Original Article

Local infiltration analgesia for total knee arthroplasty: Does a mixture of ropivacaine and epinephrine have an impact on hemodynamics? An observational cohort study

ABSTRACT

Purpose: High doses of local anesthetic administered intra-articularly and peri-articularly during local infiltration analgesia (LIA) for total knee arthroplasty (TKA) may have potential effects on patient hemodynamics. The aim of this study was to know if hemodynamic changes are associated with LIA in patients undergoing TKA.

Methods: In a prospective observational design, elective patients undergoing orthopedic surgery for TKA and treated with LIA consisting of a mixture of ropivacaine (300 mg) and epinephrine (1 mg) were investigated for changes in selected hemodynamic parameters: heart rate (HR), non-invasively registered mean arterial blood pressure (MAP), and incidence of arrhythmias during the perioperative course, consisting of the following periods: period 1. from establishment of spinal anesthesia to prior to LIA administration, period 2. from administration of LIA to before release of ischemia tourniquet, period 3. from release ischemia tourniquet to end of surgery, and period 4. from transfer to the post anesthesia care unit to the ward. Statistical analysis was done with ANOVA-RM for the difference in means in repeated measurements, and with the Tukey Test between pairs. Data are presented as mean ± standard deviation. A P value <0.05 was considered significant.

Results: Ninety-nine patients (mean age 77 ± 8 years) were included. HR increased from period 2 to period 3 up to 16% (67 ± 14 to 77 ± 13 bpm, $P < 0.001$), and from period 2 to period 4 up to 21% (67 ± 14 to 81 ± 12 bpm, $P < 0.001$). MAP showed no significant changes from period 2 to period 3 (89 ± 13 to 87 ± 13 mmHg, $P > 0.50$), and from period 2 to period 4 (89 ± 13 to 91 ± 11 mmHg, $P > 0.50$). No arrhythmias were detected during follow-up.

Conclusions: A mixture of ropivacaine and epinephrine for LIA, despite the high doses administered, does not have a negative impact on hemodynamics.

Key words: Epinephrine; hemodynamics; local infiltration analgesia; ropivacaine; total knee arthroplasty

Introduction

There is growing interest in modern analgesic techniques that allows early patient mobilization and fast recovery after total knee arthroplasty (TKA). In particular, sufficient pain control without impairment of muscle strength is needed, allowing the patient to start walking as early as 6 h after TKA.

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Over the years, various pain control modalities have been developed. The first was patient-controlled analgesia using morphine, but this has fallen out of fashion due to side effects such as nausea, vomiting, sedation, and urinary retention.[1] Another approach was lumbar epidural analgesia, but this neuroaxial technique is frequently associated with vasodilatation and subsequent hypotension or risk for an epidural hematoma.[2,3] Hypotension is a well-known complication of tourniquet deflation in knee arthroplasty. It is associated with a decrease in systemic vascular resistance due to the removal of arterial occlusion, bleeding from an unbound vessel, and release of ischemic tissue metabolite or hypovolemia.[4] Epidural anesthesia is associated with hypotension after tourniquet removal.[5]

As a consequence, new analgesic techniques have been developed to reduce perioperative pain that result in fewer hemodynamic complications. Some recent modalities include multimodal management strategy with oral analgesics, peripheral nerve blocks, and peri-articular injections. One of these, local infiltration analgesia (LIA) with anesthetic agents has been shown to improve pain control, lead to early mobilization, reduce morphine consumption during the first 48 h postoperatively, and compared with intrathecal morphine, LIA has been associated with a shorter hospital stay.[6] Recovery after LIA is documented,[7] but there is little research on the pharmacokinetics of high volumes of local anesthetics administered intra-articularly and peri-articularly, as well as on potential local and systemic adverse reactions. Two recent studies reported plasma concentrations of local single-shot ropivacaine administration in TKA,[1,8] but neither of them specifically analyzed hemodynamic or cardiac events. In another trial, up to 12% of patients developed acute postoperative hypotension after TKA, likely associated with ischemia reperfusion, cardiovascular disease, subarachnoid anesthesia, and advanced age as risk factors for hypotension.[9] In a retrospective analysis, Lameijer *et al.* described compensatory vasoconstriction occurring when a mixture of local anesthetics and a vasoconstrictor were used in TKA.[10] This could be a promising approach in order to improve the hemodynamic stability with anesthetics used in LIA. The aim of the current study was to investigate hemodynamic changes in patients undergoing TKA with LIA at our tertiary care center.

