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Research Article

Effects of Intravenous Lidocaine in Total Knee Joint Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: We hypothesized that a single preemptive bolus dose of intravenous lidocaine (IV lidocine) would result in better analgesia, reduced total opioid consumption, shortened hospital length of stay (LOS) and better functional outcomes after unilateral primary Total Knee Arthroplasty (TKA).

Methods: 62 adults undergoing unilateral primary TKA were enrolled in this prospective, randomised, double-blind, placebo-controlled trial. They received either pre-incision IV lidocaine (2mg/kg) or placebo. All received standardized spinal anesthesia, local infiltration analgesia and postoperative analgesia. Primary endpoints were postoperative pain scores, measured by Numerical Rating Scale (NRS), and cumulative opioid consumption. Secondary outcomes included LOS, walking distance, active and passive range of movement (ROM), occurrence of Local Anesthetic Systemic Toxicity (LAST), constipation, nausea and vomiting (PONV), dizziness and Modified Barthel Index (MBI).

Results: Although not statistically significant, on both postoperative day 1 and 2, the lidocaine group demonstrated a lower NRS (at rest & upon movement) and longer walking distance averaged 5 metres more ($p = 0.325$, mean ± S.D. [95% C.I.] 61.00 ± 21.67m [53.09 - 68.91] vs. 55.00 ± 25.02 m [45.87 - 64.14]). Noticeably, the lidocaine group had significantly shorter LOS ($p=0.0313$, median [IQR] 3 days [3-4] vs. 4 days [3-4]). The 2 groups did not differ significantly regarding other secondary outcomes. Importantly, no LAST was recorded.

Conclusion: While a single pre-emptive bolus of IV lidocaine (2mg/kg) failed to attain statistically significant postoperative analgesia, this regime was safe and associated with shortened LOS by 1 day in patients undergoing unilateral TKA.

Trial registration: NCT0359776

Keywords: Intravenous lidocaine; Knee Arthroplasty; Acute pain; Anaesthesia, Spinal; Length of Stay

Introduction

Primary Total Knee Joint Arthroplasty (TKA) is among the most commonly performed procedures. Every year, while more than 2000 TKA are conducted in Hong Kong, over 10 000 patients are on the waiting list in the public sector [1].

TKA is associated with significant postoperative pain [2]. Poor pain control increases the risks of myocardial infarction, pneumonia and the development of chronic pain. It also impacts the recovery by delaying mobilization and prolonging the hospital stay [3].

Lidocaine is an amide-type local anaesthetic that has been repeatedly shown to be effective pain relief in major abdominal surgeries when administered as infusion perioperatively [4]. The mechanisms of action may involve the inhibition of N-methyl-d-aspartate (NMDA) receptors [5] and polymorphonuclear (PMN) granulocyte priming [6]. Systemic lidocaine also inhibits the secretion of various inflammatory cytokines, such as IL-6, IL-8 and IL-1 Ra [7-8].

TKA involves substantial bone drilling and tissue injury, thus provoking a large inflammatory reaction. Similar to abdominal surgeries, systemic lidocaine may be effective analgesic and accelerate recovery in TKA. However, there is no randomized controlled trial done to study its effect on TKA.

We hypothesized that in adult patients undergoing TKA, a pre-

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emptive bolus dose of intravenous lidocaine would effectively reduce acute pain, decrease opioid consumption, improve rehabilitation and functional scorings in the initial postoperative period following TKA.

Methods

Study design

This was a prospective, single-center, double-blind, randomized, placebo-controlled trial. The trial was approved by the local university's Institutional Review Board (UW-18-26) and registered with an international clinical trials registry (www.clinicaltrials.gov, NCT0359776, https://clinicaltrials.gov/ct2/show/NCT03597776) before patient recruitment. Patients undergoing primary unilateral TKA were assessed for eligibility during preoperative screening visits. All eligible patients were informed about the study and written informed consent obtained. The study was conducted between January 2019 and January 2020 at the Duchess of Kent Children Hospital (DKCH), Hong Kong, in accordance with the ICH guidelines for Good Clinical Practice. CONSORT 2010 Statement was adopted as the reporting guideline. The full trial protocol is available to the reader upon request to the corresponding author.

Population

Eligible participants were all adults, aged 18-80 and with American Society of Anesthesiologists (ASA) physical status classification I-III, who were scheduled for primary unilateral TKA under spinal anaesthesia.

Exclusion criteria were defined as: any contraindications to or failed spinal anaesthesia, known intolerance or contraindication to local anaesthetics, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS) or opioids, single stage bilateral TKA / revision TKA, chronic pain other than knee pain, chronic use of opioids, substance abuse, cardiac disease (any degree of heart block / heart failure), any seizure disorder, psychiatric illness affecting pain perception; impaired renal function (defined as preoperative eGFR < 30ml /min /1.73 m2), impaired hepatic function, pregnancy, inability to use patient-controlled analgesia (PCA), patients' refusal or inability to understand Cantonese.

