfremt det ikke foreligger **sterke** kontraindikasjoner. Benzodiazepiner gis ikke.
- Blod: Blod bestilles ikke på disse pasienter på forhånd
- Utstyr/monitorering: Minimum 2 gode innganger, O2 på nesekateter, EKG-monitorering, pulsoxymetri, non-invasiv BT-måling, Urinkateter.

Peroperativt
- Anestesimetode: Som hovedregel velges regionalanestesi. Spinal er førstevalget. Settes av erfaren anestesilege. Spinalbedøvelsen settes med pasienten liggende i sideleie med operasjonsside oppe. 2.5 ml Marcain (bupivacaine) 0.5% plain
- Ca 10 min før blodtomheten slippes opp gis Cyklokapron (fibrinolysehemmer)15 mg/kg såfremt det ikke foreligger kontraindikasjoner.
- Under lukning av kneet setter ortopeden Naropin (ropivacain) 0.2% (maks 100ml) intra/peri-articulært. Dette utgjør en viktig del av den postoperative smertebehandlingen.
- Beredskapsmedikamenter: Thiopenton, Atropin, Curacit, Fenylefrin, Efedrin, antiemetika.

Postoperativt
- Væske: Rest Ringer/NaCl/kolloid og Glucose 5%. Evt. ytterligere volumbehov og evt. behov for SAG vurderes i hvert enkelt tilfelle.
- Standard smertelindring: Paracet 1/1,5g x4 po, Vimovo 1tabl x2 po, Palexia Depot 50mg x2 po. Morfin iv. v/behov. Oxynorm 5 mg vb på sengepost.
    - Dette er smertebehandling som vil fungere utmerket for over 90% av pasienter. For pasienter som ikke kan få NSAIDS eller som har stor, uforventet smerte vil andre løsninger, som for eksempel nervblokkade, epidural, PCA pumpe eller andre opioider være indisert.
- Prøver: Hb-ktr. Evt. andre prøver vurderes i hvert enkelt tilfelle.

Dokumentasjon

Dokumentasjonskilder som er benyttet: Avdelingens praksis, Metodebok for ort. operasjonsavdeling, Miller (kap 61; Anesthesia for Orthopedic Surgery).

Appendix 3. Approval from Regional Committees for Medical and Health

REK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Hilde Eikemo	73597508	06.04.2022	427044

Linn Beate Strand

Prosjektsøknad: Effekten av magnesium og ketamin på postoperative smerter etter kneprotesekirurgi. En ikke-randomisert klinisk studie.
Søknadsnummer: 427044
Forskningsansvarlig institusjon: Norges teknisk-naturvitenskapelige universitet
Samarbeidende forskningsansvarlige institusjoner: St. Olavs Hospital HF

Prosjektsøknad: Endring godkjennes

Søkers beskrivelse

Smertelindring til kneprotesepaseinter er svært utfordrende og 80% av disse pasientene opplever moderate postoperative smerter. Det er derfor viktig å evaluere smertelindringsregimer hos denne pasientgruppen. Ved St. Olavs hospital følger de fleste kneprotesepasientene et standardisert pasientforløp (fast-track) som sikrer at pasientene får en sikker og effektiv behandling og et godt postoperativt resultat. Disse pasientene får spinalbedøvelse, samt en standard smertestillende pakke. Siden januar 2020 har det i tillegg blitt tatt i bruk en kombinasjon av magnesium og ketamin. Dette kombinasjonspreparatet har i denne sammenhengen blitt omtalt som St. Patricks Pain Package Regional. Hensikten med denne studien er å undersøke om St. Patricks Pain Package Regional har en postoperativ smertelindrende effekt etter kneproteseoperasjoner. Studien baserer seg på alle fast-track kneprotesepasienter som er tilgjengelig fra 1. januar 2019 til dags dato. Pasientene deles inn i en kontrollgruppe og en intervensjonsgruppe. Deltakerne i kontrollgruppen samles fra 1. januar 2019 til 1. november 2019. VI vil ved hjelp av statistiske analyser sammenligne disse to gruppene for å se om de som har fått St. Patricks Pain Package Regional har mindre postoperative smerter enn de som ikke fikk det.

Vi viser til søknad om prosjektendring mottatt 31.03.2022 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge (REK midt) på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Du har søkt om følgende endringer:

1) å endre sluttdato fra 31.01.2023 til 31.01.2025

2) endringer i protokoll

Deltakelse i studien er basert på et bredt samtykke. Endringene i protokoll er hovedsaklig presiseringer. Ingen av endringene påvirker vår tidligere vurdering av avgitt samtykke som dekkende for omsøkte bruk. Vi tar endringene til orientering uten innvendinger.