Methods

In 2004, our center implemented a "rapid recovery protocol" for patients undergoing TKA. The protocol includes spinal or general anesthesia and the administration of a high volume (150 mL) of local anesthetic consisting of a mixture of 100 mL of ropivacaine 0.2% with 1 mg epinephrine and 50 mL of ropivacaine 0.2% without epinephrine.

In this single-center cohort study, patients treated with LIA for primary TKA between February and December 2017 were consecutively included after providing written informed consent. The study was approved by the Comité Ético de Investigación Clínica del Hospital Clinic de Barcelona–approval number: HCB/2017/0221, Chairperson: Prof. Francisco Javier Carne on April 19, 2017, and by the Catalonia Government (approval number: ACB-ROP-2017-01). All study procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. The STROBE checklist for observational studies was used to guide the methods and to structure this manuscript.

The primary outcome parameter was the change in noninvasive hemodynamic parameters during the intra- and postoperative period. The hemodynamic parameters assessed were the heart rate (HR), the mean arterial blood pressure (MAP), and the incidence of arrhythmias. Hemodynamic parameters were collected from electronic anesthesia records every 5 min [Figure 1]. Hypotension was defined, according to the current clinical practice and corresponding references,[11-13] as a MAP of less than 60 mmHg or a decrease of more than 30% from the baseline. Hypertension was defined as an increase of more than 30% from the baseline. Tachycardia was defined as a heart rate higher than 100 beats per minute (bpm) and bradycardia as a heart rate lower than 50 bpm. Arrhythmias collected were: atrial fibrillation, sinus tachycardia, sinus bradycardia, atrioventricular block, and ventricular extrasystole.

The observation period consisted of the following perioperative phases: period 1. from establishment of spinal anesthesia to prior to LIA administration, period 2. from first administration of LIA to before release of ischemia tourniquet, period 3. from ischemia tourniquet release to end of the surgery, and period 4. from patients' transfer to the post-anesthesia care unit to patients' discharge to the ward. Discharge of the patient from the PACU to the ward was allowed after an Aldrete score of >12 was reached.[14]

Vasoactive medications were allowed according to clinical standards: patients with MAP lower than 60 mmHg received IV boluses of ephedrine or phenylephrine 5 mg and 100 μg, respectively. Ephedrine was used if the HR was normal and phenylephrine was used in patients with tachycardia. If hypotension persisted despite several boluses, continuous administration of norepinephrine with 0.03 μg/kg/min was started. Antihypertensive drugs (Urapidil 5 mg or Labetalol 5 mg bolus) were given if the MAP was greater than 120 mmHg, until the MAP was in normal range. Atropine (0.01 mg/kg) was administered if the HR decreased below 45 bpm. The
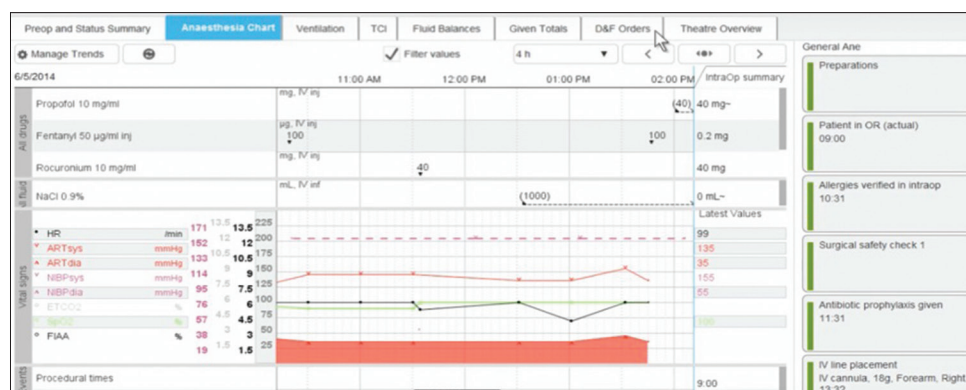
Figure 1: Anesthesia record: Electronic anesthesia record

rates of pharmacological (amiodarone, 150 mg) or electrical cardioversions were also collected.