Randomization & blinding

Patients were randomized to either the Lidocaine-group or the Placebo-group using a computer -generated random table (by a blinded research assistant) and an allocation ratio of 1:1. Allocation was concealed by enclosing assignments in sealed, opaque and sequentially numbered envelopes, which were opened only in the operation theatre. A "blinded" anaesthetist then prepared either lidocaine or saline according to the assigned group for the attending anaesthetist. Blinding of the healthcare professionals and the research personnel was maintained during the whole study period including all postoperative follow-ups.

Study intervention

For the Lidocaine-group, a bolus of intravenous lidocaine of 2mg/kg over 5 minutes was administered before skin incision. As for the Placebo-group, normal saline of equal volume was injected as bolus before skin incision.

Anesthesia and Perioperative Treatment

Pre-operative care

Routine preoperative assessment was performed at the pre-admission clinic or at the general ward. No analgesics or sedatives were prescribed as premedication. A preoperative Electrocardiogram (ECG) was recorded to document any baseline arrhythmia.

Intra-operative care

Spinal anaesthesia was performed aseptically after the establishment of intravenous cannula and attachment of standard monitoring. The choice of equipment (Whitacre or Quincke Needle), technique (landmark or ultrasound-guided) and approach (midline or paramedical) were at the discretion of the attending anaesthetists. An intrathecal dose of 2.2-2.6ml 0.5% heavy bupivacaine with 15mcg of fentanyl was given depending on the height of the patient. Vasopressors and intravenous fluids were given as necessary to maintain the patient's blood pressure within 20% of his/her baseline.

Target Controlled Infusion (TCI) of propofol under the modified Marsh effect site model was prescribed to achieve sedation. No additional systemic analgesics were given, including paracetamol, NSAIDS, ketamine and opioids intraoperatively. A standardized dose of Local Infiltration Analgesia (LIA) (40ml 0.75% ropivacaine, 0.5ml 1:200,000 adrenaline, 30mg ketorolac in 60ml normal saline) was administered by the orthopaedic team.

The surgeries were performed by the same team of orthopaedic surgeons specializing in TKA at a tertiary level university teaching hospital, using standardized surgical technique. All patients received posterior stabilized knee prosthesis.

Post-operative care

After the surgery, the patients were taken care at a dedicated postanesthetic care unit (PACU) for at least 30 minutes. Vital signs were monitored every 5 minutes in addition to continuous ECG monitoring. Signs and symptoms of local anaesthetic toxicity (LAST) were assessed at 15-minute interval.

Pain was evaluated every 5 minutes using NRS. If the score was greater than 4/10, 2mg morphine would be given intravenously every 5 minutes provided the patient's respiratory rate was >12/min and a sedation score < 1 until a NRS of < 4/10 was achieved. Then, a PCA device would be connected to deliver morphine under a standardized regime (1mg bolus with 5 min lockout, an hourly maximum of 0.1mg/kg without background infusion).

A post-op ECG was conducted at the 4th hour post administration of the study drug. LAST was also assessed clinically hourly for 4 hours after operation. Blood pressure, heart rate, pulse oxygen saturation and sedation score were monitored hourly while on PCA morphine, which was switched to 4-hourly once PCA morphine was terminated.

The standardised postoperative analgesics consisted of:

- PCA morphine for at least 1 day postoperatively. It would be terminated on postoperative day (POD) 1 if the numerate rating scale (NRS) upon movement was less than 4/10 or when 24-hour morphine consumption was less than 10mg

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- Oral paracetamol 1gram QID for 1 week, pregabalin 75 mg nocte for 1 week and celecoxib 200mg BD for 5 days if body weight (B.W.) > 50kg
- Oral paracetamol 1gram TDS for 1 week, pregabalin 50mg nocte for 1 week and celecoxib 200mg daily for 5 days if BW < 50kg
- 0.1mg/kg of intramuscular morphine Q4H as rescue analgesic for any breakthrough pain
- Intravenous ondansetron of 0.1mg/kg Q8H as necessary for nausea and vomiting

Diet was resumed on POD 0. A standardized rehabilitation programme was carried out by the same team of physiotherapists and occupational therapists with the goal of early mobilisation.

Outcome measurements

Demographics and the confounding factors were collected during the pre-op assessment, which included age, gender, ASA physical status, duration of preoperative pain, preoperative NRS (0=no pain, 10=worst possible pain) upon movement and rest, preoperative knee deformity and both active and passive ROM of the knee as assessed by the attending physiotherapists.

Primary outcomes were NRS during movement or at rest and morphine consumption. A research assistant and the pain team blinded for group allocation visited the patient three times daily to assess postoperative pain scores and the cumulative morphine consumption.

