Incidence of cardiovascular complications in knee arthroplasty patients before and after implementation of a ropivacaine local infiltration analgesia protocol: A retrospective study

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1. Introduction

Post-operative pain and adverse effects related to medication can impair early post-operative mobilization after total knee arthroplasty and may cause a prolonged length of hospital stay. Several studies have been performed to assess peri-operative, multimodal protocols for post-operative pain reduction and early mobilization [1–6]. The main focus of these fast-track protocols is to reduce post-operative pain and reduce the need for opioid medication, which leads to faster mobilization after surgery. These fast track protocols are becoming increasingly popular in total knee arthroplasty and total hip arthroplasty as opposed to protocols with epidural analgesia or peripheral nerve blocks, which can have side effects that impair early mobilization [1–11].

Local infiltration analgesia (LIA) during total knee arthroplasty as part of fast-track protocols has been shown to give a reduction in post-operative pain and opioid medication consumption. In LIA infiltration, high volumes of 150 cm³ up to 300 cm³ of 0.2% ropivacaine are applied behind the posterior capsule of the knee, in the gutters, in the peripatellar and periosteal space and in the subcutaneous tissue during surgery. This is to achieve an optimal result in reducing post-operative pain [12–15].

Cardiac and central nervous system toxicity can be complications of longer acting local anesthetics such as bupivacaine or ropivacaine, with better cardiovascular safety reported for ropivacaine [16–20]. Pre-operative cardiovascular effects of ropivacaine specifically after high volume LIA infiltration during total knee replacement have not been reported in detail before. Our hypothesis is that there is no difference in the incidence of bradycardia and hypotension during surgery and no difference in post-operative cardiovascular complications between patients treated before and after implementation of a LIA protocol for the reduction of post-operative pain.

2. Materials and methods

2.1. Outcome measures

Primary outcomes were defined as the incidence of hypotension and bradycardia during surgery, and the post-operative incidence of cardiac
2.2. Informed consent and selection of participants

This study met the criteria for exemption for obtaining informed consent. The study was conducted with one independent cohort receiving the standard treatment protocol in knee arthroplasty (cohort 1) and one independent cohort (cohort 2) also receiving the LIA protocol, the protocols are summarized in Appendices A and B respectively. The patients in cohort 1 were enrolled between November 2011 and November 2012 at the Rijnland Hospital Leiderdorp (performing ~400 knee arthroplasties annually). Patients for cohort 2 were enrolled between November 2012 and November 2013.

From November 2011 until November 2012 all patients with knee arthroplasties were screened for eligibility and included in cohort 1. Patients admitted for revision of their total knee prosthesis, patients receiving hemi prostheses, patients receiving tumor prosthesis or rotating hinge prosthesis, patients scheduled for patellofemoral resurfacing and patients with missing surgery records were excluded. In November 2012 a LIA protocol was introduced in the orthopedic department at the Rijnland Ziekenhuis with the main purpose of reducing post-operative pain, improving early mobilization and thereby reducing length of stay. During the period of November 2012 up to November 2013 patients treated with the LIA protocol were included in cohort 2. Patients treated according to the previous protocol or receiving epidural anesthesia were excluded from analysis. For this cohort, the same exclusion criteria from cohort 1 were used, with the addition of the exclusion of patients not treated according to the LIA protocol.

2.3. LIA

In the LIA protocol during surgery, infiltration of 50 cm³ of 0.2% ropivacaine with one milligram of adrenalin in the posterior joint capsule, 50 cm³ of 0.2% ropivacaine with one milligram of adrenaline in the peripatellar and periosteal space and gutters and 50 cm³ of ropivacaine 0.2% without adrenaline in the subcutaneous tissue was used. No drain was inserted during surgery to allow for early mobilization. In both procedures, patients were treated with compression bandages afterwards for 24 h.

2.4. Data collection

All the variables mentioned in the tables were retrospectively registered in the digital hospital information system Xcare Patient (McKesson, San Francisco, USA). Data was extracted from discharge letters, anesthesiology reports, surgery reports and the patients’ clinical file (both written and electronic versions). The files used for obtaining data are specified in Appendix D.

In the patients treated with the standard peri-operative protocol, bradycardia during surgery was described as either present or not present and was defined as a heart rate lower than 60 beats per minute during three consecutive measurements during surgery. Hypotension during surgery was described as either present or not present and was defined as a systolic pressure lower than 90 mm Hg or a diastolic pressure lower than 60 mm Hg during two consecutive measurements during surgery.

