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COMPARISON BETWEEN LOCAL INFILTRATION ANALGESIA (LIA) AND EPIDURAL ANALGESIA FOR POSTOPERATIVE PAIN MANAGEMENT IN TOTAL KNEE REPLACEMENT SURGERY

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Abstract

Background: Local infiltration analgesia (LIA) is a novel and trending method for decreasing postoperative pain. The advantages of effective postoperative pain management include patient comfort and satisfaction, early ambulation, faster recovery with less likelihood of the development of neuropathic pain, and reduced cost of care. This Study was conducted to evaluate the efficacy of LIA over epidural analgesia. **Methods**: A total of 54 participants (27 in each group) who were undergoing total knee arthroplasty under spinal anaesthesia received epidural analgesia and local infiltration analgesia alternatively, both of which is standard post operative analgesic technique. The patients were followed up for post operative pain score and also watched for other adverse effects of the both procedure. **Results:** It was found that post operative pain at 24th hour was comparatively better in both the groups compared to 6th and 12th hour as the p value of 0.000 was statistically significant. Pain score was lesser in LIA group when compared with epidural group at all times as p value 0.000 was statistically significant. It was noted that mobilization time was better in LIA group when compared to epidural group. Incidence of nausea and vomiting was higher in epidural group.

Conclusion: In knee arthroplasty surgery, compared to epidural analgesia, LIA is seen to provide greater pain relief, is more economical and allow patient mobilization sooner.

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Keywords: Total knee arthroplasty, Local infiltration analgesia, epidural analgesia and visual analogue scale.

Introduction

Total knee arthroplasty (TKA) is one of the most successful surgeries, with 90% survival rate at 10–15 years and it is an elective surgical procedure that is reserved for patients experiencing chronic, debilitating symptoms that continue to persist despite of all conservative and non-operative treatment modalities [1-2]. The total knee and hip arthroplasties are one of the most cost-effective interventions which has increased quality-adjusted life expectancy. It is performed to relieve joint pain, increase mobility, and improve quality of life in end-stage diseases of the knee [3].

Multimodal analgesia includes preoperative, intraoperative, and postoperative analgesic regimens, aiming to maximize the analgesic efficacy through the combination of several analgesic regimens, while minimizing undesired adverse effects [4]. Adequate pre-emptive analgesia could prevent pain nociceptors from entering a state of hyperalgesia, and make acute postoperative pain easier to control, ultimately reducing opioid consumption there by providing opioid free anaesthesia [5]. Intra-operatively, Local infiltration analgesia (LIA) is performed by a surgeon at the end of the procedure that directly prevents the generation and conduction of pain signals from incision [6]. Increasing evidence shows that the anesthesia and analgesia agents administered in the perioperative period may affect the rates of surgical site infection, urinary retention, nausea and vomiting.

After total knee arthroplasty (TKA), there are a number of treatments for managing postoperative pain; however, each has drawbacks. It has long been standard practice to manage postoperative pain after major knee surgery by using peripheral nerve blocking or neuraxially given painkillers [7]. One type of neuraxially administered analgesic regimen that is widely accepted for postoperative pain control following total knee arthroplasty (TKA) is epidural analgesia (EA). It is more effective than intravenous opioids at relieving a variety of pain states. Its superiority has been hampered, although, by narcotic-related side effects such nausea, vomiting, hypotension, urine retention, pruritus, dizziness, somnolence, respiratory depression, and an increased risk of spinal infection or hematoma (in patients on anticoagulants) [8]. Peripheral nerve block (PNB) is another type of regional blockade (RB) that is frequently used to manage postoperative pain after major orthopaedic procedures. With a better side-effect profile and a lower risk of serious neuraxial problems, peripheral block offers postoperative analgesia that is on par with or even better than that acquired with EA or systematic opioids [9]. In theory, the procedures that are most commonly used during knee surgery include femoral nerve block (FNB), sciatic nerve block, obturator nerve block, and adductor canal block. FNB is the most often used of these. Surgeons' attention has been steadily drawn to delayed ambulation and unintentional in-hospital falls related to motor block. Usually utilized as adjuncts to FNB are obturator nerve block and sciatic nerve block. While uncommon, complications including localized infections and nerve injury cannot always be prevented.

