ejpmr, 2019,6(10), 181-190

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

PERIOPERATIVE DEXMEDETOMIDINE VERSUS KETAMINE INFUSION FOR PREVENTION OF CHRONIC PAIN AFTER TOTAL KNEE REPLACEMENT: A PLACEBO-CONTROLLED STUDY

Dr. Tarek Refat El Hefni, M.D.*[1], Dr. Mohamed Zaki Youssef, M.D.[2], Dr. Mohamad Abou Al-Neaj, M.D.[3], Dr. Ahmed Hassan Abouhelwo, M.D.[4] and Dr. Mohamed Mahmoud Elfekky, M.D.[5]

[1,2]Consultant Anesthesia, Hatta Hospital, Dubai Health Authority.
[3]Consultant Anesthesia, Head of Department and Medical Director of Hatta Hospital, Dubai Health Authority.
[4]Consultant and Head of Department Orthopedics, Hatta Hospital, Dubai Health Authority.
[5]Senior Specialist of Orthopedics, Hatta Hospital, Dubai Health Authority.

***Corresponding Author: Dr. Tarek Refat El Hefni**
Consultant Anesthesia, Hatta Hospital, Dubai Health Authority.

Article Received on 12/08/2019 **Article Revised on 02/09/2019** **Article Accepted on 22/09/2019**

ABSTRACT

Objectives: To evaluate effect of perioperative administration of Dexmedetomidine or ketamine infusion during Total Knee Replacement on acute postoperative pain and chronic neuropathic pain. **Patients & Methods:** Sixty patients assigned for Total knee replacement were divided into Group C received placebo, Group D and Group K received bolus followed by Intraoperative and Postoperative infusions of Dexmedetomidine and Ketamine, respectively. Intraoperative monitoring included heart rate and mean arterial pressure. Postoperative monitoring included pain severity assessed using numeric rating scale for 24-hr and somatic/sensory NPP using Douleur neuropathique 4 questions (DN4) Neuropathic pain diagnostic questionnaire evaluated preoperatively and 6-weeks and 3-months Postoperative. Patients satisfaction with the analgesic procedure was assessed with 4-points scale questionnaire. **Results:** Hemodynamic measures, especially in response to induction and intubation, were increased with Ketamine, but decreased with Dexmedetomidine infusion. During rest, pain scores and number of requests of rescue analgesia were significantly lower with Dexmedetomidine and Ketamine than placebo with significant difference in favor of Dexmedetomidine and 16 patients did not require rescue analgesia as long as they are in rest. During movement, 56 patients required rescue analgesia with significantly lower frequency with Dexmedetomidine than Ketamine and placebo and with Ketamine versus placebo. Duration till first request during rest was significantly longer and consumed dose of morphine was significantly lower with Dexmedetomidine than Ketamine and placebo and with Ketamine versus placebo. DN4 scores significantly improved than preoperative scores in all patients with significantly lower scores with Dexmedetomidine than Ketamine and placebo and with Ketamine versus placebo. All patients were satisfied by their 3-month outcome with significantly higher scores with Dexmedetomidine than Ketamine and placebo and with Ketamine versus placebo. **Conclusion:** Perioperative analgesic infusion helped to improve functional outcome through acute and chronic pain alleviation. Dexmedetomidine perioperative infusion did better than Ketamine infusion for pain relieve and improvement of functional outcome and patients' satisfaction.