In cohort 2, treated with the LIA protocol, bradycardia was described in three different ways: first whether bradycardia was seen throughout the entire surgery, second whether bradycardia was already present before LIA was administered and no sudden increase of bradycardia was monitored after administration of LIA and thirdly, whether bradycardia was monitored for the first time after administration of LIA, and whether there was a direct relation between onset of bradycardia and moment of LIA administration. Hypotension during surgery in cohort 2 was described in the same way as was bradycardia in cohort 2. The specific definition used for bradycardia and hypotension in both cohorts can be found in Appendix D.

Patients were followed until 12 months post-operatively and complications were registered from discharge letters, surgery reports, electronic files and complication registration databases. This follow-up duration was chosen because 12-month follow-up data was available through the database, which was also built for other research purposes.

2.5. Data analysis

Data were presented as mean (standard deviation: SD) if normally distributed and median. (Interquartile range: IQR) if data were rightly skewed. Distribution of data was analyzed with the Shapiro–Wilk test. Descriptive categorial data were analyzed using χ²-tests. Continuous data were analyzed with a Student’s t-test when appropriate.

Binary logistic regression was used to analyze confounding effect of pre-operative hemoglobin levels, American Society of Anaesthesiologists-scores, type of anesthesia on bradycardia and hypotension. Correction was performed for multiple measurements. Stratification of cohorts was used to correct for potential confounders.

Binary logistic regression was used to analyze the association between LIA administration and the incidence of atrial fibrillation, other cardiac arrhythmias and myocardial infarction. Each complication was analyzed separately and correction for multiple measurements was performed. No stepwise regression was used in the statistical analysis. P-value of P < 0.05 was considered statistically significant. All data were analyzed using SPSS statistics (SPSS version 21.0, IBM, New York, USA).

3. Results

3.1. Patient characteristics and inclusion

Initially, 849 knee arthroplasty patients were screened for eligibility. For cohort 1, treated according to the standard knee protocol, 417 patients were screened for eligibility. After screening, 38 patients were excluded from analysis, leaving 379 primary total knee patients eligible for inclusion in this study. Patients were excluded because they needed revision surgery (N = 22), patella resurfacing (N = 12), hemi prosthesis/tumor prosthesis (N = 3) or data were missing (N = 1). In cohort 2, 432 knee arthroplasty patients were screened for eligibility. After screening, 68 patients were excluded from analysis, leaving 365 primary knee arthroplasty patients eligible for inclusion in this study. Patients were excluded because they needed revision surgery (N = 40), patellar resurfacing (N = 12), hemi prosthesis/tumor prosthesis (N = 3) or did not receive local anesthetic infiltration (N = 5). Data were missing in 10 patients, which after research appeared to be lost in the process of digitizing patient files. This was also true for the patient in cohort 1 with missing data. In Appendix C the number per exclusion criterion is reported.

In Table 1, patient characteristics for each cohort are presented. The two cohorts were comparable at baseline, except for ASA scores and cardiac arrhythmias (other than atrial fibrillation) e.g. supraventricular extrasystoles. (See Table 1.)

3.2. Bradycardia during surgery

In the patients treated by the LIA protocol 96 people presented with bradycardia during surgery versus 107 people in the group treated without ropivacaine. Bradycardia occurring for the first time during surgery after administration of ropivacaine was seen in seven patients. The mean time that elapsed after LIA administration was 12 min, ranging from five to 30 min. In the other 89 patients bradycardia had already been present before infiltration and no new episode of bradycardia occurred after infiltration. The difference in number of patients presenting with bradycardia before and after implementation of the LIA protocol was not statistically significant (Pearson’s χ²-test P = 0.55).

3.3. Hypotension during surgery

Hypotension during surgery occurred in 250 patients treated with the standard knee prosthesis protocol. In the LIA protocol, 205 patients had an episode of hypotension during surgery. The first episode of hypotension occurred after LIA infiltration in 18 patients. The mean time elapsed after infiltration was 16 min, ranging from five to 35 min. In the other 187 patients, hypotension was not directly related to LIA administration. The difference in hypotension was analyzed and proved to be statistically significant (Pearson’s χ²-test P = 0.01).
Type of anesthesia and pre-operative medical history (as mentioned in Table 1).