In terms of postoperative pain control after total knee arthroplasty (TKA), local infiltration analgesia (LIA), as a multimodal analgesic strategy, has been the most significant

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advancement in recent years [10-11]. According to a prior study, intraoperative multimodal periarticular injection dramatically decreased the number of analgesics used after surgery, enhanced patient satisfaction, and showed no obvious concerns during the first 24 hours. Many level I trials have demonstrated that LIA is a viable substitute for RB in the management of postoperative pain, with a low incidence of side effects and an excellent safety profile. Conversely, some came to the conclusion that LIA had yielded inconsistent findings and been of ambiguous usefulness [12]. There is ongoing debate over the analgesic potential, functional value, and safety profile of LIA in comparison to regional block protocols that are frequently used, including PNB and EA.

Good analgesia after total knee replacement surgery (TKR) is of utmost importance to permit early mobilization of the joint. Local infiltration analgesia (LIA) is a novel and trending method for decreasing postoperative pain. The advantages of effective postoperative pain management include patient comfort and satisfaction, early ambulation, faster recovery with less likelihood of the development of neuropathic pain, and reduced cost of care. This Study was conducted to evaluate the efficacy of LIA over epidural analgesia.

Materials and Methods

This Quasi experimental study was conducted in department of anesthesia collaborated with Department of Orthopaedics, Yenepoya medical college and hospital, Mangalore, Karnataka. A total 54 participants who were undergoing total knee arthroplasty were put into two groups, group 1 is 27 participants Epidural (ED) and remaining 27 were local infiltrative analgesia (LIA) considered as group 2 and post operative pain is documented using visual analogue scale (VAS), blood pressure and heart rate at 6th, 12th& 24th hour post operatively. Time of restoration of joint movement, patient mobilization time and if any postoperative complications are noted. All the study participants were recruited after taken approval from the institutional ethics committee (IEC) along with that we also took consent form from all the study participants.

Criteria of the study

All the study participants aged between fifty (50) to seventy (70) years. The patients underwent total knee replacement surgery under spinal anaesthesia. ASA grade 2, 3 were included in this study. Patients having history of hemodynamic instability, disturbance of autonomic function, chronic analgesic therapy and impaired higher mental function were excluded.

Clinical examination

General pre operative assessment and pre anaesthetic assessment were done. Participants were given first-hand information about how the assessment was done.

Technique for group 1: Epidural catheter was placed in the epidural space using Tuohy needle by loss of resistance technique under aseptic precautions. 0.1 % ROPIVACAINE was used for postoperative on continuous infusion. Postoperative pain was analysed using visual analogue scale graded from 10 – 1, pulse rate and blood pressure after 6,12 and 24 hrs. Time of restoration of joint movement, patient mobilization time and if any postoperative complications were noted for both groups. Assessment of pain started as soon as the patient was shifted to the post operative room and followed up at 6^{th}, 12^{th}& 24^{th} hour interval or the

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point at which rescue analgesia was needed. Pain assessment was done by a 10 cm visual analogue scale (VAS); 0 no pain 10 worst imaginable pain. Change in heat rate and blood pressure were also monitored. Patient was reassessed for any side effects like nausea, vomiting, gastric irritation and respiratory depression at 30 minutes, 1,2,6,12 and 24 hours or till the need of rescue analgesia which was provided if the VAS was more than 5. Time of restoration of joint movement, patient mobilization time was documented.

Group LI: In group LI, local infiltration injection of a mixture COCKTAIL comprising of 100 ml Normal saline, 0.75 % of Ropivacaine 40 ml, Clonidine 75 mcg 1ml, Ketorolac 1 ml of 30 mg/ml, Adrenaline 1:1000 ½ cc of 1mg/1ml drugs was given using 20G hypodermic needle.