Inclusion/Exclusion criteria

Inclusion criteria were patients undergoing TKA under ischemia tourniquet who agreed to participate and signed the informed consent. Exclusion criteria were patients allergic to local anesthetics, previous knee replacement with prosthesis, general anesthesia, TKA performed without the use of ischemia tourniquet, and history of atrial fibrillation, or other rhythm disturbances [Appendix A].

Surgical technique

All TKA procedures were performed using the same surgical protocol.[15] A low-pressure (250 mmHg) ischemia cuff tourniquet was used on the patient's thigh. The articular approach was medial para-patellar with patellar eversion. Several different prosthetic models were used, with the femoral component of the cemented prosthesis and the tibial component cemented or not depending on the characteristics of the patient. The patellar prosthesis component was not routinely inserted at the discretion of the surgeon. The wound was closed after the release the ischemia cuff and hemostasis control. No drains were placed.

Anesthesia technique

Patient monitoring was performed according to the standards set by the American Society of Anesthesiologists, with measurement of peripheral oxygen saturation, noninvasive blood pressure, and electrocardiogram. If the patient has no previous history of cardiac arrhythmia and preoperative electrocardiogram was normal, subarachnoid block was performed with doses between 8 and 10 mg of 0.5% isobaric bupivacaine; all patients had an effective spinal anesthesia and no one had a level above T10. LIA was performed with a high volume (150 ml) and high dose (300 mg) mixture comprising of ropivacaine 0.2 % (300 mg) and epinephrine (1 mg) epinephrine was injected with a 14-gauge needle in the posterior joint capsule and both collateral ligaments

before inserting the prosthesis [Figure 2]. Thereafter, the rest of the mixture (50 ml) was injected along the edges of the bone, where the retractors were placed, inside the capsule, in the quadriceps tendon intra-patellar ligaments and in the soft tissues [Figure 3]. Before wound closure, 50 mL of ropivacaine 0.2% without epinephrine was placed in the subcutaneous tissue [Figure 4]. As part of the post-surgical analgesia protocol, patients received paracetamol 1 g IV during the wound closure and no other analgesic or hypnotic was administered during intraoperative and post-anesthesia care unit (PACU) stay; after surgery, 1000 mg paracetamol per oral (p.o.) every 8 h, 50 mg dexketoprofen p.o. every 8 h, and 50 mg tramadol p.o. on demand.

Data collection and statistical analysis

Analyses were done with ANOVA-RM for the difference in means in repeated measurements, and with the Tukey Test between pairs. A $P < 0.05$ was considered significant. The study power was 85.7%. Data are presented as number (percent), mean (standard deviation, SD), and 95% confidence interval, CI. IBM-SPSS-22 was used for statistical analyses (IBM SPSS Statistics v. 22.0 for Windows; Armonk, NY, USA).

Results

Of 190 knee arthroplasty patients screened for eligibility, 99 patients were included in the study. Patients were excluded because of the placement of a previous prosthesis ($n = 46$), surgery without ischemia tourniquet ($n = 40$) or preoperative atrial fibrillation, sinus tachycardia, sinus bradycardia, atrioventricular block, or ventricular extrasystole ($n = 5$). Patient characteristics and demographic data are presented in Table 1.