The regression model was built using age, gender, pre-operative hemoglobin levels, ASA scores, and can produce confounding effects because of systemic effects of bupivacaine, which are more likely in patients with multiple comorbidities, and those patients might have in fluid balance and possible adverse effects of LIA, which influenced the occurrence of hypotension. Logistic regression was performed to correct for these potential confounding effects. A binary logistic regression model was built using age, gender, pre-operative hemoglobin levels, ASA scores, type of anesthesia and pre-operative medical history (as mentioned in Table 1).

The binary regression model showed that pre-operative hemoglobin levels and ASA scores were not statistically significant predictors of the incidence of hypotension and bradycardia during surgery. The incidence of bradycardia was lower in patients receiving spinal anesthesia with an OR of 0.348 (95% CI: 0.207 to 0.586). The effect of spinal anesthesia on the incidence of bradycardia was statistically significant (P = 0.01). The incidence of hypotension was lower in patients receiving spinal anesthesia with an OR of 0.584 (95% CI: 0.418 to 0.814). This effect of spinal anesthesia on hypotension was also statistically significant (P = 0.01). Stratification to correct for these effects was used to check the Pearson’s X²-tests’ assumptions, and the same effect of LIA on bradycardia and hypotension, as found in the Pearson X²-tests, was observed.

Logistic regression after controlling for possible confounders as mentioned above, showed no statistically significant influence of LIA on hypotension on the occurrence of hypotension. After stratification for type of anesthesia, the same absence of a statistically significant effect was observed.

Logistic regression showed that using ropivacaine as LIA had a statistically significant (P = 0.01) negative effect on the occurrence of hypotension during surgery with an odds ratio of 0.607 (95% CI: 0.411 to 0.834). This showed that the incidence of hypotension was lower after implementation of the LIA protocol. The same statistically significant influence of LIA on hypotension was observed when stratification for type of anesthesia was performed.

3.5. Cardiovascular complications and death

During surgery, three or five lead EKG-monitors were used and on indication 12 lead EKGs were performed after surgery. The three or five lead EKGs recorded during surgery were not available for analysis. Cardiovascular complications were registered during 12 months after surgery. Cardiac arrhythmia (including atrial fibrillation) and myocardial infarction were recorded, including treatment, but no statistically significant differences were found between the standard protocol and the LIA protocol.

Two patients in cohort 1 presented with new onset atrial fibrillation within 72 h of surgery. In these patients no atrial fibrillation was present during or directly after surgery. Three patients in cohort 2 presented with atrial fibrillation. Two patients were diagnosed with new onset atrial fibrillation, one patient after 48 h and the other after 120 days after surgery. One patient was already diagnosed with paroxysmal atrial fibrillation before surgery and suffered from a new episode after surgery 48 h after surgery. Two patients in cohort 1 suffered from myocardial infarction within two days after surgery. One patient in cohort 1 suffered from myocardial infarction in the night after surgery and one patient within two days of surgery. One patient in cohort 2 suffered from myocardial infarction within two days after surgery. There was no statistically significant difference between cohorts in the occurrence of cardiovascular complications.

In the standard protocol there were five deceased patients at the 12 month follow-up point. One patient died during admission to the ward after an un witnessed arrest with post-anoxic encephalopathy. The other causes of death were unrelated to knee replacement surgery. In the LIA protocol there was one deceased patient at the 12 months of follow-up point. This patient died within one month after surgery because of ventricular fibrillation occurring after vascular surgery for coronary artery disease. There was no statistically significant difference in mortality (P = 0.11) between the standard protocol and LIA protocol (Table 2).

4. Discussion

During the past decade, several authors have described cardiovascular and neurotoxic adverse effects of local anesthetic agents [7,16,21]. These adverse effects may impair early mobilization and affect the recovery of patients enrolled in fast-track protocols. Commonly reported cardiovascular effects in ropivacaine use are slightly elevated systolic and diastolic pressure and tachycardia at lower doses. Higher concentrations of ropivacaine can result in sinus bradycardia, sinus arrest, partial or complete AV dissociation, cardiac arrhythmias and hypotension. The present study focuses on bradycardia, hypotension, cardiac arrhythmias and other cardiovascular complications such as myocardial infarction [7,16,21–23].