Components of the LIA mixture

Ropivacaine: Local anaesthetics diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane Na^+ channels; here they combine with hydrogen ions to form a cationic species which enters the internal opening of the Na^+ channel and combines with a receptor. This produces blockade of the Na^+ channel, thereby decreasing Na^+ conductance and preventing depolarization of the cell membrane. S-Ropivacaine is more potent and less cardio toxic than R-Ropivacaine. Their other properties of Ropivacaine have encouraged its use in knee replacement like vasoconstriction, anti-bactericidal property against Staphylococcus aureus and Pseudomonas aeruginosa, and anti-inflammatory effects. Adverse effects of Ropivacaine includes dizziness, tinnitus, circumoral paraesthesia, taste perversion, shivering, muscle twitching, tremors, generalized tonic clonic seizure, respiratory depression, tachycardia and hypertension.

Clonidine: Clonidine acts acutely by stimulating alpha-2 (pre-synaptic) adrenoceptors, thereby decreasing noradrenaline release from sympathetic nerve terminals and consequently decreasing sympathetic tone; it also increases vagal tone. The drug acts chronically by reducing the responsiveness of peripheral vessels to vasoactive substances and to sympathetic stimulation. The analgesic effects are also mediated by activation of alpha-2 adrenoceptors in the dorsal horn of the spinal cord.

Ketorolac: Ketorolac is a non-specific inhibitor of cyclooxygenase (CoX) which converts arachidonic acid to cyclic endo-peroxidases, thus preventing the formation of prostaglandins, thromboxanes, and prostacyclin leading to pain relief. Adverse effects include bleeding, cardiovascular risks and renal risks.

Adrenaline. Adrenaline is a directly acting sympathomimetic amine that is an agonist of alpha- and beta-adrenoreceptors; it has approximately equal activity at both alpha- and beta-receptors. Due to vasoconstrictor effect adrenaline causes less blood loss. Adrenaline also exerts analgesic effect through α2-agonists, and adrenoceptors can modify certain K+-channels in the axons of peripheral nerves, potentiating the impulse blocking actions of any Na+ -channel inhibitor. The injection is made in three stages using 50-mL syringes.

The first 50 mL was injected before implantation of components into the posterior capsule, peri-articular soft tissues postero-medially and laterally in extended position. Special care was taken to avoid infiltration of the common peroneal nerve and popliteal fossa to avoid injury to vessels and sciatic nerve. Then, while the cement was curing, the quadriceps mechanism and the retinacular tissues were infiltrated with an additional 50 mL of the mixture. Finally, before

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wound closure, the subcutaneous tissues were infiltrated with remaining solution and post operative pain was analysed using visual analogue scale graded from 10 – 1, pulse rate and blood pressure after 6,12 and 24 hrs. Time of restoration of joint movement, patient mobilization time and if any postoperative complications were noted.

Statistical analysis

The data distribution was tested by using Kolmogorov Smirnov test, where the normally distributed data was expressed as mean ± standard deviation (SD). The differences among the four groups of the study were analysed by independent t-test. The distribution between the variables and groups was done by bar diagrams. The statistical analysis was done by using Microsoft excel and SPSS software's. The P Value <0.05 is considered statistically significant.

Results

Table 1: Shows the descriptive statistics of the variables

Variables		**Mean (Standard Deviation)**
VAS Score 6th Hour	Epidural Analgesia	4.70 (1.163)
	Local Infiltration	3.37 (1.418)
VAS Score 12th Hour	Epidural Analgesia	4.07 (1.035)
	Local Infiltration	2.93 (0.874)
VAS Score 24th Hour	Epidural Analgesia	3.33 (0.832)
	Local Infiltration	2.41(0.747)
Systolic BP 6th Hour	Epidural Analgesia	124.37 (14.262)
	Local Infiltration	125.93 (12.788)
Systolic BP 12th Hour	Epidural Analgesia	131.48 (19.553)
	Local Infiltration	123.33 (12.089)
Systolic BP 24th Hour	Epidural Analgesia	124.44 (10.127)
	Local Infiltration	122.96 (11.030)
Diastolic BP 6th Hour	Epidural Analgesia	76.30 (10.432)
	Local Infiltration	77.19 (7.509)
Diastolic BP 12th Hour	Epidural Analgesia	74.07 (8.884)
	Local Infiltration	75.63 (8.431)
Diastolic BP 24th Hour	Epidural Analgesia	74.44 (8.006)
	Local Infiltration	76.67 (6.202)
Heart Rate 6th Hour	Epidural Analgesia	86.30 (15.312)
	Local Infiltration	81.78 (12.861)
Heart Rate 12th Hour	Epidural Analgesia	84.89 (14.937)
	Local Infiltration	81.67 (9.950)
Heart Rate 24th Hour	Epidural Analgesia	80.44 (9.171)
	Local Infiltration	81.26 (7.624)

