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A prospective, randomized controlled, double-blinded study comparing dexmedetomidine and clonidine as an adjuvant to ropivacaine in femoral nerve block for postoperative analgesia in patients undergoing total knee arthroplasty

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Abstract

Background: Total knee arthroplasty (TKA) causes significant postoperative pain, imposing a limitation on postoperative mobilization crucial in regaining joint function. Ultrasound (US)-guided femoral nerve block (FNB) in complex knee surgeries is associated with better pain scores and fewer hospital admissions. Alpha-2 (α2) adrenoreceptor agonists have been the recent focus of interest as additives to local anesthetic. We aimed to compare the equivalent dose of dexmedetomidine and clonidine as an adjuvant to ropivacaine in US-guided FNB in TKA. A prospective, randomized, controlled, double-blinded study was conducted involving 80 American Society of Anesthesiologists' physical status (ASA-PS) I, II, and III patients scheduled to undergo TKA under subarachnoid block. Group 1 ($n = 40$) patients received 1 μg/kg dexmedetomidine and group 2 ($n = 40$) patients with 1 μg/kg clonidine as adjuvants added to 20 ml of 0.75% ropivacaine. Duration of postoperative analgesia, pain scores, sedation scores, hemodynamics, rescue analgesia requirement, complications, and patient satisfaction were compared.

Results: The total duration of analgesia in group 1 was better compared to group 2 ($p < 0.001$).
The patients were better sedated and the mean NRS scores were significantly lower ($p < 0.05$) in group 1 up to 24 h postoperatively. Total analgesic consumption was reduced in group 1, with a p value < 0.001. Patient satisfaction was significantly better ($p < 0.001$) in group 1 compared to group 2.

Conclusion: We conclude that dexmedetomidine added as an adjuvant in FNB increased the duration of analgesia when compared to clonidine with decreased NRS scores, reduced postoperative tramadol requirement, and better sedation and patient satisfaction.

Trial registration: Researchregistry6709, "Retrospectively registered" on 31 March 2021.

Keywords: Total knee arthroplasty, Femoral nerve, Nerve block, Regional anesthesia, Dexmedetomidine, Clonidine, Ultrasonography

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Background

Pain after total knee arthroplasty (TKA) imposes a major limitation on early postoperative mobilization which is crucial in regaining joint function (Momoli et al. 2017). Inadequately managed acute postoperative pain can lead to increased incidence of chronic pain (Wylde et al. 2018). Postoperative pain control promotes patient ambulation and physiotherapy leading to early recovery, fewer complications, and a shorter hospital stay (Karlsen et al. 2017). Peripheral nerve blocks (PNBs) are being used as effective methods (Turnbull et al. 2017). Femoral nerve block (FNB) in the complex knee of postoperative pain management after TKA surgeries is associated with better pain scores and fewer hospital admissions following day-care surgeries (Heo et al. 2016). The use of ultrasound (US)-guided FNB has various advantages including precise needle insertion, fewer vascular punctures, less block administration time, improved block quality, and decreased dosage of local anesthetic (LA) (Forouzan et al. 2017). Numerous studies were done to investigate suitable additives to PNB with drugs that prolong the duration of analgesia but with minimal adverse effects (Swain et al. 2017). Alpha-2 (α_2) adrenergic receptor agonists have been the focus of interest for their sedative, analgesic, perioperative sympatholytic, and cardiovascular stabilizing effects with reduced anesthetic requirements. The effect of clonidine in PNB may be explained by four mechanisms including centrally mediated analgesia, α_{2b} receptor-mediated vasoconstriction, attenuation of the inflammatory response, and direct action on the nerve (Pöpping et al. 2009). Dexmedetomidine is a potent α_2 adrenoceptor agonist which is approximately 8 times more selective towards the α_2 adrenoceptor than clonidine. In previous studies, intravenous dexmedetomidine resulted in significant opioid-sparing effects as well as a decrease in inhalational anesthetic requirements. Dexmedetomidine has also been reported to enhance sensory and motor blockade along with increasing the duration of analgesia (Tripathi et al. 2016). We hypothesized that an equivalent dose of dexmedetomidine as an adjuvant to ropivacaine in US-guided FNB has a greater beneficial effect in prolonging the duration of postoperative analgesia in patients scheduled for TKA surgery under the subarachnoid block (SAB) than clonidine which was our primary outcome under investigation. Secondary outcomes were the comparison of sedation scores, hemodynamics, rescue analgesia requirement, complications, and patient satisfaction.