Greater incidence of hypotension was found in patients treated according to the standard protocol, suggesting that the occurrence of hypotension is unrelated to local infiltration analgesia. However, this must be interpreted with caution because in the LIA protocol investigated in this study, several pre-operative preparations were implemented to optimize the patients before surgery, such as optimal fluid balance and pre-operative analgesia. These might influence the occurrence of hypotension during surgery. Before the implementation of the LIA protocol no standard guidelines were used to optimize fluid balance, whereas after implementation, anesthesiologists were more focused on optimal fluid balance and possible adverse effects of LIA, which might have influenced the occurrence of hypotension.

Two of the ropivacaine infiltrations are prepared with the use of one milligram of adrenaline, which might have a protective effect for the occurrence of hypotension, and a protective effect on the occurrence of bradycardia, especially when the tourniquet is deflated and redistribution of blood flow in the leg is taking place. After analyzing surgery records for hypotension and tachycardia, it was concluded that there was no statistically significant difference between the standard protocol and LIA protocol.
and LIA protocol in the occurrence of tachycardia or hypertension. However, it cannot be determined if the ropivacaine in the mixture produces hypotension and bradycardia, which is antagonized at the same time by hypertension and tachycardia induced by adrenaline.

A recent study published by Schotanus et al. investigated the use of adrenalin in local infiltration analgesia, and concluded that adrenaline did not improve analgesia when compared to the use of ropivacaine alone [24]. The use of adrenalin also causes a vasoconstrictive response locally, which could amplify the known vasoconstrictive effect of ropivacaine, and causes local tissue damage [25]. This merits further consideration and research regarding the usefulness of adrenalin in LIA mixtures in the future. This would also allow for evaluation of cardiovascular safety of ropivacaine infiltration alone, without the interference of possible cardiovascular effects of the added adrenalin.

Local infiltration analgesia has been shown to give effective analgesia in the early post-operative period after knee replacement and is part of pain treatment in many fast-track protocols [7,26,27,28]. LIA studies are very diverse because of different concentrations and volumes of anesthetics, various sites of injection and the use of catheters and different adjuvants in the LIA mix [26,27,28]. This heterogeneity in studies makes it difficult to give accurate results about the advantage of local anesthetics and more research is needed to develop standard protocols [7,26,27,28].

In vitro and vivo studies have been conducted to investigate the effect of local anesthetics on the cardiovascular system [26,28]. Though several mechanisms have been proposed, there is no consensus as to which mechanism causes the cardiovascular effects. Ropivacaine electrophysiology studies show inhibition of ion currents in cardiac tissues, reducing action potential amplitude, depolarization velocity and shortening action potentials [23]. These factors influence effectiveness of the cardiac tissue and can affect cardiovascular parameters during surgery. Unfortunately, analysis of the conduction intervals after ropivacaine infiltration was not possible in this study because the standard protocol applied for total knee replacement surgery did not include a post-operative EKG. Future research in cardiotoxicity of ropivacaine injection should include standard EKGs after infiltration with ropivacaine to assess the influence on conduction intervals.

The reported cardiac arrhythmias in both cohorts took place at a minimum of 48 h after surgery, and it is therefore unlikely that this was related to ropivacaine infiltration, which has a half-life of 4.2 h. One patient in the LIA protocol died with one month of surgery due to ventricular fibrillation after surgery for cardiovascular disease. It is highly unlikely this death was related to ropivacaine injected during total knee replacement surgery.

There are several limitations to this study. First, the retrospective setup of the study makes it impossible to randomize patients, which could introduce selection bias, even though the cohorts are comparable at baseline. Because the LIA protocol was followed in every primary total knee arthroplasty performed after introduction, we think that the selection bias is largely reduced, however it cannot be completely eliminated. Because of the protocol being implemented in every total knee arthroplasty at once, a learning curve of adequate infiltration can be expected, with a decreased possibility of accidental injection of ropivacaine into vessels. Though Kerr and Kohan do not describe precautions to avoid intravascular injection by aspirating before infiltration, it was routinely performed during surgery at our center which reduces the possibility of intravenous injection of ropivacaine [15].

A second, important limitation concerns the occurrence of arrhythmia. Many patients with a previous history of cardiac arrhythmia or new onset arrhythmia report no complaints of this disorder, and therefore it cannot be ruled out that undetected arrhythmias occur in the post-operative phase. Because of the relatively short half-life of ropivacaine (several hours), we expected cardiac arrhythmias caused by LIA infiltration to occur during surgery. Because protocol did not dictate that a post-operative EKG should be performed, it is possible however that cardiac arrhythmias that occurred during the post-operative phase without eliciting symptoms, were missed.