KEYWORDS: Total knee replacement, Dexmedetomidine, Ketamine, Postoperative pain, chronic neuropathic

INTRODUCTION

Chronic post-surgical pain is a distressing disease process that may induce long-term disability, reduced quality of life, and increased health care spending.[1] Chronic postoperative (PO) pain remains a frequent pathology with an impact approximates 20 and 30% and accounts for 20% of the consultations in a pain center.[2]

Persistent PO pain (PPP) is a common finding after total knee arthroplasty (TKA) with an estimated prevalence of patients reported minor or no symptom improvement ranging from 5% to 40%.[3] Chronic pain after joint replacement is common, affecting about 20% of patients after total knee replacement (TKR) and 10% of patients after total hip replacement[4] and is associated with slower PO mobilization, poorer physical function, and greater psychological distress.[5]

Independent risk factors for PPP are the length of the operative procedure, medical history of diabetes mellitus, presence of preoperative flexion contracture and patellofemoral joint overstuffing.[3]

The exact mechanism of development of PPP is unknown; however, nerve injury and inflammation may lead to peripheral and central sensitization.[1] There is

little evidence for effective interventions for management of PPP especially after joint replacement surgeries[6] and because of its complexity; no novel treatment has been identified[1], so multimodal and individualized interventions matched to pain characteristics are tried.[6]

Dexmedetomidine (DEX) is a highly selective α2-adrenergic agonist[7] with sedative, sympatholytic and analgesic properties[8] and hence, it can be a very useful adjuvant in anesthesia as stress response buster and analgesic[7] and to provide good sedation.[9]

The N-methyl-D-aspartate (NMDA) receptor, an amino acid receptor that was implicated in multiple physiological and pathological phenomena including central sensitization associated with the development of hyperalgesia.[10] Stimulation of NMDA receptors present in central nervous system by afferent nociceptive input, activates neuronal sensitization process that enhances pain perception[11] and may also decrease neuronal sensitivity to opioid receptor agonists.[12]

Ketamine (Ket) hydrochloride is a rapidly acting, non-barbiturate general anesthetic[13] and is used as a painkiller[14] acting mainly as NMDA antagonist.[15] Moreover, ketamine was found to have neuroprotective, anti-inflammatory and anti-tumor effects.[13]

OBJECTIVES

This study aimed to evaluate the effect of perioperative administration of DEX or KET bolus and infusion during TKR on acute PO pain and chronic pain.

Design

Prospective double-blinded placebo-controlled clinical trial.

Setting

Anaesthesia Department, Hatta Hospital, Dubai Health Authority, United Arab Emirates.

PATIENTS AND METHODS

The study protocol was approved by Dubai Scientific Research Ethical Committee (DSREC) and patients or their near relative signed a written fully-informed consent to participate in the study and received the assigned lines of pain management. All patients assigned for TKR, irrespective of indication, were eligible for evaluation. Patients maintained on opioid analgesia for long preoperative duration, patients with bleeding diathesis, endocrinopathy inducing exaggerated stress response, or disturbed mineral homeostasis, patients with advanced malignant lesions, severely deteriorated cardiac function, patients with history of complicated recovery of anesthesia, or sensitivity to anesthetic or study drugs and patients with disturbed mental status were excluded from the study.

Preoperative assessment and preparation

Individualized perioperative management was required based on preoperative history and physical examination. Diabetic patients were maintained on subcutaneous injection of regular insulin every 6 hours with dose adjusted according to regular urine examination for glucose so as to maintain fasting blood glucose (FBG) level <160 mg/dl, with no ketonuria. Hypertensive patients were maintained on Ca-channel blockers and β-adrenergic agonists so as to maintain systolic and diastolic arterial pressure at ≤130 and ≤90 mmHg, respectively. Patients receiving treatment for chronic obstructive pulmonary diseases (COPD) were maintained on bronchodilators and β-adrenergic agonists. All patients with medical diseases were continued postoperatively on the same lines of treatment applied preoperatively.

Randomization and grouping

Patients fulfilling the inclusion criteria were randomly assigned into one of three groups using sealed envelops each contained a card labeled by group title and were prepared by a blinded assistant who is blinded about the study target and infusion type. Envelops were chosen by patient him/herself or by nearest relative and opened in theater prior to induction of anesthesia.

Grouping was designed according to type of analgesic infusion used into Group C included controls who received a bolus and infusion of placebo, Group D included patients who received DEX bolus and infusion and Group K included patients who will receive KET bolus and infusion.