The team also assessed secondary outcomes including signs and symptoms of LAST, nausea/vomiting (PONV), dizziness and constipation. The physical therapists charted patients' ability to mobilise (i.e. the active and passive ROM of the knee joint and walking distance). The patients' self care ability, including toileting, the ability to wear trousers and the Modified Barthel Index (MBI), was gauged by the occupational therapists. Both the physical and occupational therapists were blinded for the group allocation. The length of hospital stay (LOS) of each patient was also retrieved after discharge.

Statistical Analysis

Sample size

Our null hypothesis was that there was no difference in the postoperative NRS pain score or total morphine consumption between the Lidocaine-group and the Placebo group.

In a local study that used a 10-point VAS pain scale, the mean (standard deviation) postoperative VAS pain score was around 3.1 (1.1) in patients who underwent primary TKA with a similar LIA regimen [9]. On this basis, the sample size necessary to detect at least a 30% difference with 80% probability and alpha < 0.05 was 38 patients in total (19 in each group). A 30% difference in NRS pain score was chosen because this has been shown to correspond to 'much improvement' in pain relief [10].

Regarding morphine consumption, a review of the literature on TKA in Chinese patients showed that the total does of postoperative morphine consumption was around 20mg (6.8) [11]. With an expected 25% reduction in morphine consumption, at an alpha set at 0.05 and 80% power, a total of 60 patients (30 in each group) would be required. Given that a 35% reduction in cumulative morphine consumption was reported in patients undergoing major abdominal surgeries [4], allowing some margins of errors, an expected 25% reduction in total morphine consumption was opted.

As a result, the minimal target sample size was 60. Considering potential drop-outs, we proposed to include 90 patients in total (45 in each group).

Data analysis

The statistical analyses were conducted using an intention-to-treat analysis with SPSS Statistics version 25 (IBM Corp., USA) and GraphPad Prism version 8.4.3 (GraphPad Software, Inc.,La Jolla, CA). Parametric data were presented as mean ± S.D using an unpaired Student t Test. Non-parametric data were presented as median + Inter-Quartile Range (IQR) and compared with a Man-Whitney U Test. Categorical data were presented as percentages and compared with Chi-Square Test or Fisher's exact test. A p-value of < 0.05 was considered significant.

Results

The recruitment chart is shown below (Figure 1). Among the 199 patients who were assessed, while 101 patients were excluded, 36 patients declined to participate. Thus, 62 patients were randomized to the Lidocaine-group (n = 31) or Placebo-group (n = 31). All enrolled subjects received the allocated intervention and were included in the intention-to-treat population. The drop-out was 0%. The whole recruitment started from January 2020 to December 2020

Preoperative Assessment and Intra-Operative Data

Patients' baseline characteristics, intra-operative and PACU-related measures were all comparable (Table 1, 2).

Primary Outcomes

Although not statistically significant, NRS was generally lower in the Lidocaine-group compared to the Placebo-group on POD 1 morning and afternoon; for POD1 morning (P = 0.877; mean ± S.D. [95% C.I.] 2.81 ± 2.44 [1.93-3.69] vs. 2.97 ± 2.67 [1.99-3.94] NRS at rest; P = 0.827; 3.92 ± 2.33 [3.08 – 4.76] vs. 4.20 ± 2.52 [3.28 – 5.12] NRS upon movement) and for POD1 afternoon (P = 0.741; 2.89 ± 2.92 [1.84 – 3.94] vs. 3.00 ± 2.71 [2.03 – 3.97] NRS at rest; P = 0.741; 5.34 ± 2.63 [4.39 – 6.29] vs. 5.47 ± 2.36 [4.62 – 6.32] NRS upon movement) (Figure 2, Table 3).

The cumulative PCA consumption (p=0.624, mean ± S.D. [95% C.I.] 2.36 ± 3.06mg [1.23-3.48] vs. 1.97 ± 3.13mg [0.82-3.11]) did not show any statistically significant difference between the 2 groups postoperatively (Table 3). Both groups did not receive any IMI rescue morphine or oral opioids.

Secondary Outcomes

The Lidocaine-group had statistically significant shorter hospital LOS (p=0.0313, median [IQR] 3 days [3-4] vs. 4 days [3-4]) (Figure 3).