Vedtak

Godkjent

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Hilde Eikemo

Sekretariatsleder, ph.d.

REK midt

Kopi til:

Appendix 4. Checklist of Transparent Reporting of Evaluations with Nonrandomized design

Paper Section/ Topic	Item No	Descriptor	Reported?	
				Pg #
Title and Abstract				
Title and Abstract	1	Information on how unit were allocated to interventions	x	2
		Structured abstract recommended	x	2
		Information on target population or study sample	x	2
Introduction				
Background	2	Scientific background and explanation of rationale	x	3
		Theories used in designing behavioral interventions		
Methods				
Participants	3	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	x	5
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	x	5
		Recruitment setting	x	5
		Settings and locations where the data were collected	x	5
Interventions	4	Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:		
		○ Content: what was given?	x	5
		○ Delivery method: how was the content given?	x	5
		○ Unit of delivery: how were the subjects grouped during delivery?	x	5
		○ Deliverer: who delivered the intervention?	x	5
		○ Setting: where was the intervention delivered?	x	5
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?		

		○ Time span: how long was it intended to take to deliver the intervention to each unit?	x	5-6
		○ Activities to increase compliance or adherence (e.g., incentives)		
Objectives	5	Specific objectives and hypotheses	X	4
Outcomes	6	Clearly defined primary and secondary outcome measures	X	4
		Methods used to collect data and any methods used to enhance the quality of measurements	x	6
		Information on validated instruments such as psychometric and biometric properties	x	6
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	x	6
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	x	5
		Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	x	
		Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	x	13

Blinding (masking)	9	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.		
Unit of Analysis	10	Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	x	8
		If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)		
Statistical Methods	11	Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	x	6
		Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	x	7
		Methods for imputing missing data, if used		
		Statistical software or programs used	x	7

Results				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	x	8
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	x	8
		○ Assignment: the numbers of participants assigned to a study condition	x	8
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	X	8
		○ Follow-up: the number of participants who completed the followup or did not complete the follow-up (i.e., lost to follow-up), by study condition		
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	x	8
		Description of protocol deviations from study as planned, along with reasons		
Recruitment	13	Dates defining the periods of recruitment and follow-up	x	5
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	x	
		Baseline characteristics for each study condition relevant to specific disease prevention research	x	
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition		
		Comparison between study population at baseline and target population of interest	x	8
Baseline equivalence	15	Data on study group equivalence at baseline and statistical methods used to control for baseline differences	x	8
Numbers analyzed	16	Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible		

		Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses		
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	x	8-9
		Inclusion of null and negative findings	x	8-9
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any		
Ancillary analyses	18	Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	x	8-9
Adverse events	19	Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	x	20
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	x	10-14
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	x	10-14
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	x	10-14
		Discussion of research, programmatic, or policy implications	x	10-14
Generalizability	21	Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	x	10-14
Overall Evidence	22	General interpretation of the results in the context of current evidence and current theory	x	10-14

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of*

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Tables

Table 1. Patient and anaesthetic characteristics of patients.

		Control group (2019) (*n*=115)	**Intervention group (2020) (*n*=134)**	
		Mean ± SD	**Mean ± SD**	***P* value**
Age (years)		67.27 ± 8.74	65.10 ± 9.39	0.06
Height (m)		1.72 ± 0.093	1.71 ± 0.087	0.347
Weight (kg)		87.01 ± 19.93	86.45 ± 14.95	0.942
BMI (kg m^{-2})		29.28 ± 5.37	29.62 ± 4.56	0.472
Duration of anaesthesia (min)		178.69 ± 22.17	173.22 ± 22.98	0.026
Duration of surgery (min)		85.95 ± 18.52	85.77 ± 22.84	0.428
Baseline SBP (mmHg)		140.83 ± 22.62	135.87 ± 21.74	0.064
Baseline MAP (mmHg)		94.56 ± 14.85	93.83 ± 16.82	0.718
Mean SBP (mmHg)		119.76 ± 15.28	119.13 ± 12.82	0.713
Mean MAP (mmHg)		82.93 ± 7.96	84.13 ± 7.96	0.237
Baseline HR (pulse min^{-1})		72.49 ± 12.18	72.07 ± 13.0	0.682
Mean HR (pulse min^{-1})		68.43 ± 9.84	70.44 ± 10.06	0.114
		***n* (%)**	***n* (%)**	***P* value**
Sex	Female Male	68 (59.1%) 47 (40.9%)	90 (67.2%) 44 (32.8%)	0.189
ASA	I 2 3	11 (9.6%) 84 (73.0%) 20 (17.4%)	26 (19.4%) 89 (66.4%) 19 (14.2%)	0.089
Tourniquet	Yes	14 (12.2%)	10 (7.5%)	0.209
Atropine	Yes	2 (1.7%)	2 (1.5%)	0.024
Midazolam	Yes	3 (2.6%)	6 (4.5%)	0.512
Nausea intraoperatively	Yes	4 (3.5%)	12 (9.0%)	0.079
Nausea postoperatively	Yes	0 (0%)	2 (1.5%)	0.188
Hallucinations	Yes	1 (0.9%)	0 (0%)	0.279