Methods

We designed a prospective, randomized controlled, double-blinded study which was approved by the Institutional Ethics Committee (DNBT-45/2019, dated 31 July 2019). Written informed consent was obtained from all patients recruited from August 2019 to May 2020. This study included 80 American Society of Anesthesiologists' physical status (ASA-PS) I, II, and III patients posted for elective TKA under SAB including both genders, aged 18–75 years Obese patients, patient refusal, patients with bradyarrhythmia, history of substance abuse, psychiatric disorders, neuropathy, hypersensitivity to LA, impaired renal/liver function tests, and ASA-PS IV or beyond formed the exclusion criteria. During the pre-anesthetic checkup, the patients were explained about the study, the advantages, and the risks, and an informed consent was obtained. Patients were instructed about the numerical rating scale (NRS) score and patient satisfaction score and were instructed to demand analgesia as per requirement.

Randomization was obtained by a computer-generated random number list. The group assigned was enclosed in sealed opaque envelopes, to ensure concealment. All patients were given oral sedative premedication (0.5 mg alprazolam), the night before surgery and nil by mouth kept for 6 h prior to surgery. In the operation theater, after standard anesthesia monitors were connected, a 20G intravenous cannula was secured and co-loading was done with 10–15 ml/kg ringer lactate during SAB. Baseline heart rate, blood pressure, and oxygen saturation were recorded.

SAB technique was standardized for all patients, with the patient in a sitting position using a midline approach. Under all aseptic precautions, skin infiltration was done in L2-3 or L3-4 interspaces and SAB was performed using a 25 G Quincke spinal needle with 3 ml of 0.5% bupivacaine (heavy). A sensory level of T8 dermatome was achieved in all patients. After the surgery was over, patients were shifted to postanesthesia care unit where FNB was performed. After proper positioning, US-guided FNB was given in allocated patients with the respective drug solutions, prepared by an anesthetist who was not involved in the study.

FNB was performed in a supine position with the extremity to be blocked rotated externally.

After skin disinfection with povidone-iodine, sterile drapes were applied. Femoral nerve and vessels were identified in short-axis view using a linear probe (8–12 Hz) covered with a sterile plastic sheath and with sufficient application of the sterilized gel. After identification, a skin wheal with 2–3 ml of 2% lidocaine with a 26G ½ inch hypodermic needle was made on the lateral aspect of the thigh 1 cm away from the lateral edge of the transducer. An 18G 55-mm echogenic Stimuplex needle (Stimuplex® A, B.Braun Medical Inc., USA) was inserted under US-guided in-plane technique and positioned between the fascia iliaca and iliopsoas muscle near the lateral corner of the femoral nerve. The needle passage

through the fascia iliaca was felt as a "pop" sensation. The needle was advanced until the tip was adjacent to the nerve. After checking the exact location of the needle tip, 1 ml of LA was injected to open the plane, and after confirmation of the hypoechoic area on the USG image, the remaining drug solution with a specific adjuvant was given.

Group 1 ($n = 40$) received 20 ml of 0.75% ropivacaine with 1 μg/kg dexmedetomidine as an adjuvant. Group 2 ($n = 40$) patients received 20 ml of 0.75% ropivacaine with 1 μg/kg clonidine as an adjuvant. The patients were evaluated for pain, rescue analgesic requirements, hemodynamic parameters, sedation, and complications at 0-min, 30-min, 1-h, 2-h, 4-h, and 4-h intervals thereafter up to 24 h post-FNB. The next day, patient satisfaction with the procedure was recorded. Rescue analgesia included intravenous injection of tramadol 50 mg when the numerical rating scale (NRS) was more than 4. A maximum 400 mg of tramadol was allowed per day. Patients rated their pain by the 11-point NRS score. Sedation was assessed using the Ramsay Sedation Scale (1—anxious and agitated or restless or both; 2—cooperative, oriented, and tranquil; 3—responds to commands only; 4—brisk response to a glabellar tap or loud auditory stimulus; 5—sluggish response to a light glabellar tap or loud auditory stimulus; 6—no response to a light glabellar tap or loud auditory stimulus). Patient satisfaction was assessed by a 3-point patient satisfaction score (1—good, 2—fair, 3—poor). Duration of analgesia was the primary objective in our study. Rescue analgesic requirement, sedation, hemodynamic, complications, and patient satisfaction formed the secondary outcomes.