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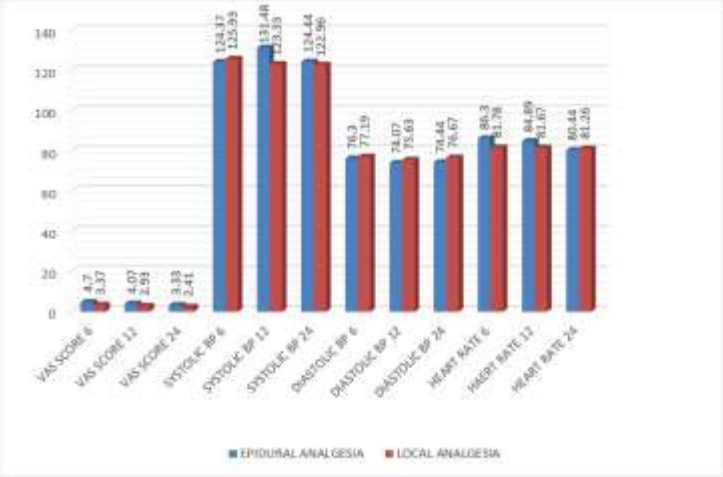

Figure 1: Shows the graphical representation of blood pressure

We performed RA-NOVA to compare between epidural analgesia and local infiltration analgesia at 6th, 12 and 24th hour time point for visual analogue score (VAS), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and $p < 0.05$ is considered as significant.

Table 2: Shows the tests of within-subjects' effects

Variables	Mean Square	P Values
VAS Sphericity Assumed	18.414	0.000
Systolic BP Sphericity Assumed	188.173	0.198
Diastolic BP Sphericity Assumed	49.210	0.292
Heart Rate Sphericity Assumed	149.463	0.063

Here in this table (within the subject) we performed Fisher's exact test to see the relation between VAS score, blood pressure, heart rate. we found that there is a significant difference between scores VAS within the groups at different time points of 6 12 and 24 hrs. VAS score is better at 24th hour compared to 12th hour and 6th hour in both epidural and local infiltration analgesia. whereas there is no significant difference in the Systolic & diastolic blood pressure or heart rate at 6th, 12th and 24th hour i.e. $p < 0.05$ which is significantly explained by sphericity assumption.

Table 3: Shows the tests of between-subjects effects

Group	F	P - Value
VAS Between ED & LI	1012.820	0.000
Systolic BP Between ED & LI	7696.894	0.351

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Diastolic BP Between ED & LI	7147.338	0.389
Heart Rate Between ED & LI	3390.630	0.420

Here in this table (Tests of Between-Subjects Effects) we can see that p value in VAS score is statically significant for epidural group and local infiltration group. mean VAS score is better in local infiltration analgesia group compared to epidural group. There is no significant difference in the Systolic & diastolic blood pressure or heart rate between the two study groups.

Table 4: OTHER VARIABLES

Variables		**Study Groups**		**P - Values**
		Epidural analgesia	**Local infiltration analgesia**	
Nausea / Vomiting	No	19	23	0.327
	Yes	8	4	
Mobilization Time	< or = to 24 hours	15	27	0.000
	> 24 hours	12	0	
Hospital Stay	< or = to 5 days	7	12	0.254
	> 5 days	20	15	
Rescue Analgesia	No	15	25	0.004
	Yes	12	2	

Here in this table, we can see that p value in mobilization time and rescue analgesia is statistically significant for epidural group and local infiltration group. It signifies that mobilization time is better in local infiltration analgesia group compared to epidural group and also the need of rescue analgesia for epidural group is more compared to local infiltration group. There is no significant difference in episodes of nausea/vomiting and the duration of hospital stay between the two subjects.