Data is presented as mean (SD) or n (%), and p value.
BMI = Body Mass Index
SBP = Systolic blood pressure
MAP = Mean arterial pressure
HR = Heart rate
ASA = American Society of Anesthesiologist

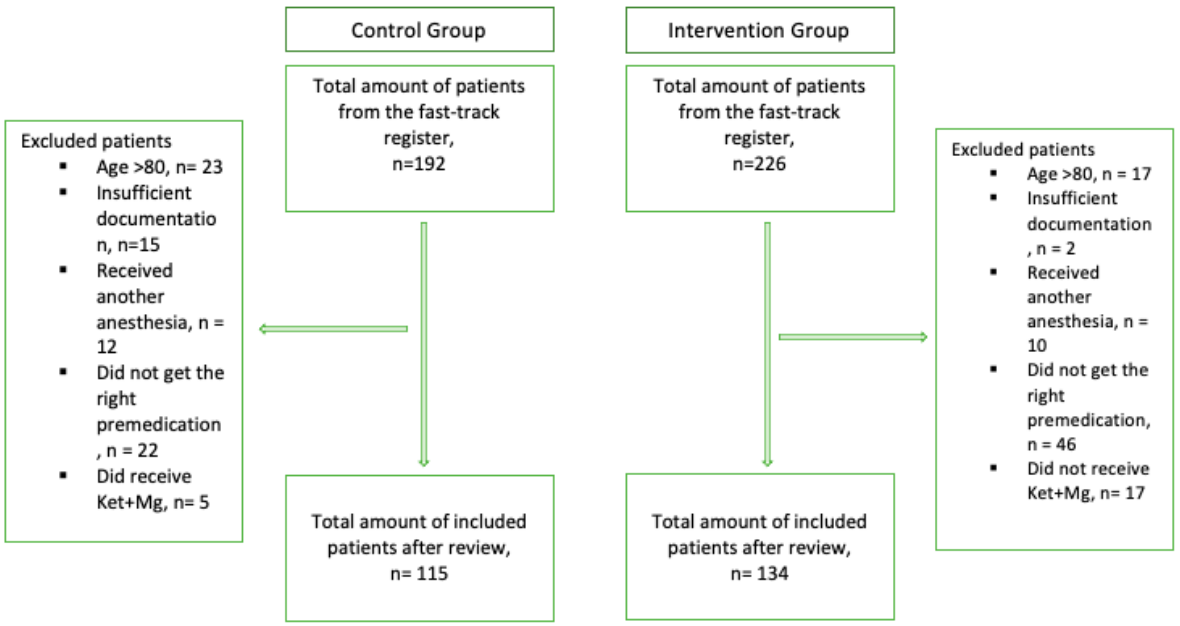
Table 2. Logistic regression of hemodynamics and linear regression of propofol.