Analgesic protocol

A) Preparations

The study drug bags were prepared in the morning of day of surgery by an anesthesia technician not involved in the care of the study patients and labeled with a secret code number to allow double-blindness.

- Group K: 250 mg of KET and 10 mg of midazolam were mixed in 500 ml saline.
- Group D: 1 mg (1000 µg) of DEX was mixed in 500 ml saline.
- Group C: 500 ml of plain saline as placebo.

B) Administration protocol

- In the theater, 10 minutes before induction of anesthesia all patients received a bolus dose of the study drug in a dose of 0.5 ml/kg of patient body weight over ten minutes.
- Throughout operation all patients received a continuous infusion of the study drug at rate of 0.25 ml/kg /hr.
- After the end of operation and for 24-hr PO, all patients received a continuous infusion of the study drug at rate of 0.1 ml/ kg/ hr.

C) Dose adjustment

1. Group C: Bolus dose was 0.5 ml/kg of plain saline over 10 minutes, IO infusion rate was 0.25 ml/kg/hr and PO infusion rate was 0.1 ml/kg/hr for 24-hr.
2. Group K: one ml of prepared infusion contained 0.5 mg KET and 20 µg midazolam, so that bolus dose was 0.5 ml/kg over 10 minutes, IO infusion rate was 0.25 ml/kg/hr and PO infusion rate was 0.1 ml/kg/hr for 24-hr
3. Group D: one ml of prepared infusion contained 2 µg of DEX, so that bolus dose was 0.5 ml/kg over 10 minutes, IO infusion rate was 0.25 ml/kg/hr and PO infusion rate was 0.1 ml/kg/hr for 24 hours.

Anesthetic procedure

The same anesthetic technique was applied for all patients. Before induction, patients were preoxygenated and base line blood pressure, heart rate, respiratory rate and O_2 saturation were recorded. Anesthesia was induced with a bolus of fentanyl 2 µg/kg, followed by propofol 1.5 mg/kg and cis-atracurium 0.15 mg/kg to facilitate orotracheal intubation. General anesthesia was maintained by balanced anesthesia with 2% end-tidal sevoflurane in oxygen and Nitrous oxide. Ventilation was controlled and minute ventilation was adjusted to maintain end tidal CO_2 at 35±5mmHg. Intraoperative neuromuscular block was produced with cis-atracurium. At the end of surgery, atropine sulphate 0.02 mg/kg and neostigmine 0.04 mg/kg were administered I.V. for reversal of muscle relaxation and the trachea was extubated. Following extubation, the patients were maintained on supplemental O_2 until awake in the recovery room.

Intraoperative monitoring included recording heart rate (HR) and mean arterial pressure (MAP) before induction of anesthesia (T0), after induction of anesthesia and intubation (T1) and after extubation (T2). Duration of surgery and occurrence of intraoperative anesthetic or surgical problems were recorded. Times since discontinuation of maintenance anesthetic till awakening as judged by opening eyes on verbal command and orientation as judged by correctly telling date, place, and person were determined was determined. Then, all patients were transferred to the post-anesthesia care unit (PACU) and time till being discharged from the PACU was also recorded.