Heart Rate

HR increased from period 2 to period 3 up to 16% (67 ± 14 to 77 ± 13 bpm, $P < 0.001$), and from period 2 to period 4 up to 21% (67 ± 14 to 81 ± 12 bpm, $P < 0.001$). The results are shown in Table 2 and Figure 5.
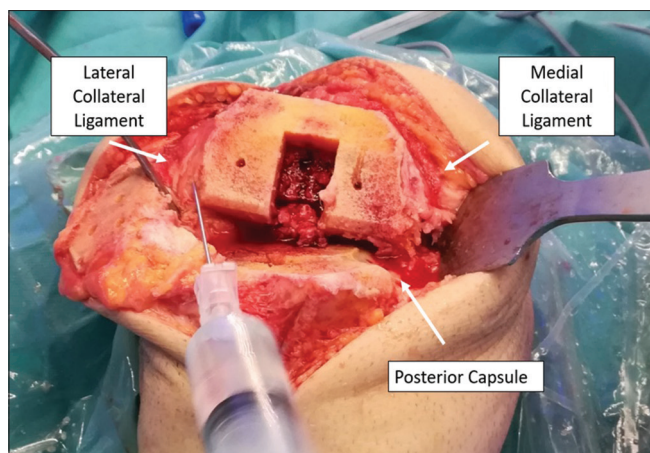
Figure 2: LIA before inserting the prosthesis: The first 100 mL with 1 mg epinephrine injected in the posterior joint capsule and both collateral ligaments before inserting the prosthesis
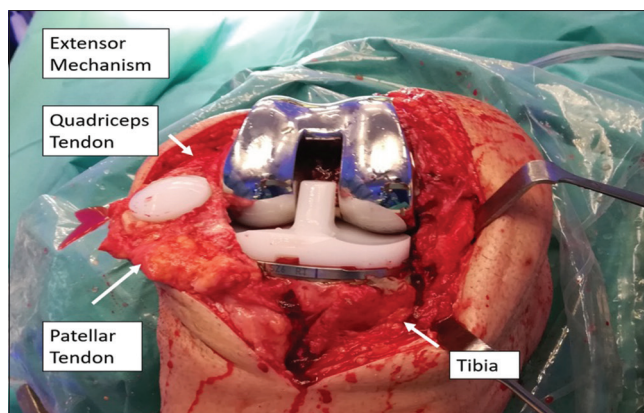

Figure 3: LIA after inserting the prosthesis: The rest of the mixture (50 ml) injected along the edges of the bone, where the retractors were placed, inside the capsule, in the quadriceps tendon intra-patellar ligaments and in the soft tissues

Figure 4: LIA subcutaneous tissue: Before wound closure, 50 mL of ropivacaine 0.2% without epinephrine in the subcutaneous tissue
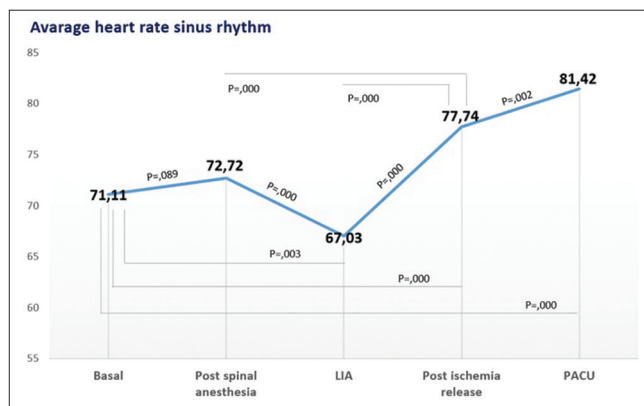

Figure 5: Heart rate sinus rhythm.(bpm). LIA: Local Infiltration Analgesia, PACU: Post anesthesia care unit

Seven patients (7%) had bradycardia during periods 1 and 2, with only one requiring atropine. Four patients (4%) had bradycardia during period 3 and one patient (1%) had an episode of bradycardia during period 4.

Mean arterial blood pressure
MAP showed no significant changes from period 2 to period 3 (89 ± 13 to 87 ± 13 mmHg, $P > 0.50$), and from period 2 to period 4 (89 ± 13 to 91 ± 11 mmHg, $P > 0.50$), respectively.