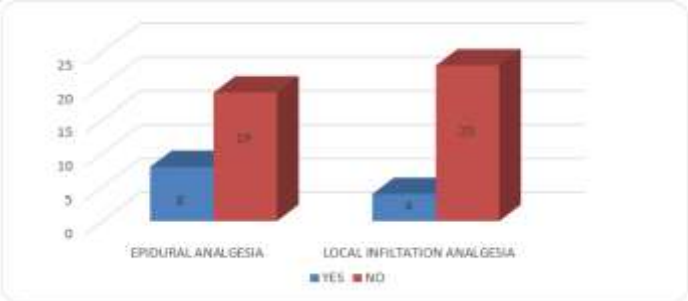

Figure 1:Distribution of nausea and vomiting amongst study group

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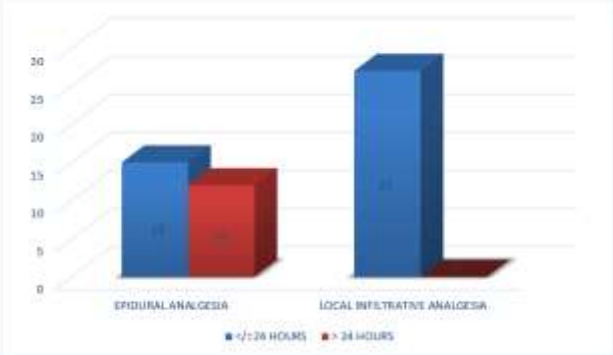

Figure 2: Distribution of mobilization time

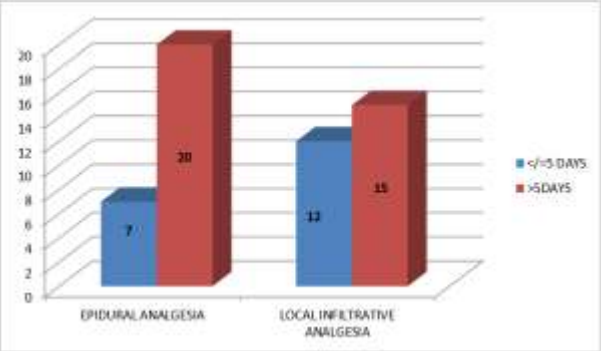

Figure 3: Hospital stay amongst study groups

Discussion

Early and effective pain relief after knee replacement surgery is necessary not only for patient satisfaction but also for early mobilization, faster rehabilitation and better outcome. Both LIA and EA resulted in low average pain intensity after 24 hours, at 6th and 12th hour assessment there is not statistically different. The LIA allows for early mobilization as it does not weaken the muscles [13]. The application of continuous epidural analgesia has been reported to lengthen motor block and bilateral effect compared to local infiltrative analgesia. In this study, the duration of motor block in patients with epidural analgesia was longer than that of the local infiltrative analgesia group [14]. The VAS scores of patients receiving continuous epidural infusion of 0.1% Ropivacaine were higher at 24th hour than those receiving LIA with ketorolac and ropivacaine. Nausea-vomiting has been noticed to occur more with epidural analgesia than with infiltrative analgesia but not statistically significant. This is considered as disadvantage of the epidural method. Hypotension was seen more frequently in the epidural analgesia [15].