Outcome evaluation

- Pain severity was assessed using an 11-point numeric rating scale (NRS) with numbers from 0 to 10 where 0 indicates no pain and 10 indicates worst pain imaginable. NRS was chosen for being more practical than the graphic visual analogue scale, easier to understand for most people, and does not need clear vision, dexterity, paper, and pen.[16] Pain score was determined preoperatively and 4-hourly for 24-hr PO. During 48-hr PO, all patients received regular analgesia in the form of paracetamol (Perfalgan, Bristol-Meyers Squibb; Anagni, Italy; 1 gm paracetamol in 100 ml IV infusion every 6 hrs) and parecoxib (Dynastat, 40 mg IV every 6-hr) and rescue analgesia was provided in the form of intramuscular morphine 5 mg on NRS pain score of ≥7 and was repeated if required. Average 24-hr dose of morphine was calculated according to patient's age as 100-age and was titrated according to the effect.[17]
- Evaluation of somatic/sensory neuropathic pain using Douleur neuropathique 4 questions (DN4) neuropathic pain (NPP) diagnostic questionnaire that evaluated pain characteristic; burning, painful cold, or electric shocks; is pain associated with tingling, pins and needles, numbness, or itching sensation in the same area; and on examination of area of pain is it pain associated with touch and/or pricking hypoaesthesia and if it is induced or increased by brushing. Result of ND4 was graded as 0 if no and 1 if yes for a score range of 0-10 and score of ≥4 has 90% specificity for diagnosis of neuropathic pain.[18] ND4 score was evaluated at 6-wk and 3-m PO.
- Patients' satisfaction with the analgesic procedure was assessed with a 4-point scale questionnaire, ranging from 4 points (very satisfied) to 1 point (very dissatisfied).

RESULTS

The study included 77 patients; 17 were excluded and 60 patients (Fig. 1); 37 females and 23 males with mean age of 69±11.5 years were included in the study. Patients' enrolment data showed non-significant ($p>0.05$) difference between studied groups (Table 1).

Table (1): Enrolment Data of Patients of Studied Groups.

Group Parameter	Group C	Group D	Group K	P value
Age (years)	68.1±12.9	69.3±8.7	69.6±13	0.726
Sex; Males: Females	12:8	14:6	11:9	0.694
Weight (kg)	90.6±17.2	93.7±19.2	93.9±15.4	0.629
Height (cm)	169.3±3.1	169.5±3.2	170.4±3.7	0.819
Body mass index (kg/m^2)	31.5±5.5	32.6±6.3	32.4±5.9	0.793
ASA grade; I:II:III	8:7:5	7:6:7	5:8:7	0.598
Other morbidities; Yes:No	17:3	15:5	16:4	0.673