Though not statistically significant, the Lidocaine-group mobilised better with longer walking distance both on POD 1 (p = 0.325, mean ± S.D. [95% C.I.] 61.00 ± 21.67m [53.09 - 68.91] vs. 55.00 ± 25.02 m [45.87 - 64.14]) and POD 2 (p = 0.193,

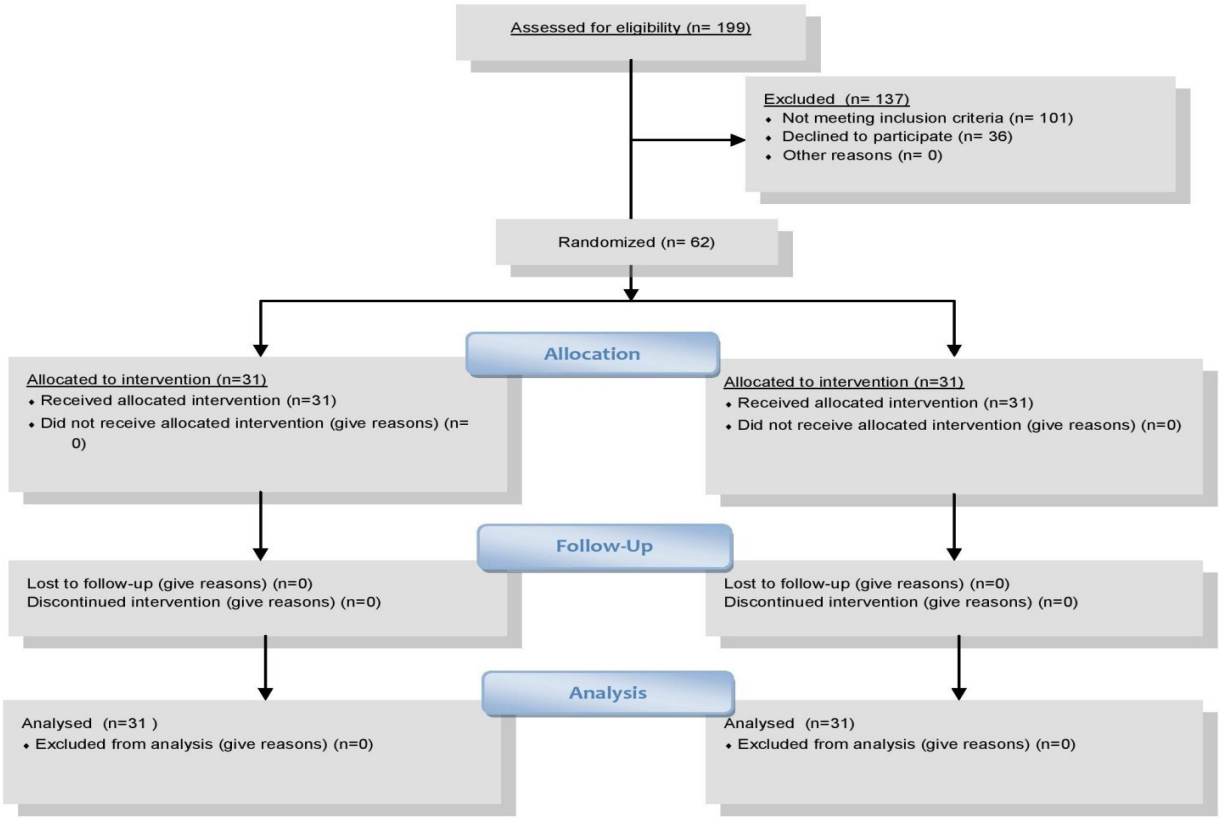

Figure 1: Patient's recruitment.