Four patients (4%) had hypotension during surgery (period 3), with three requiring ephedrine (10 mg) and one requiring phenylephrine (100 µg). The results are shown in Table 3 and Figure 6.

With respect to the use of vasoactive drugs that can affect the heart rate and blood pressure, six patients received atropine during period 1 and seven patients received ephedrine during period 2. One patient required urapidil and one patient required ephedrine and atropine during period 3. In period 4, one patient required phenylephrine, one patient required atropine, and one patient required urapidil.

Table 1: Demographic data

Average age (year)	72±8
Gender	
Male	24 (24%)
Female	75 (75%)
Average BMI	30±7.97
ASA (%)	
I	19 (19%)
II	60 (60%)
III	21 (21%)
Medical History	
Hypertension	56 (56%)
Ischemia Time (min)	56±16
Average stay PACU (min)	160±17

ASA=American Society of Anesthesiology, AV=Atrioventricular, PACU=Post-anesthesia care unit. Values are mean (standard deviation) or number (percent), BMI=Body Mass Index

Table 2: Changes of heart rate in the observation periods

	HR (bpm)		Changes of HR					Incidence of bradycardia *n* (%)
	Mean (SD)	95% C.I.	Baseline	Period 1	Period 2	Period 3	Period 4	
Baseline	71 (9.9)	69.1/73.1	--	0.089	0.003**	0.000**	0.000**	
Period 1	72 (11.6)	70.4/75.0		--	0.000**	0.000**	0.000**	7 (7)
Period 2	67 (13.8)	64.3/69.8			--	0.000**	0.000**	7 (7)
Period 3	77 (12.9)	75.1/80.3				--	0.002**	4 (4)
Period 4	81 (12.3)	78.9/83.9					--	1 (1)

Period 1. Establishment of spinal anesthesia to prior to LIA administration, period 2. Administration of LIA to before release of ischemia tourniquet, period 3. Ischemia tourniquet release to end of the surgery, Period 4. Patients' transfer to the post-anesthesia care unit to patients' discharge to the ward. SD, standard deviation, C.I., confidence interval, HR, heart rate in beats per minute. Statistical analyzes were performed as ANOVA-RM with the Tukey Test between the periods. Differences were considered significant (**) if *P*<0.05

Table 3: Changes of mean arterial pressure in the observation periods

	MAP (mmHg)		Change of MAP				
	Mean (SD)	95% C.I.	Baseline	Period 1	Period 2	Period 3	Period 4
Baseline	99 (10.9)	97.5/101.9	--	0.000**	0.000**	0.000**	0.000**
Period 1	87 (8.1)	85.7/88.9		--	0.226 NS	0.844	0.003**
Period 2	89 (12.6)	86.4/91.4			--	0.143	0.111
Period 3	87 (12.7)	84.5/89.6				--	0.007**
Period 4	91 (11.4)	89.2/93.7					--

Period 1. Establishment of spinal anesthesia to prior to LIA administration, period 2. Administration of LIA to before release of ischemia tourniquet, period 3. Ischemia tourniquet release to end of the surgery, period 4. patients' transfer to the post-anesthesia care unit to patients' discharge to the ward. SD, standard deviation, C.I., confidence interval, MAP, mean arterial pressure in mmHg. Statistical analyzes were performed as ANOVA-RM with the Tukey Test between the periods. Differences were considered significant (**) if *P*<0.05
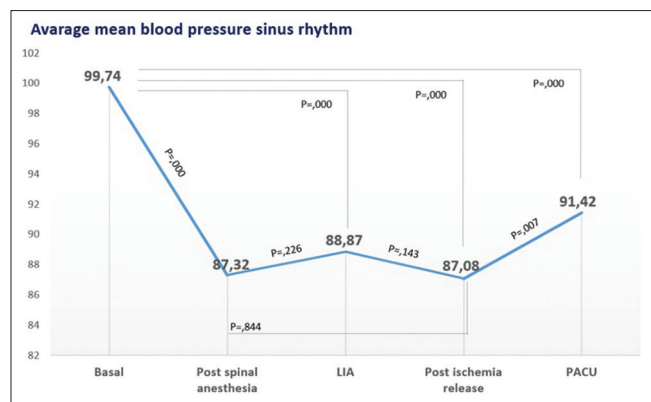