The previous meta-analysis studies indicates that LIA has an equivalent efficacy for pain relieving and mobilization at early period when compared to EA after TKA and the range of motion was greater in LIA than EA at an early period after TKA [16-17]. The LIA had decreased occurrence of nausea and the length of hospital stay compared to EA. There was no significant difference between the occurrence of infection. Another systematic review and meta-analysis studies are reported on LIA and EA, the pain intensity was measured as VAS score at postoperative periods of 12, 24, 48, and 72 h after TKA and it was noted to be statistically insignificant [18-19]. The recent study performed a Cochrane review and

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concluded that EA may be useful for postoperative pain relief at early (4 to 6 hours) postoperative period following TKA [20]. Another recent study used the statistical network meta-analysis approach and found no differences between LIA and EA study groups comparing in terms of analgesia or opioid consumption 24 h after total hip arthroplasty [21].
The range of motion of the knee, was superior in LIA than EA in the early period after TKA. The drawback of LIA is the range of motion may not be an indicator for favourable pain control as the range of motion is increased due to motor block. Early functional recovery will be strengthened by functional quadriceps [22]. The other outcome variables compared were occurrence of nausea and infection. Epidural analgesia with a variety of opioids has a beneficial role in reducing pain intensity after surgeries. A high frequency of nausea or vomiting was present with opioids [23]. Local anesthesia is being considered as gold standard for postoperative pain control and the results show that LIA had decreased occurrence of nausea than EA. Along with that more nausea has been reported to occur with morphine used in EA compared to LIA and this is the disadvantage of the EA method compared to LIA [24]. The incidence of wound infection was comparable between both groups and kept at low level. There was no statistically significant difference between the occurrence of infection. Considering advantages and disadvantages of both methods it was difficult to conclude the superiority amongst the two groups.
In another recent randomized controlled trial comparing LIA with EA, compared a peri- and intra-articular technique with continuous epidural infusion combined with intravenous ketorolac treatment they found that the LIA was associated with an opioid-sparing effect and reduced intensity of pain for 48 hours [25]. Time spent in the post-operative care unit and number of days until discharge were shorter. But side effects were comparable except for constipation and urinary retention which was more in epidural. Patients in the study received 300 mg ropivacaine followed by 384 mg over a 48-hour period [26]. No toxic symptoms due to local analgesics were reported. In many previous studies, infiltration with 400 mg ropivacaine with or without intraarticular injection of 150 mg ropivacaine has shown plasma concentrations far below the toxic level (0.6 μg/mL). The non-steroidal anti-inflammatory drugs are commonly used analgesics for minor surgery and are useful adjunctive analgesics in patients undergoing major surgery, reducing pain and opioid requirements [27]. To our knowledge, this is the first study that has had adjustment for the systemic effects of intra-articular ketorolac. The two recent studies have investigated the effect of continuous intra-articular infusion after TKA, both the studies were assessed intra-articular infusion with bupivacaine compared to PCA epidural analgesia and they found no or poor effect.
There is no “gold standard” treatment to which all other treatment regimens can be compared therefore the epidural regime chosen for this study may not be optimal. Epidural analgesia can be improved through the synergistic effect of opioids. However, no difference in pain intensity scores between peri- and intra-articular injection of ropivacaine and ketorolac compared with continuous epidural infusion of ropivacaine plus morphine in 80 patients after total hip arthroplasty. However, they demonstrated an opioid-sparing effect and reduction in side effects using the intraarticular administration. There has been concern about the risk of infection with the use of intraarticular or wound catheters after major orthopaedic surgery.

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Conclusion

Pain relief after LIA in knee arthroplasty was better compared to epidural analgesia, and was better at 24th hour compared to 6th and 12th hour in both groups. Intra-articular technique offers advantages in its simplicity and minimal risk of complications compared to epidural analgesia. The opioid free good analgesia can be achieved with LIA compared to epidural analgesia. The LIA is more cost effective compared epidural procedure. In this study early mobilization of the joint was seen in LIA. The need of rescue analgesia was more in case of epidural analgesia. The same safety considerations as for intravenous or intramuscular ketorolac can be applied for ketorolac in LIA. RCTs are required to study the long-term effects of LIA for pain control after TKA.