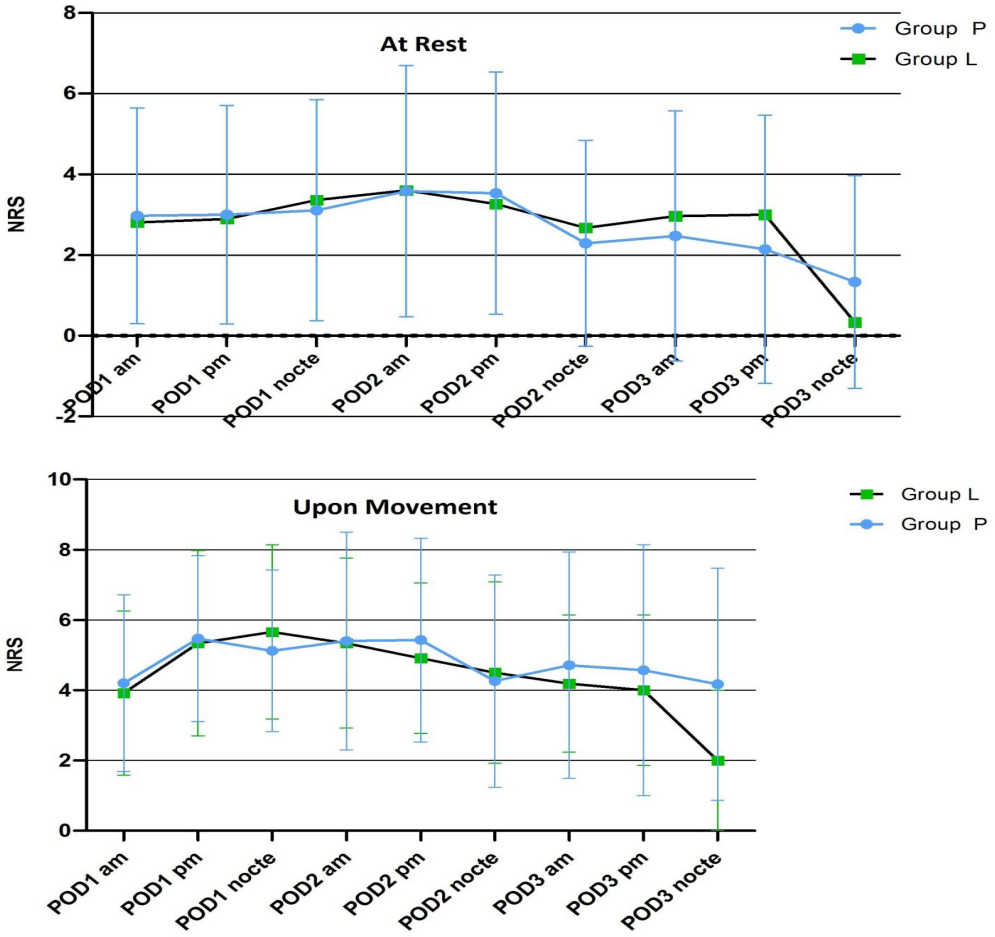

Figure 2: Initial post-operative pain scores at rest and upon movement.
**Although no significant difference was detected, the mean NRS was generally lower in the Lidocaine group both at rest and upon movement.*
† Data presented as mean ± S.D.
‡ am: morning; Group L: The Lidocaine group; Group P: The Placebo group; nocte: night; NRS: numeric rating scale.

Table 1: Pre-operative characteristics. Values in mean ± SD (range) or % (n).

	Placebo (n=31)	Lidocaine (n=31)	*p* value
Pre-operative characteristics			
Body weight (kg)	63.1 ±10.1	68.6 ±12.0	0.054
	(46.0 – 86.4)	(43.8 – 88.5)	
Body height (cm)	153.6 ±5.9	154.4±7.4	0.642
	(143 – 166)	(130 – 170)	
Age	67.5± 6.0	67.52 ± 8.6	0.445
	(52-76)	(46-80)	
ASA			0.867
● ASA I	19.4% (6)	16.1% (5)	
● ASA II	61.3% (19)	67.7% (21)	
● ASA III	19.4 % (6)	16.1% (5)	
Sex			0.52
● Male	22.6% (6)	16.1% (5)	
● Female	77.4% (24)	83.9% (26)	
Pre-operative pain			
NRS during movement	5.8 ± 3.2	5.8 ± 1.9	0.848
	(0 – 10)	(2 – 10)	
NRS at rest	1.2 ± 2.4	1.4 ± 2.2	0.61
	(0 – 8)	(0 – 6)	
Pain duration (months)	105.7 ± 60.1	99.5 ±60.9	0.615
	(6 – 240)	(6 – 240)	
Pre-operative range of movement			
Active extension (°)	3.5 ± 3.9	4.7 ± 4.3	0.237
	(0 – 15)	(0 – 15)	
Active flexion (°)	101.9 ± 11.1	101.0 ± 13.4	0.737
	(80 – 120)	(70 – 125)	
Passive extension (°)	3.5 ± 3.9	4.7 ± 4.3	0.272
	(0 – 15)	(0 – 15)	
Passive flexion (°)	102.3 ± 10.9	101.3± 12.8	0.626
	(80 – 120)	(75 – 125)	
Others			
Tibio-femoral angle(°)	7.2 ± 0.73 (varus)	7.4 ± 1.4 (varus)	0.693
	(5.4 – 9.0)	(6.3 – 14)	
Pre-existing Arrhythmia	0% (0)	0% (0)	1

**ASA: American Society of Anesthesiologists physical status classification; NRS: numerical rating scale*

Table 2: Intra-operative and PACU-related measures. Values in mean ± SD (range) or % (n).

	Placebo (n=31)	Lidocaine (n=31)	*p* value
Intra-operative			
Volume of heavy marcaine used (ml)	2.5±0.10	2.5±0.11	0.349
	(2.2 – 2.6)	(2.3 – 2.6)	
Arrhythmia	0% (0)	0% (0)	1
LAST	0% (0)	0% (0)	1
Post-Anesthesia Care Unit			
NRS during movement	0 ± 0	0 ± 0	1
	(0 – 0)	(0 – 0)	
NRS at rest	0 ± 0	0 ± 0	1
	(0 – 0)	(0 – 0)	
Intravenous morphine (mg)	0 ± 0	0 ± 0	1
	(0 – 0)	(0 – 0)	
Arrhythmia	0% (0)	0% (0)	1
LAST	0% (0)	0% (0)	1