Our sample size calculation was decided based on the study by Chaudhary et al. (Chaudhary et al. 2016) The authors recruited 60 patients in 2 groups of 30 each to achieve a power of 0.8 and a type-1 error (alpha) of 0.05. We recruited 40 patients in each group to avoid possible dropout and to have a better power of study. Statistical software Windostat version 9.2 was used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs, tables, etc. Unpaired t-test, chi-square test, and analysis of variance (ANOVA) were applied to know the difference between two groups. A value of $P < 0.05$ was considered statistically significant. Continuous variables were presented as mean ± standard deviation and categorical variables were presented as percentage.

Results

The total number of patients included was 80 with no dropouts. Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram. The 2

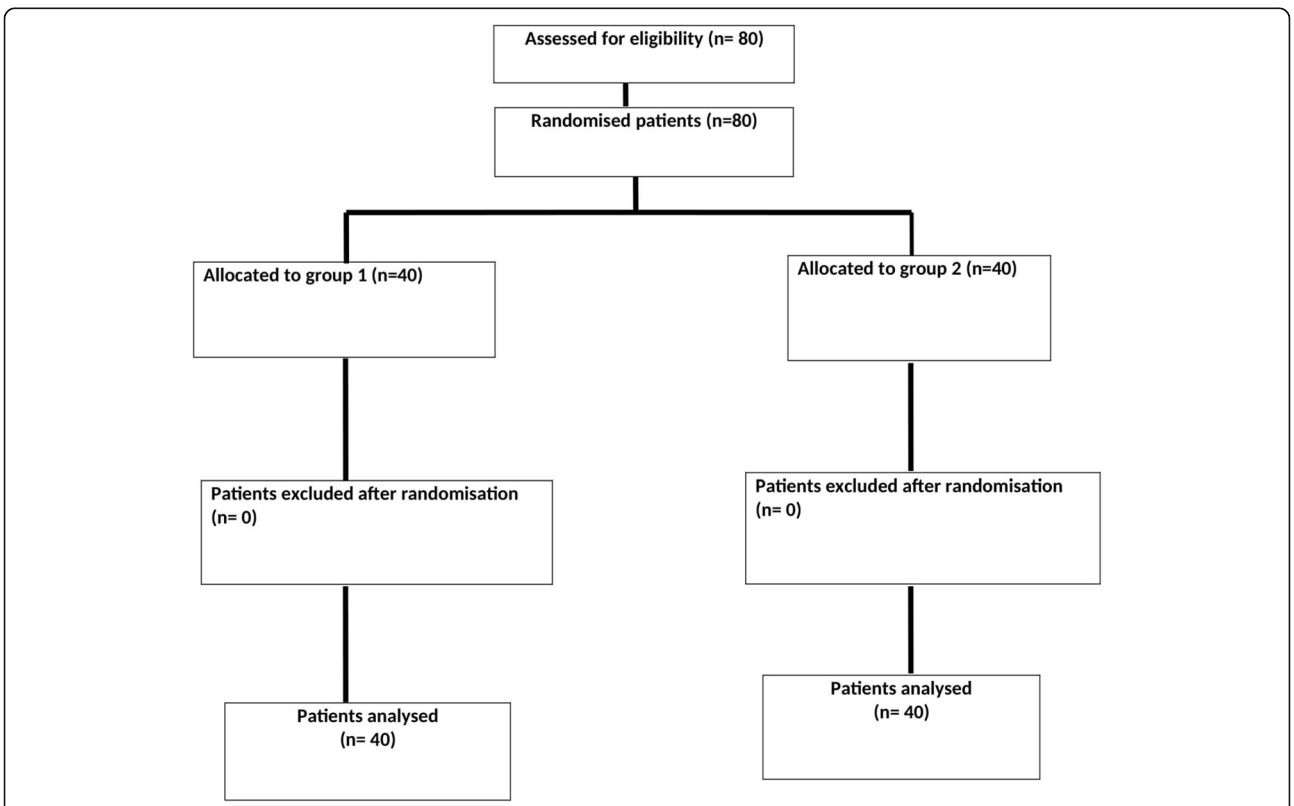

Fig. 1 CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing patients recruited, randomized, and analyzed