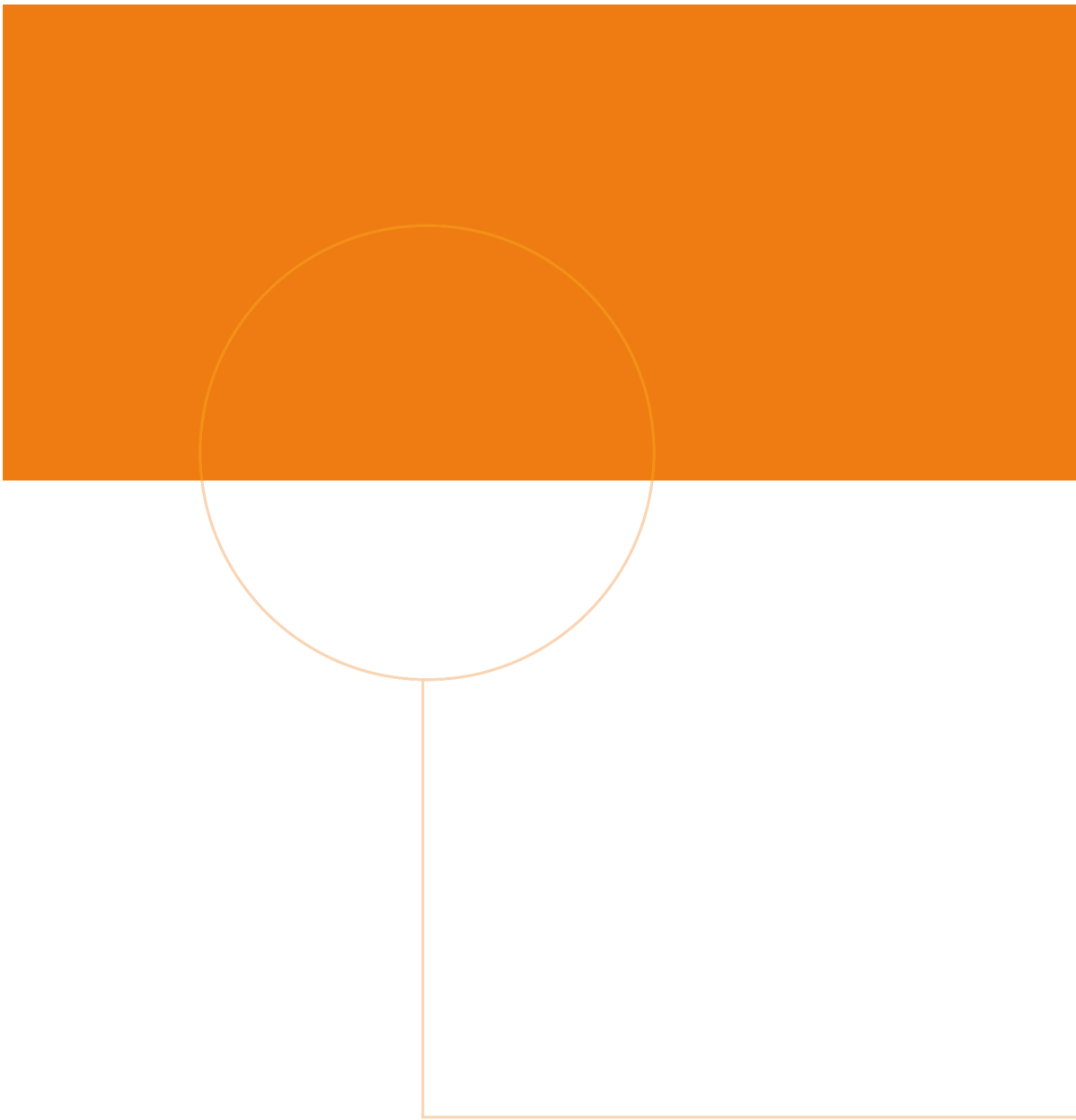
	Model 1			**Model 2**		
	B	**95% CI**	***P* value**	**B**	**95% CI**	***P* value**
Propofol (mg)	19.244	-88.838 - 127.325	0.726	10.074	-99.216 - 119.365	0.856
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Hypotension SBP	0.521	0.293 - 0.929	0.027	0.520	0.288-0.940	0.03
Hypotension MAP	0.708	0.382 - 1.314	0.274	0.711	0.378-1.336	0.289
Vasopressors	1.019	0.582 - 1.786	0.946	0.981	0.544-1.770	0.950
Bradycardia	0.590	0.248 - 1.403	0.233	0.655	0.265-1.617	0.359

Model 1: Adjusted for age, sex
Model 2: Propofol adjusted for age, sex, ASA, BMI, use of tourniquet, duration of surgery, midazolam.
Hypotension and bradycardia adjusted for age, sex, ASA, BMI, use of tourniquet, duration of anaesthesia, atropine
Vasopressors adjusted for age, sex, ASA, BMI, use of tourniquet, duration of anaesthesia atropine.
Hypotension SBP = Mean systolic blood pressure decrease with >20% from baseline
Hypotension MAP = Mean of mean arterial pressure decrease with >20% from baseline
Vasopressors = Ephedrine and Phenylephrine
Bradycardia = Heart rate <45 pulse min^{-1}

Figures

Figure 1. Flow chart of selection process.





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