Data are shown as mean ± SD & ratios

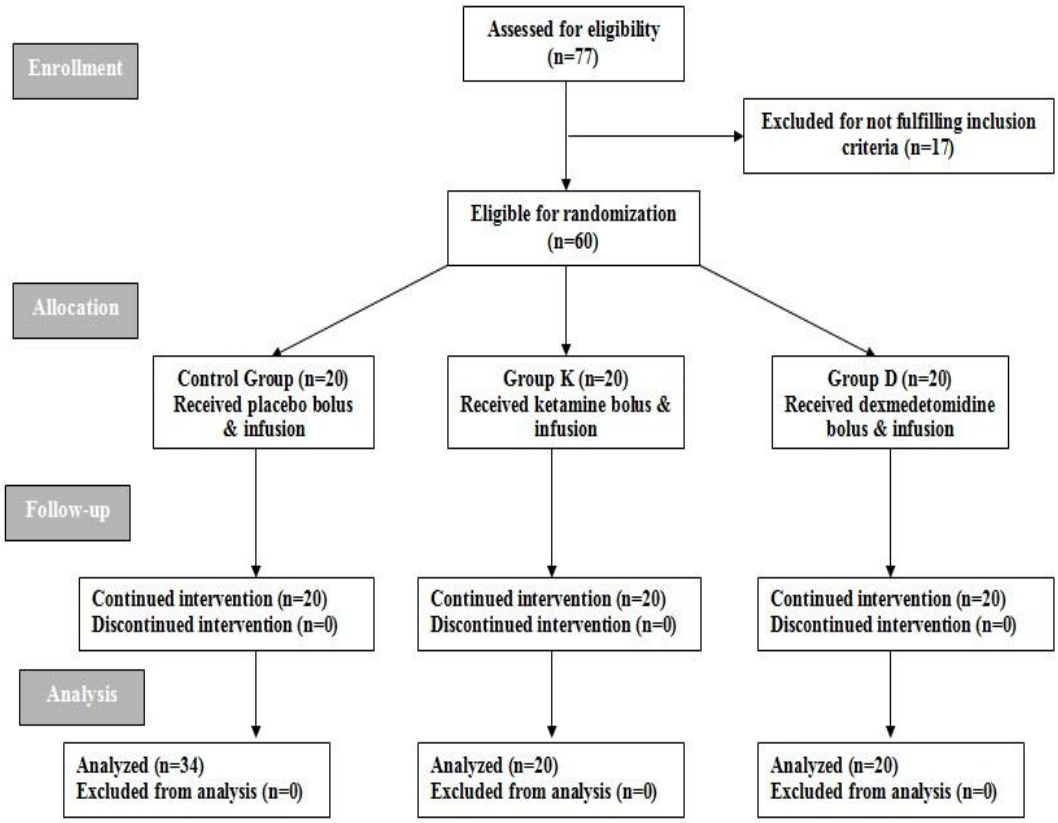

Figure 1: Consort Flow sheet

Induction of anesthesia and intubation induced vasopressor effects manifested as significantly ($p<0.05$) higher HR and MAP measurements in all patients with significant ($p<0.05$) difference versus baseline measures with more pronounced effect in group K. DEX significantly ($p<0.05$) ameliorated vasopressor effects as evidenced by the significant ($p<0.05$) difference among the three groups at T1 and T2 measurements. Operative time, and extent of blood loss and frequency of need for blood transfusion showed non-significant ($p>0.05$) difference between studied groups (Table 2).

Table (2): Hemodynamic and Operative Data of Patients of Studied Groups.

Group Parameter		Group C	Group D	Group K	P value
Heart rate (beats/min)	T0	82.1±3.5	81.8±3.9	83.1±2.9	0.464
	T1	84.7±2.7	76.4±3.8	87.7±5.2	0.0001
	T2	79.4±2.1	71.6±3.2	86.2±6.1	0.0001
	P value	0.0001	0.0001	0.0144	
MAP (mmHg)	T0	97.1±4.5	96.9±5.7	97.2±4.5	0.863
	T1	103.1±4.6	99.1±7.1	104. ±3.1	0.003
	T2	96.7±5.4	92.8±4.9	98.4±3.8	0.0013
	P value	0.0001	0.0054	0.0001	
Operative time (min)		202±27.4	195±28.1	198.5±24.4	0.711
Operative blood loss (ml)		567.7±140.4	555.7±123.2	591.7±128.4	0.677
Patients needed transfusion		13 (65%)	11 (55%)	14 (70%)	0.309

Data are shown as mean ± SD & numbers; P value indicates variance between the three groups; P1: indicates variance between measurements of the same group

Preoperative median NRS pain scores showed non-significant ($p>0.05$) differences between patients of studied groups. Throughout 48-hr PO determined pain scores, both during rest and movement, were significantly lower in groups D and K compared to group C. Pain scores determined immediate PO and at 4-hr and 20-hr PO during rest were significantly lower, while other determined scores were non-significantly lower in patients of group D compared to patients of group K (Table 3).

Table (3): Postoperative pain NRS scores of patients of studied groups.