Bibliography

1. Baier C, Springorum HR, Gotz J. Comparing navigation based in vivo kinematics pre- and post-operatively between a cruciate-retaining and a cruciate-substituting implant. Int Orthop. 2013;37(3):407-14.
2. Becker MW, Insall JN, Faris PM. Bilateral total knee arthroplasty: one cruciate retaining and one cruciate substituting. Clin Orthop Relat Res. 1990;(271):122-4.
3. Dennis DA, Komistek RD, Hoff WA. In vivo knee kinematicsnderived using an inverse perspective technique. Clin Orthop Relat Res. 1996;(331):107-17.
4. Gioe TJ, Killeen KK, Grimm K. Why are total knee replacementsnrevised? Analysis of early revision in a community knee implant registry. Clin Orthop Relat Res. 2004; 428:100-6.
5. Busch CA, Shore BJ, Bhandari R, Ganapathy S, MacDonald SJ, Bourne RB, *et al.* Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. J Bone Joint Surg Am 2006; 88:959-63.
6. Vendittoli PA, Makinen P, Drolet P, Lavigne M, Fallaha M, Guertin MC, *et al.* A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. J Bone Joint Surg Am 2006; 88:282-9.
7. Husted H, Solgaard S, Hansen TB, Soballe K, Kehlet H. Care principles at four fasttrack arthroplasty departments in Denmark. Dan Med Bull 2010;57: A4166-73.
8. Parvizi J. Pain management following total joint arthroplasty: making strides. J Bone Joint Surg Am 2012; 94:1441.
9. Sinnott CJ, Cogswell IL, Johnson A, Strichartz GR. On the mechanism by which epinephrine potentiates lidocaine's peripheral nerve block. Anesthesiology 2003; 98:181-8.
10. Kampe S, Poetter C, Buzello S, Wenchel HM, Paul M, Kiencke P, *et al.* Ropivacaine 0.1% with sufentanil 1 microg/mL inhibits in vitro growth of Pseudomonas aeruginosa and does not promote multiplication of Staphylococcus aureus. Anesth Analg 2003; 97:409-11.
11. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop 2011; 82:679-84.
12. Piegeler T, Votta-Velis EG, Liu G, Place AT, Schwartz DE, Beck-Schimmer B, *et al.* Antimetastatic potential of amide-linked local anesthetics: inhibition of lung

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 03, 2024

adenocarcinoma cell migration and inflammatory Src signaling independent of sodium channel blockade. Anesthesiology 2012; 117:548-59.
13. Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. Am Fam Physician 2001; 63:1979-84.
14. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97:534-40.
15. Nikolajsen L, Brandsborg B, Lucht U, Jensen TS, Kehlet H. Chronic pain following total hip arthroplasty: a nationwide questionnaire study. Acta Anaesthesiol Scand 2006; 50:495-500.
16. Cederholm I, Evers H, Lofstrom JB. Skin blood flow after intradermal injection of ropivacaine in various concentrations with and without epinephrine evaluated by laser Doppler flowmetry. Reg Anesth 1992; 17:322-8.
17. Gherardini G, Samuelson U, Jernbeck J, Aberg B, Sjostrand N. Comparison of vascular effects of ropivacaine and lidocaine on isolated rings of human arteries. Acta Anaesthesiol Scand 1995; 39:765-8.
18. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia II: recent advances and current trends. Can J Anaesth 2001; 48:1091-101.
19. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Can J Anaesth 2001; 48:1000-10.
20. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain 2002; 3:159-80.
21. Stoelting RK, Weinger MB. Dangers of postoperative opioids: is there a cure? Bull Am Coll Surg 2010; 95:21-2.
22. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. Anesth Analg 2008; 107:325-32.
23. Blumenthal S, Borgeat A, Pasch T, Reyes L, Booy C, Lambert M, *et al.* Ropivacaine decreases inflammation in experimental endotoxin-induced lung injury. Anesthesiology 2006; 104:961-9.
24. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology 2008; 109:180-7.
25. Martin F, Martinez V, Mazoit JX, Bouhassira D, Cherif K, Gentili ME, *et al.* Fletcher Anti-inflammatory effect of peripheral nerve blocks after knee surgery: clinical and biologic evaluation. Anesthesiology 2008; 109:484-90.
26. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105:660-4.
27. Wienzek H, Freise H, Giesler I, Van Aken HK, Sielenkaemper AW. Altered blood flow in terminal vessels after local application of ropivacaine and prilocaine. Reg Anesth Pain Med 2007; 32:233-9.