The patients of cohort 1 were included from 2011 until 2012, while the patients of cohort 2 were included from 2012 until 2013. In both cohorts four different surgeons performed total knee arthroplasties following the same standardized protocols. Difference in surgical experience can result in variations that may give a confounding effect which is difficult to correct in statistical analysis.

The exact volume of bupivacaine administered in spinal anesthetics was not obtained from the anesthetics file which might influence cardiovascular parameters during surgery. However, standard doses within protocol were used for all patients receiving spinal anesthesia.

In summary this retrospective observational study shows that intraoperative LIA administration does not cause a difference in the incidence of bradycardia during surgery. A significant lower incidence of hypotension during surgery though was found in the group treated with the LIA protocol (P < 0.01). These results have to be interpreted with care, due to the implementation of a new protocol which also put emphasis on adequate fluid balance before surgery, and the use of adrenalin in the LIA mixture which could cause masking of hypotension and bradycardia. Otherwise, no increase in post-operative cardiovascular complications and mortality was found after comparison of both cohorts before and after implementation of the LIA protocol. This allows for safe use of high volumes of ropivacaine combined with adrenalin as local infiltration analgesia in knee replacement surgery.

Author contributions

JL helped in designing the study, collected data, performed statistical analyses and wrote the manuscript.

FV collected data and edited the manuscript.

JG edited the manuscript and was involved in the implementation of the LIA protocol.

JJ invented the study idea, designed the study and edited the manuscript, was involved in the implementation of the LIA protocol and was one of the surgeons who performed total knee arthroplasty.

Conflicts of interest and funding

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Appendix A. The standard protocol for knee prosthesis

The standard knee protocol was in effect until the 14th of November 2012. The same surgical procedure was used as the procedure used in the LIA protocol.

During the first day after surgery, patients were allowed to do some foot exercises, sit in a chair for 45 min times two a day and were allowed to rock their leg at the side of the bed. During the first or second day after surgery the Bellovac drain, catheter and compression bandage were removed. On the second day after surgery, patients started mobilization with crutches. If insufficient flexion was observed, continuous passive motion was used to improve function.

During surgery:

- Bellovac™ drain (Wellspect, Sweden) was inserted before the wound was closed.
- All patients received a patient controlled anesthesia (PCA) pump.
- Some patients received epidural analgesia.
A.1. Prevention of thromboembolic processes

All patients are treated with a prophylactic dose (0.3 ml subcutaneous) of nadroparine (heparin) daily during six weeks. If the medical history is positive for thromboembolic processes, this dose can be changed after consulting a hematologist.

Appendix B. The LIA protocol

The protocol focuses on several aspects before, during and after surgery to reduce the amount of post-operative pain and allow for early mobilization. Mobilization is optimized by treating patients without leaving a wound drain, without placing a urine catheter and preventing the need for patient controlled anesthesia-devices. Immediately after surgery, even as early as the recovery department, the patient is instructed to start active movement of the knee (flexion and extension). When the patient is re-admitted to the ward he or she is stimulated to start mobilization four hours after surgery. On day one, the physiotherapist starts the recovery phase by introducing walking aids and helping patients with exercises to allow early and safe mobilization over greater distances (20 to 30 m).

B.1. During surgery

One hundred cubic centimeters of ropivacaine 0.2% with one milligram adrenaline.
Fifty cubic centimeters of ropivacaine 0.2% without adrenaline.

B.2. Technique of local anesthetic infiltration

Fourteen gauge needle, inserted three to five millimeters into the site of surgery.
The first step is to leave 50 cm³ in the posterior aspect of the joint capsule. The second step is to leave 50 cm³ in the gutters and the peripatellar and periosteal space. The third step is to infiltrate the skin with the 50 cm³ of ropivacaine without adrenaline.

B.3. Prevention of thromboembolic processes

All patients are treated with a prophylactic dose (0.3 ml subcutaneous) of nadroparine (heparin) daily during six weeks. If the medical history is positive for thromboembolic processes, this dose can be changed after consulting a hematologist.
Appendix D. Recorded parameters

Gender, age, medical history and patient characteristics were recorded from the patients’ electronic file, digitalized paper file and discharge letters. The parameters during surgery were obtained from the surgery record by the anesthesiology department. The complications were obtained from discharge letters, outpatient clinic visits, emergency department visits and general practitioners’ letters.

References