Figure 6: Mean arterial blood pressure (mmHg). LIA: Local Infiltration Analgesia, PACU: Post-anesthesia care unit

Cardiac rhythm

Seven patients showed ventricular extrasystole (7%) and eight experienced sinus tachycardia up to 125 bpm (8%). No other arrhythmias were found. These rhythm changes were observed after release of the ischemia tourniquet and during the stay in the PACU. Pharmacological or electrical cardioversion treatment was not necessary. We reviewed the clinical history since 24 h after LIA to discharge of hospital and no adverse events were reported.

Discussion

Patients in our study did not experience clinically significant hemodynamic compromise despite high volume (150 ml) and high dose (300 mg) of LIA for TKA.

Interest in LIA and in the effects of peri-articular infiltration (the absorption process, safety profile, and possible collateral effects) developed from 2010 when a reduction in overall morphine consumption and in pain intensity was observed with LIA.[6] Although currently considered a safe technique,[1,7] LIA could have a high incidence of toxic effects of ropivacaine as well as epinephrine due to vasoconstriction and a tachycardia effect. Unintentional intravascular injection of local anesthetics during regional anesthesia could produce severe cardiotoxic reactions, including hypotension, atrioventricular block, idioventricular rhythms, and arrhythmia such as ventricular tachycardia and fibrillation.[16]

It is known that ropivacaine is absorbed,[1] but when epinephrine is added it is not clear whether the combined vasoconstrictor effect would allow greater hemodynamic stability, with less bradycardia and hypotension than were reported before the administration of LIA, since epinephrine could mask hypotension and bradycardia. Hypotension in TKA could be related to ischemia tourniquet, which is widely used during orthopedic surgery and the value of which is debated. Ischemia produces free oxygen radicals and induces many kinds of tissue damage, such as the disturbance of intracellular homeostasis, lipid peroxidation, membrane disintegration, and hyperkalemia.[17] After deflation of the ischemia tourniquet, sudden hypotension (MAP <60 mmHg or MAP decrease of more than 30% from baseline) could be attributed to reactive hyperemia to the leg and to systemic absorption of locally produced metabolites.

On the other hand, in 2016 a retrospective study was performed investigating the cardiovascular safety of ropivacaine as part of high-volume LIA.[10] This study showed that intraoperative LIA administration does not cause a difference in the incidence of bradycardia during surgery, but a significantly lower incidence of hypotension was found in the group treated with the LIA protocol. It was surmised that there could be a protective factor with respect to hypotension, but until now no studies have evaluated the hemodynamic changes associated with LIA administration.

Ropivacaine is known to inhibit the rapid inward flow of sodium ions into cardiac cells during depolarization, thereby slowing the rate at which the action potential increases during phase 0. Recovery from sodium channel block is faster after treatment with ropivacaine than after bupivacaine,[18] which means that ropivacaine's safety profile is better than that of other local anesthetics. Ropivacaine is less toxic in terms of cardiovascular and central nervous systems effects,[19] and has intrinsic vasoconstrictive properties that help reduce absorption.[20] This could be related to its lower cardiotoxicity in comparison with levobupivacaine and bupivacaine. Doses of ropivacaine used for LIA or peripheral nerve blocks are considered high doses because they often exceed the recommended maximum of 3–4 mg/kg.[21] Therefore, it is not unreasonable to assume that adverse hemodynamic effects could be associated with LIA; the doses used were greater than recommended although average BMI in our patients group was 30 Kg/M^2. Fenten *et al.* described a median time of 240 min to reach a maximum plasma concentration after tourniquet release following administration of a single shot of ropivacaine (200 ml 0.2%) with epinephrine,[22] and a later peak when ropivacaine was given without epinephrine.[19] After peri-articular LIA for total knee arthroplasty and despite a great inter-individual variability, the authors found that the serum concentrations of ropivacaine remained below the assumed systemic toxic thresholds of 4.3 mg/ml (ropivacaine) and 0.56 μg/ml (epinephrine) after single-shot ropivacaine (200 ml 0.2%) and 0.75 mg epinephrine (1000 μg/ml). In addition, these were not correlated with hemodynamic changes and concentration peaks.[22]