** NRS: numerical rating scale; LAST: local anaesthetic systemic toxicity; PACU: Post-Anesthesia Care Unit*

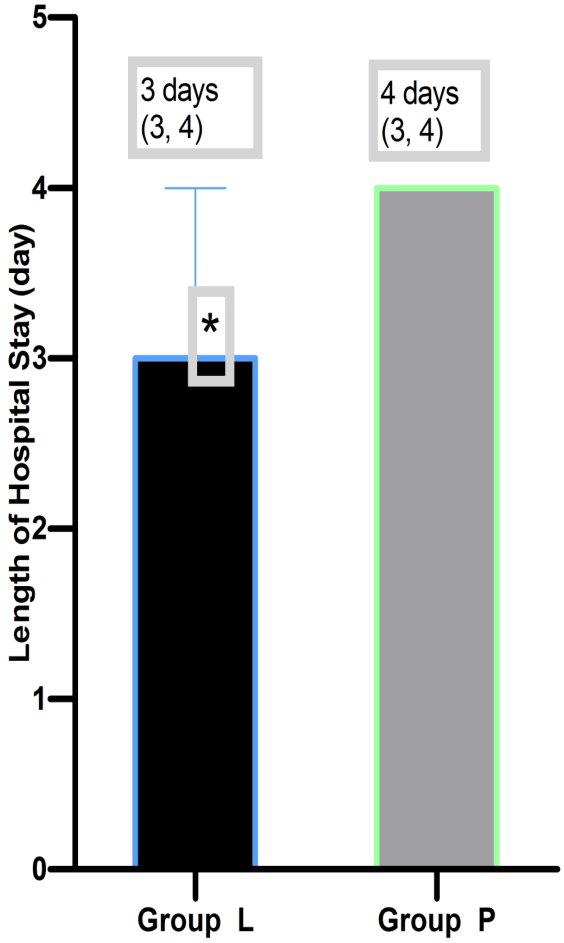

Figure 3: Hospital length of stay.
** The Lidocaine-group had a statistically significant shorter hospital LOS (p=0.0313, median [IQR] 3 days [3-4] vs. 4 days [3-4]).*
† Group L: The Lidocaine group; Group P: The Placebo group

70.00 ± 0.00 m [70.00-70.00] vs. 65.33 ± 13.56m [58.33 - 72.33]) (Table 4).

No statistically significant differences were detected in the other secondary outcomes such as active and passive ROM, the incidence of PONV, dizziness, return of bowel function, use of laxatives and antiemetics and various ADL scores. It is worth mentioning that no LAST or arrhythmia was reported in the Lidocaine-group (Table 4).

Discussion

The initially planned sample size was 90 in total with drop-outs taken into consideration. However, this study was terminated prematurely due to the COVID-19 outbreak, which suspended all clinical trials and elective operations. Yet given a 0% drop-out rate, the minimal target sample size of 60 was still reached without compromising the power of the study.

In general, the NRS scores (both at rest and upon movement) and the cumulative morphine consumptions were low in both groups. None of the patients requested the administration of intramuscular morphine as rescue analgesics. These features reflected the efficacy of the standard perioperative analgesic regime used and might explain the low incidence of PONV and dizziness observed.

Table 3: Post-operative pain. Values in mean ± SD (95% C.I.) or % (n).

	Placebo	Lidocaine	*p* value
	(n=31)	**(n=31)**	
NRS at rest			
PostOp Day 1 am	2.97 ± 2.67	2.81 ±2.44	0.877
	(1.99 – 3.94)	(1.93 – 3.68)	
PostOp Day 1 pm	3.00 ±2.71	2.89 ±2.92	0.741
	(2.03 – 3.97)	(1.84 – 3.94)	
PostOp Day 1 nocte	3.11±2.74	3.36 ± 3.07	0.852
	(2.13 – 4.10)	(2.25 – 4.46)	
PostOp Day 2 am	3.58 ± 3.11	3.60 ± 3.38	0.864
	(2.46 – 4.70)	(2.38 – 4.81)	
PostOp Day 2 pm	3.53±3.00	3.26 ± 2.71	0.729
	(2.45 – 4.62)	(2.25 – 4.27)	
PostOp Day 2 nocte	2.29±2.55	2.67 ±2.86	0.749
	(1.17 – 3.40)	(1.31 – 4.02)	
PostOp Day 3 am	2.47±3.10	2.96 ±2.38	0.385
	(0.97 – 3.98)	(1.64 – 4.28)	
PostOp Day 3 pm	2.14±3.32	3.00 ±2.51	0.297
	(0.37 – 3.92)	(1.23 – 4.77)	
PostOp Day 3 nocte	1.33 ±2.64	0.33± 0.58	1
	(-0.19 – 2.86)	(-0.33 – 1)	
NRS upon movement			
PostOp Day 1 am	4.20±2.52	3.92±2.34	0.827
	(3.28 – 5.12)	(3.08 – 4.76)	
PostOp Day 1 pm	5.47±2.36	5.34±2.63	0.848
	(4.62 – 6.32)	(4.39 – 6.29)	
PostOp Day 1 nocte	5.12±2.30	5.66±2.48	0.304
	(4.28 – 5.96)	(4.77 – 6.55)	
PostOp Day 2 am	5.40±3.10	5.34±2.42	0.551
	(4.29 – 6.52)	(4.47 – 6.21)	
PostOp Day 2 pm	5.43±2.90	4.91±2.14	0.248
	(4.38 – 6.49)	(4.12 – 5.71)	
PostOp Day 2 nocte	4.26±3.02	4.50±2.58	0.897
	(2.92 – 5.62)	(3.26 – 5.72)	
PostOp Day 3 am	4.71±3.22	4.19±1.95	0.563
	(3.15 – 6.27)	(3.11 – 5.28)	
PostOp Day 3 pm	4.57±3.57	4.00±2.14	0.764
	(2.67 – 6.48)	(2.49 – 5.51)	
PostOp Day 3 nocte	4.17±3.30	2.00±2.00	0.365
	(2.26 – 6.07)	(-0.31 – 4.31)	
Post-operative opioid consumption			
PostOp cumulative PCA consumption (mg)	4.17±3.13	4.17±3.13	0.624
	(0.82-3.11)	(0.82-3.11)	
Rescue IMI morphine (mg)	0	0	N/A
Rescue oral opioids	0	0	N/A