groups were comparable in terms of demographics (age, sex, weight, and ASA-PS) (Table 1). The total duration of analgesia in group 1 was 18.55 ± 2.935 h, compared to 12.00 ± 2.64 h in group 2 which was statistically significant (p value < 0.001) (Table 2). The mean NRS scores were lower in group 1 than in group 2 with statistical significance at 4 h, 8 h, 12 h, 16 h, and 24 h (p values < 0.05) (Table 3).

The total number of rescue analgesia consumption over 24 h after FNB in group 1 was 1.48 ± 1.037 compared to 3.95 ± 0.714 in group 2 which was statistically significant (p value < 0.001). Heart rate in group 1 was significantly lower than that in group 2 during the entire observational period ($p < 0.05$) of 24 h post-FNB although MAP showed no significant difference except at 20 h (Table 4). The patients of group 1 scored more in RSS compared to group 2 with no residual sedation in both groups after 4 h. No complications of FNB were observed in this study. Three patients in group 1 developed bradycardia requiring 0.6 mg atropine but this was not significant ($p = 0.2405$). Patients in group 1 reported better satisfaction scores than group 2 (p value < 0.001) (Table 2). We did a post hoc analysis of power taking into consideration the end-point means and a type-1 error of 0.05 and arrive at a power of 100% (https://clincalc.com/stats/power.aspx).

Discussion

In our study, we found that the use of dexmedetomidine as an adjuvant to US-guided FNB increased the duration of analgesia, decreased NRS scores, reduced postoperative rescue analgesic requirement, and provided better sedation and patient satisfaction when compared to clonidine without producing any significant side effects.

Table 1 Comparison of the demographic data

Demographics	Group 1	Group 2	*p* value
Age			0.649
≤ 50 yrs	3	2	
51–60 yrs	20	17	
61 and above	17	21	
Sex			0.633
Males	14	12	
Females	26	28	
Weight kgs	71.38 ± 9.588	72.8 ± 9.258	0.501
ASA-PS			0.638
I	5	3	
II	31	31	
III	4	6	

Group 1: dexmedetomidine 1 μg/kg adjuvant, group 2: clonidine as 1 μg/kg as adjuvant

TKA is a common surgical procedure and is associated with substantial and sustained pain after surgery. Inadequate analgesia impedes early ambulation and recovery and delays hospital discharge. (Li et al. 2019) Multimodal analgesia including regional anesthesia techniques like FNB is used to control acute pain, post-TKA. Poor pain control initially is strongly associated with chronic pain. Hence, optimal pain relief, with preserved motor functions, remains the mainstay of postoperative pain management in TKA.

The meta-analysis by Chan et al. published in 2014 attested the fact that FNB provided effective analgesia than opioid and comparable to epidural analgesia with less PONV (Chan et al. 2014). US-guided adductor canal blocks have been shown to prevent quadriceps weakness which occurs after a FNB which facilitates early mobilization (Koh et al. 2017). However, the systematic review and meta-analysis by Kuang et al. mentioned that although quadriceps power is preserved after adductor canal blocks, the analgesic efficacy is similar (Kuang et al. 2017). Our practice of using 0.75% ropivacaine for FNB provided effective pain relief. Also, we mobilize our patients the next day after surgery and thus quadriceps weakness gets resolved by that time, if any. We designed this study to find out the best adjuvant for FNB so as to prolong its duration of action effectively and safely. Researchers used adjuvants like magnesium sulfate and dexamethasone in FNB with variable success earlier. (Jebali et al. 2018; Ekmekci et al. 2013; Sherif and Elsersy 2016)

McCartney et al. performed a systematic, qualitative review of randomized controlled trials (27 studies) to understand the advantages of clonidine when used in peripheral nerve block (doses used were 30–300 μg) (McCartney et al. 2007). The authors concluded that adding clonidine did improve the duration of analgesia and anesthesia but the optimal dose could not be defined. The anesthetic requirements get reduced to a large extent by the usage of α2 agonists, because of their analgesic properties and augmentation of the LA effect. They cause hyperpolarization of nerve tissue by altering the trans-membrane potential and ion conductance and also cause sedation by inhibiting the release of nor-epinephrine at locus coeruleus in the brain stem. Sedation gives an extra advantage for regional anesthesia, as it reduces the stress associated with surgery, but associated bradycardia and hypotension need to be monitored (Krishna Prasad et al. 2020; Bailard et al. 2014).