Group Parameter Time		Group C	Group D	Group K	P1 value	P2 value
NRS during rest	Preoperative	6±1	5.9±0.9	5.8±1.2	0.819	0.713
	Immediate PO	3±0.7	2.3±0.6	2.9±1	0.012	0.014
	4-hr PO	4.8±1.5	2.2±0.7	3.1±1.3	<0.00001	0.0026
	8-hr PO	5.5±1.7	2.6±1.2	3.7±1.8	<0.00001	0.057
	12-hr PO	5.3±1.9	3±1.8	4.1±1.8	0.0012	0.059
	16-hr PO	5.1±1.6	2.8±2.3	4.3±2.1	0.0029	0.0015
	20-hr PO	5.4±1.8	3.1±2.2	4.3±2.5	0.006	0.126
	24-hr PO	5.6±2	3.9±2.4	4.5±1.9	0.039	0.385
	28-hr PO	5.7±2	4±2.6	4.6±2.1	0.048	0.664
	32-hr PO	5.8±1.9	3.9±2.7	4.65±1.9	0.031	0.316
	36-hr PO	5.85±1.8	4.1±2.7	4.6±2	0.043	0.443
	40-hr PO	5.8±2.1	3.95±2.8	4.7±2	0.047	0.332
	44-hr PO	5.9±2.2	3.95±3.1	4.55±2.2	0.044	0.491
	48-hr PO	6±2.3	4.05±3	4.7±3.4	0.042	0.414
NRS during movement	4-hr PO	0	5±1.4	5.7±1.6		0.687
	8-hr PO	7.2±0.9	4.5±1.8	4.9±2.4	0.000027	0.541
	12-hr PO	5.7±1.7	4.4±1.8	4.6±1.7	0.048	0.674
	16-hr PO	6±1.6	5.2±1.5	5.3±1.9	0.254	0.93
	20-hr PO	5.6±2	3.8±2.4	5±2.3	0.0478	0.107
	24-hr PO	5.9±1.9	4.4±2	4.7±1.9	0.036	0.713
	28-hr PO	5.75±1.8	4.45±2.5	4.65±2.6	0.039	0.805
	32-hr PO	5.85±1.8	4.4±1.9	4.75±2.1	0.032	0.586
	36-hr PO	5.8±1.9	4.55±2	4.7±2.32	0.040	0.827
	40-hr PO	5.85±1.95	2.45±2.1	4.65±2.2	0.044	0.771
	44-hr PO	5.9±1.8	4.5±2	4.6±2.5	0.046	0.827
	48-hr PO	5.85±1.87	4.45±1.9	4.65±1.7	0.041	0.685

Data are shown as mean ± SD & numbers; P1 value indicates variance between the three groups; P2: indicates variance between groups D and K

During rest, all control patients received rescue analgesia, while 26 patients of study groups; 17 in group K and 9 in group D required rescue analgesia. Fourteen patients did not require rescue analgesia as long as they in rest. During movement, out of patients of study groups, only 3 patients in group D did not require rescue analgesia, while 15 patients required rescue analgesia once, 19 patients requested it twice and three required it three times, while in group C, 8 patients required rescue analgesia twice and another 12 required it three times. The frequency of requesting rescue analgesia was significantly ($p<0.05$) lower with DEX than KET and placebo with significantly ($p<0.05$) lower frequency with KET versus placebo.

Among patients requested rescue analgesia, duration till 1st request during rest was significantly ($p<0.05$) longer in groups D and K compared to group C with significantly ($p>0.05$) longer duration with DEX than KET, while during movement the duration of analgesia showed non-significant ($p>0.05$) difference between groups, but was in favor of DEX. Consumed dose of morphine was significantly lower in study groups compared to control group both at rest and during movement with significantly lower dose with DEX than with KET (Table 4, Fig. 2).

Table (4): Frequency of rescue analgesia requesting and duration till 1st requesting it.

			Group C	Group D	Group K	P value
Frequency of requests	During rest	No	0	11 (55%)	3 (15%)	P1<0.001 P2<0.001 P3<0.001
		Once	5 (25%)	8 (40%)	10 (50%)	
		2-times	11 (55%)	1 (5%)	7 (35%)	
		3-times	4 (20%)	0	0	
	During movement	No	0	3 (15%)	0	P1<0.001 P2<0.001 P3<0.001
		Once	0	10 (50%)	5 (25%)	
		2-times	8 (40%)	7 (35%)	12 (60%)	
		3-times	12 (60%)	0	3 (15%)	
Duration till 1st request of rescue PO analgesia (hr)		Rest	11.6±5.6	20±3.7	16.5±5	P1<0.0001 P2=0.0017 P3=0.0064
		Movement	8.6±5.1	11±6.1	9.2±1.9	P1=0.216 P2=0.187 P3=0.621
Consumed dose of morphine (mg)		Rest	9.75±3.4	2.5±3	6.75±3.7	P1<0.0001 P2=0.012 P3=0.003
		Movement	13±2.5	6±3.5	9.5±3.2	P1<0.0001 P2=0.0004 P3=0.002
		Total	22.75±5.5	8.5±2.9	16.25±4.3	P1<0.0001 P2=0.0002 P3<0.0001

Data are shown as mean ± SD & numbers; P1 value indicates significance of difference between groups C & D; P2 value indicates significance of difference between groups C & K; P3 value indicates significance of difference between groups D & K.