**am: morning; IMI: intramuscular injection; nocte: night; N/A: not applicable; NRS: numerical rating scale; pm: afternoon; PCA: patient-controlled analgesia; PostOp: post-operative*

Of the two groups, the Lidocaine-group showed lower NRS at rest (POD 1 am & pm, POD 2 pm) and upon movement (POD 1 am & pm, POD 2 pm). The Lidocaine-group also demonstrated a longer walking distance on an average of 5metres on both POD1 and POD2.Although no statistically significant differences were observed for these outcomes individually, they may have cumulatively contributed to a statistically significant shorter hospital LOS of 1 day in the Lidocaine-group.

It has been shown that lidocaine exhibits a dose-dependent analgesic effect. In small doses (2 µg/ml), lidocaine inhibits ectopic impulse generation in peripheral nerves that are chronically injured; in moderate doses (5 µg/ml), lidocaine suppresses cen-

Table 4: Secondary Outcomes. Values in mean ± SD (95% C.I.) or % (n).

	Placebo	Lidocaine	*p* value
	(n=31)	**(n=31)**	
ROM – active extension (°)			
POD 1	16.21 ± 9.42	18.83 ± 8.38	0.262
	(12.71 - 19.70)	(15.78 - 21.89)	
POD 2	16.67 ± 13.20	18.75 ± 10.25	0.641
	(9.05-24.29)	(13.63 - 23.87)	
ROM – active flexion (°)			
POD1	91.90 ± 6.18	90.67 ± 8.68	0.535
	(89.60 – 94.19)	(87.50-93.84)	
POD 2	90.77 ± 10.58	90.00 ± 7.75	0.822
	(84.90 - 96.64)	(86.13 - 93.87)	
ROM – passive extension (°)			
POD 1	8.39 ± 6.88	10.67 ± 4.10	0.123
	(5.92 - 10.86)	(9.17 - 12.16)	
POD 2	9.64 ± 7.46	12.81 ± 7.06	0.242
	(5.66 - 13.63)	(9.28 - 16.34)	
ROM – passive flexion (°)			
POD 1	91.94 ± 8.33	93.17 ± 7.82	0.554
	(88.94 – 94.93)	(90.31 - 96.02)	
POD 2	93.85 ± 6.82	93.13 ± 6.02	0.765
	(90.07-97.63)	(90.12-96.14)	
Walking distance (metres)			
POD 1	55.00 ± 25.02	61.00 ±21.67	0.325
	(45.87 - 64.14)	(53.09 - 68.91)	
POD 2	65.33 ± 13.56	70.00 ±0.00	0.193
	(58.33 - 72.33)	(70.00-70.00)	
ADL Toilet			
POD1	96.8% (30)	93.3% (28)	0.612
POD2	100% (25)	100% (22)	1
ADL Trousers			
POD 1	96.8% (30)	93.3% (28)	0.612
POD 2	100% (25)	95.5% (21)	0.468
ADL MBI			
POD 1	89.54±5.19	89.41± 4.29	0.921
	(87.58 – 91.50)	(87.76 – 91.06)	
POD 2	92.41± 1.1	92.21± 1.45	0.716
	(91.74 – 93.08)	(91.37 – 93.05)	
Nausea			
POD 1	16.13% (5)	9.68% (3)	0.449
POD 2	9.68% (3)	6.50% (2)	1
POD 3	6.3% (1)	11.1% (1)	1
Vomiting			
POD 1	0% (0)	6.5% (2)	0.492
POD 2	0% (0)	6.5% (2)	0.492
POD 3	0% (0)	0% (0)	1
Dizziness			
POD 1	0% (0)	6.5% (2)	0.492
POD 2	0% (0)	6.7% (2)	0.238
POD 3	0% (0)	0% (0)	1
Constipation			
POD 1	35.48% (11)	16.13% (5)	0.082
POD 2	29.03% (9)	22.58% (7)	0.562
POD 3	18.75% (3)	10.0% (1)	1
Others			
Total dose of post-operative ondansetron (mg)	1.29 ±3.164	0.52 ±1.71	0.288
	(-0.04-2.62)	(-0.11-1.14)	
Use of laxative	54.84% (17)	43.33% (13)	0.309
Incidence of arrhythmia	0% (0)	0% (0)	1
Incidence of LAST	0% (0)	0% (0)	1