We observed significant differences between the average HR values during the different study periods, including a major increase of 16% after the post-ischemia release and with a moderate increase of 4.7% on arrival at the PACU together up to 20%. MAP remained similar, without significant changes from the start of LIA until the arrival of the patient in the PACU. If this were associated with release of the ischemia tourniquet, it would have the same effect as starting a perfusion with local anesthetics and LIA. Ohmura *et al.* noted a significant increase in MAP after the beginning of drug infusion with ropivacaine 0.5% at a rate of 2 mg/kg/min,[20] and Knudsen *et al.* described a mean increase in systolic pressure of 7% and an increase of up to 12% in HR after starting ropivacaine infusion with a ropivacaine total dose of 160 mg IV in healthy volunteers.[18]

Increase in HR without significant variation in MAP after release of tourniquet periods 3 and 4 observed in our study could be related to ropivacaine absorption. The 1 mg of epinephrine, also absorbed, would make a synergy to avoid hypotension and bradycardia and exceeds the hemodynamic impact of the ischemia release, masking the changes that were observed before the installation of LIA.

Kastelik *et al.* have compared LIA versus sciatic nerve and adductor canal block for fast-track knee arthroplasty. This study concludes that both analgesic regimens allow early mobilization after TKA with high patient satisfaction, but the intraoperative blood loss was higher in LIA group (365 ml ± 158 vs. 347 ml ± 154, *P* = 0.065)[23] which could be in relation with higher MAP, although in this study MAP data were not collected.

Some patients could be more susceptible to rhythm changes and could experience arrhythmias. In our study, up to 15% of our patients had some sort of rhythm disturbance, for instance, sinus tachycardia and extrasystole. This is important to take into account, especially in patients with a history of cardiac arrhythmia who could benefit, for example, from the administration of ropivacaine without epinephrine or the use of ropivacaine in a lower dose or even from a lack of LIA administration.

The growing interest in developing new techniques for post-TKA pain management has led to several studies where a comparison with the LIA is essential.[24] Recently, LIA vs. intrathecal morphine has been compared[25] and found that pain control is better in LIA compared with intrathecal morphine 0.3 mg at 24 and 48 h following TKA, but in the majority of studies, intraoperative data were not collected about the hemodynamic changes with respect to the techniques evaluated.

LIA has so far been difficult to overcome in terms of analgesic efficacy, surgical time, early mobilization, and adverse effects. Our study provides more information in favor of LIA in terms of hemodynamic stability, analyzing HR, MAP, and arrhythmias by period, which could influence the decision of which analgesic technique is superior. Currently,

there is considerable debate regarding the optimal choice of postoperative pain management PROSPECT.[26]

The main limitation of our study is that the results and findings are preliminary. They must be confirmed in a randomized controlled trial which also includes a control group. A second limitation was our inability to keep patients in the PACU for an extended period. None of patients had presented any adverse event related to hemodynamics, neither required ICU admission for any events. A further limitation is that blood pressure was measured non-invasively every 5 min, whereas other parameters were measured constantly and collected by the departmental anesthesia software. Thus, some hemodynamic events could have gone unnoticed.

In conclusion, the administration of 1 mg of epinephrine in the context of local infiltrative analgesia with ropivacaine seemed to contribute to hemodynamic stability during the withdrawal of preventive ischemia. The increase in HR, although statistically significant, did not have an impact on hemodynamics' profiles, without events suggest systemic local anesthetics' toxicity.

Randomized controlled studies with a control group receiving LIA without epinephrine are necessary to further evaluate these preliminary results.

Acknowledgements

Authors' Statements

Informed consent

Informed consent has been obtained from all individuals included in this study.

Ethical approval

This study was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board.

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Conflicts of interest

There are no conflicts of interest.

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