Dexmedetomidine and clonidine have been used as adjuvants in peripheral nerve block extensively. In a systematic review by El-Boghdadly et al., the authors concluded perineural dexmedetomidine enhanced sensory, motor, and analgesic block characteristics when compared to clonidine as an adjuvant to US-guided

Table 2 Comparison of duration of analgesia, total rescue analgesic doses administered, Ramsay sedation score, patient satisfaction scores, and bradycardia in both groups

Variables	Group 1	Group 2	*p*-value
Duration of analgesia (hrs)	18.55 ± 2.935 95% CI [17.642–19.458]	12.00 ± 2.64 95% CI [11.18–12.82]	< 0.001
Total rescue analgesia required	1.48 ± 1.037 95% CI [1.1608–1.7992]	3.95 ± 0.714 95% CI [3.73–4.17]	< 0.001
Ramsay sedation score			
30 min	2.7 ± 0.464	2.1 ± 0.304	< 0.001
60 min	2.4 ± 0.496	1.83 ± 0.385	< 0.001
120 min	1.8 ± 0.405	1 ± 0	< 0.001 NA
240 min	1 ± 0	1 ± 0	
Satisfaction scores	1.25 ± 0.439	2 ± 0.506	< 0.001
Bradycardia (Y/N)	3/37	0/40	0.2405

supraclavicular block but at the cost of having transient bradycardia (El-Boghdadly et al. 2017). The findings were similar for the systematic review and meta-analysis published by Hussain et al. and Vorobeichik et al. regarding the use of dexmedetomidine in brachial plexus block (Hussain et al. 2017 and Vorobeichik et al. 2017). Kirksey et al. performed a systematic qualitative review of PNB adjuvants and on analysis concluded that both dexmedetomidine and clonidine are effective in prolonging the duration of analgesia in a PNB (grade of recommendation A, level of evidence 1a,b) (Kirksey et al. 2015). Helal et al. randomized 60 patients in 2 groups of 30 each undergoing below-knee surgeries. One group received bupivacaine alone and another received bupivacaine-dexmedetomidine combination with US-guided femoral-sciatic block. The authors concluded that the addition of dexmedetomidine enhanced the duration of analgesia significantly (Helal et al. 2016). Packiasabapathy et al. compared 2 doses of dexmedetomidine (1 μg/kg and 2 μg/kg) as adjunct to 60 patients divided into two groups undergoing TKA (Packiasabapathy et al. 2017). On analysis of results, the authors concluded that the use of dexmedetomidine at 2 μg/kg dose in femoral nerve block is superior to 1 μg/kg for providing analgesia after TKA. However, the authors suggested to explore the dose appropriate for early ambulation in the postoperative period. In our study, we used 1 μg/kg dexmedetomidine and compared with 1 μg/kg of clonidine as an adjuvant for TKA in FNB. We demonstrated that an equivalent dose of dexmedetomidine was convincingly better than clonidine in terms of prolonging analgesia after TKA.

Table 3 Comparison of NRS scores in both groups

NRS	Group 1	Group 2	*P* value (unpaired t-test)
0 min	4.5 ± 0.599	4.53 ± 0.599	0.852
4 h	0 ± 0	0.4 ± 0.744	0.001
8 h	0 ± 0	1.75 ± 1.463	< 0.001
12 h	0.83 ± 1.13	2.9 ± 1.194	< 0.001
16 h	2.15 ± 1.642	2.95 ± 0.959	0.009
20 h	2.58 ± 1.279	2.78 ± 0.62	0.376
24 h	2.03 ± 0.891	2.88 ± 0.686	< 0.001