**ADL: activities of daily living; LAST: local anesthetic systemic toxicity; MBI: Modified Barthel Index; NBO: no bowel opening; POD: postoperative day; ROM: range of movement*

tral sensitization and neuronal hyperexcitability; and in large doses (10 µg/ml), lidocaine exhibits general analgesic effects [12].

However, the routine use of LIA intraoperatively, which contained 300 mg of ropivacaine, significantly restricted the dose of lidocaine that could be administered without the concerns of causing LAST. Furthermore, continuous of infusion lidocaine postoperatively in the ward would require the patient to be connected to an infusion pump, which may be inconvenient and may thereby hinder the patient's mobilisation.

As such, a relatively low dose of lidocaine was opted, which may not be potent enough to produce clinically significant improvement in pain and other physical parameters.

Current studies and meta-analyses have suggested that IV lidocaine infusion provides significant analgesic effects and improves bowel function primarily in patients undertaken major abdominal surgeries [13-15]. However, such efficacy is not routinely demonstrated in patients having orthopaedic surgeries [16-17], including this study.

The reason for the discrepancy observed is not clear. Biochemically, the blood level of inflammatory mediators has been shown to be smaller and briefer after unilateral total hip replacement than after major abdominal surgeries [18]. Thus, for orthopaedic procedures, such as joint arthroplasty, which might possibly cause a lesser degree of inflammation , IV lidocaine might be less effective given anti-inflammation as one of its main mechanisms.

Clinically, patients undertaken orthopaedic surgeries are commonly encouraged to resume oral feeding and to mobilise through a more rigorous and structured rehabilitation program than patients undertaken major abdominal surgeries. These principles of ERAS, including multimodal opioid-sparing analgesia such as the regime used in this study, promote bowel movement. The effects of IV lidocaine on improving the bowel functions might therefore be less apparent in this patient population.

Moreover, the present study was powered solely for the primary endpoints. Significant difference on return of bowel function could possibly be unveiled after inclusion of a larger patient population. In fact, although not statistically significant, a lower incidence of constipation was observed in the Lidocaine group on POD 1-3 with less proportion of patients in the Lidocaine group in need of laxatives. For POD 1 ($p = 0.082$, 16.13% vs. 35.48%); POD 2 ($p = 0.562$, 22.58% vs. 29.03%); POD 3 ($p = 1$, 10.00% vs. 18.75%).

One limitation of this study was the relative low dose of a single bolus of IV lidocaine used. It is understood that a single bolus is less ideal than infusion in damping the inflammatory storms after TKA, which typically surge on POD 3 [19]. However, as discussed above, without the benefits of previous trials demonstrating the safety profiles of IV lidocaine in TKA, such was constrained by the concomitant use of LIA and the intent of promoting early mobilisation.

Secondly, the lidocaine concentrations and the cytokines levels were not measured in the present study. These parameters are believed to be important as they might explain the apparently varied effects of IV lidocaine between TKA and other major abdominal surgeries.

Thirdly, we did not study the long-term outcomes of perioperative IV lidocaine administration. In fact, some available data now suggest that a brief period of perioperative lidocaine administration, despite the lack of short-term benefits, may improve long-term outcomes after complex spine surgeries [20] and breast surgeries [21].

Whilst this study failed to demonstrate a statically significant reduction in NRS and morphine consumption in the Lidocaine group, it suggested an improvement in other parameters that may have led to a shorter hospital stay.

Further research should therefore aim at studying the biochemical pattern of inflammatory mediators generated after TKA and thereby attempt to devise an optimal dosing regimen of IV lidocaine for patients undergoing unilateral primary TKA. IV lidocaine remains an affordable and widely available addition to the analgesic regime that is integral to the enhanced recovery and rehabilitation of TKA.

Conclusion

The Lidocaine-group had lower NRS at rest and upon movement on POD 1 am & pm and longer walking distance averaged 5 metres on both POD1& POD2. Although no statistically significant differences were observed for these outcomes individually, they may have cumulatively contributed to a statistically significant shorter length of hospital stay of 1 day in the Lidocaine-group.

Type of the Manuscript

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