Table 4 Comparison of heart rate and mean arterial pressure in both groups

	Group 1	Group 2	*P* value (unpaired t-test)
HR			
0 min	82.35 ± 11.063	89.65 ± 7.601	0.001
30 min	72.25 ± 12.695	77.65 ± 8.304	0.027
1 h	67.6 ± 9.945	74.35 ± 8.198	0.001
2 h	69.83 ± 10.463	75.65 ± 7.695	0.006
4 h	74.55 ± 11.562	79.95 ± 6.706	0.013
8 h	78.73 ± 9.964	84.95 ± 7.2	0.002
12 h	79.03 ± 9.169	88.73 ± 7.331	< 0.001
16 h	82.38 ± 9.175	87.9 ± 7.351	0.004
20 h	83.63 ± 9.437	86.35 ± 5.842	0.125
24 h	79.98 ± 7.495	84.4 ± 5.973	0.005
MAP			
0 min	103.35 ± 5.233	100.5 ± 6.687	0.037
30 min	86.9 ± 5.418	89.96 ± 8.184	0.052
1 h	82.58 ± 6.716	85.21 ± 7.817	0.111
2 h	82.82 ± 6.186	84.09 ± 5.745	0.346
4 h	85.35 ± 5.158	86.19 ± 6.47	0.522
8 h	87.49 ± 4.893	89.57 ± 6.652	0.116
12 h	90 ± 6.835	92.92 ± 6.362	0.052
16 h	90.92 ± 7.472	92.45 ± 6.9	0.343
20 h	90.58 ± 8.02	94.05 ± 4.862	0.022
24 h	89.32 ± 6.136	91.07 ± 5.063	0.17

Conclusion

In conclusion, we suggest 1 μg/kg dexmedetomidine *over* 1 μg/kg of clonidine as an adjuvant to FNB to prolong the duration of analgesia and for hemodynamic stability, acceptable sedation score, and better patient satisfaction after a TKA.

Abbreviations

TKA: Total knee arthroplasty; US: Ultrasound; FNB: Femoral nerve block; ASA-PS: American Society of Anesthesiologists' physical status; SAB: Subarachnoid block; NRS: Numerical rating scale; PNB: Peripheral nerve block; ANOVA: Analysis of variation; CONSORT: Consolidated Standards of Reporting Trials; MAP: Mean arterial pressure; PONV: Postoperative nausea/vomiting

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Authors' contributions

AS: Literature review, manuscript preparation, and followed up the patients. GF: Manuscript review, data analysis, and followed up the patients. BV: Concepts and design. AN: Literature review, manuscript editing, final draft, and data analysis. All authors read and approved the final version of the manuscript.

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Availability of data and materials

Not applicable

Declarations

Ethics approval and consent to participate

The study was approved by Ethics Committee of Yashoda Hospitals, Secunderabad, Telangana State, India (DNBT-45/2019, dated 31st July, 2019). Written informed consent was obtained from all patients.

Consent for publication

Not applicable

Competing interests

All authors declare that they have no competing interests.

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References

Bailard NS, Ortiz J, Flores RA (2014) Additives to local anesthetics for peripheral nerve blocks: evidence, limitations, and recommendations. Am J Health Syst Pharm 71:373–385

Chan EY, Fransen M, Parker DA, Assam PN, Chua N (2014) Femoral nerve blocks for acute postoperative pain after knee replacement surgery. Cochrane Database Syst Rev 2014:CD009941

Chaudhary SK, Verma RK, Rana S, Singh J, Gupta B, Singh Y (2016) Ultrasound-guided femorosciatic nerve block for post-operative analgesia after below knee orthopaedic surgeries under subarachnoid block: comparison between clonidine and dexmedetomidine as adjuvants to levobupivacaine. Indian J Anaesth 60:484–490

Ekmekci P, Bengisun ZK, Akan B, Kazbek BK, Ozkan KS, Suer AH (2013) The effect of magnesium added to levobupivacaine for femoral nerve block on postoperative analgesia in patients undergoing ACL reconstruction. Knee Surg Sports Traumatol Arthrosc 21:1119–1124

El-Boghdadly K, Brull R, Sehmbi H, Abdallah FW (2017) Perineural dexmedetomidine is more effective than clonidine when added to local anesthetic for supraclavicular brachial plexus block: a systematic review and meta-analysis. Anesth Analg 124:2008–2020

Forouzan A, Masoumi K, Motamed H, Gousheh MR, Rohani A (2017) Nerve stimulator versus ultrasound-guided femoral nerve block; a randomized clinical trial. Emerg 5:e54

Helal SM, Eskandr AM, Gaballah KM, Gaarour IS (2016) Effects of perineural administration of dexmedetomidine in combination with bupivacaine in a femoral-sciatic nerve block. Saudi J Anaesth 10:18–24

Heo BH, Lee HJ, Lee HG, Kim MY, Park KS, Choi J Il et al (2016) Femoral nerve block for patient undergoing total knee arthroplasty: prospective, randomized, double-blinded study evaluating analgesic effect of perineural fentanyl additive to local anesthetics. Medicine 95:e4771

Hussain N, Grzywacz VP, Ferreri CA, Atrey A, Banfield L, Shaparin N, Vydyanathan A (2017) Investigating the efficacy of dexmedetomidine as an adjuvant to local anesthesia in brachial plexus block: a systematic review and meta-analysis of 18 randomized controlled trials. Reg Anesth Pain Med 42:184–196

Jebali C, Kahloul M, Hassine N et al (2018) Magnesium sulfate as adjuvant in prehospital femoral nerve block for a patient with diaphysial femoral fracture: a randomized controlled trial. Pain Res Manag 2018:2926404

Karlsen AP, Wetterslev M, Hansen SE, Hansen MS, Mathiesen O, Dahl JB (2017) Postoperative pain treatment after total knee arthroplasty: a systematic review. PLoS One 12:e0173107

Kirksey MA, Haskins SC, Cheng J, Liu SS (2015) Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic qualitative review. PLoS One 10:e0137312

Koh IJ, Choi YJ, Kim MS, Koh HJ, Kang MS, In Y (2017) Femoral nerve block versus adductor canal block for analgesia after total knee arthroplasty. Knee Surg Relat Res 29:87–95

Krishna Prasad GV, Khanna S, Jaishree SV (2020) Review of adjuvants to local anesthetics in peripheral nerve blocks: current and future trends. Saudi J Anaesth 14:77–84

Kuang MJ, Ma JX, Fu L, He WW, Zhao J, Ma XL (2017) Is adductor canal block better than femoral nerve block in primary total knee arthroplasty? A GRADE analysis of the evidence through a systematic review and meta-analysis. J Arthroplast 32:3238–3248 e3

Li JW, Ma YS, Xiao LK (2019) Postoperative pain management in total knee arthroplasty. Orthop Surg 11:755–761

McCartney CJ, Duggan E, Apatu E (2007) Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. Reg Anesth Pain Med 32:330–338

Momoli A, Giarretta S, Modena M, Micheloni GM (2017) The painful knee after total knee arthroplasty: evaluation and management. Acta Biomed 88:60–67

Packiasabapathy SK, Kashyap L, Arora MK, Batra RK, Mohan VK, Prasad G, Yadav CS (2017) Effect of dexmedetomidine as an adjuvant to bupivacaine in femoral nerve block for perioperative analgesia in patients undergoing total knee replacement arthroplasty: a dose-response study. Saudi J Anaesth 11:293–298

Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR (2009) Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. Anesthesiology. 111:406–415

Sherif AA, Elsersy HE (2016) Dexamethasone as adjuvant for femoral nerve block following knee arthroplasty: a randomized, controlled study. Acta Anaesthesiol Scand 60:977–987

Swain A, Nag DS, Sahu S, Samaddar DP (2017) Adjuvants to local anesthetics: current understanding and future trends. World J Clin Cases 5:307–323

Tripathi A, Sharma K, Somvanshi M, Samal RL (2016) A comparative study of clonidine and dexmedetomidine as an adjunct to bupivacaine in supraclavicular brachial plexus block. J Anaesthesiol Clin Pharmacol 32:344–348

Turnbull ZA, Sastow D, Giambrone GP, Tedore T (2017) Anesthesia for the patient undergoing total knee replacement: current status and future prospects. Local Reg Anesth 10:1–7

Vorobeichik L, Brull R, Abdallah FW (2017) Evidence basis for using perineural dexmedetomidine to enhance the quality of brachial plexus nerve blocks: a systematic review and meta-analysis of randomized controlled trials. Br J Anaesth 118:167–181

Wylde V, Beswick A, Bruce J, Blom A, Howells N, Gooberman-Hill R (2018) Chronic pain after total knee arthroplasty. EFORT Open Rev 3:461–470

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