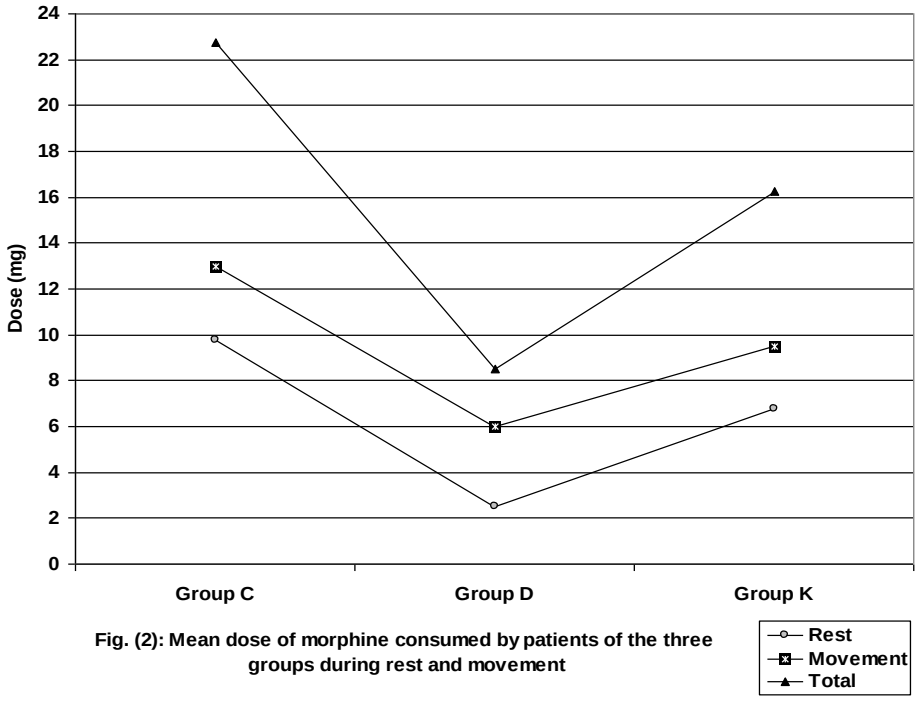

Fig. (2): Mean dose of morphine consumed by patients of the three groups during rest and movement

As regards chronic neuropathic pain sensation, at 6-wk and 3-m evaluations ND4 scores were significantly lower in patients received analgesic infusion compared to placebo infusion with significantly lower ND4 scores with DEX versus KET infusions (Table 5).

Table (5): Data of chronic neuropathic pain scores.

Group		Group C	Group D	Group K	P value
6-wk PO	Median (IQR)	3 (2-4)	2 (1-3)	2 (2-3)	0.00025
	P1			0.014	
3-m PO	Median (IQR)	4 (3-4)	2 (2-3)	2 (2-3)	<0.00001
	P1			0.043	
	P2	0.024	0.428	0.110	

Data are shown as median (Inter-quartile range); P value indicates variance between the three groups; P1: indicates variance between 6-wk measurements of groups D and K; P2: indicates variance between 6-wk and 3-m measurements of the same group.

All patients were satisfied by their 3-m outcome; however, mean of satisfaction score was significantly lower in control group compared to both DEX ($p<0.001$) and KET ($p=0.028$) groups with significantly ($p=0.031$) lower satisfaction scores with KET versus DEX analgesia (Fig. 2).

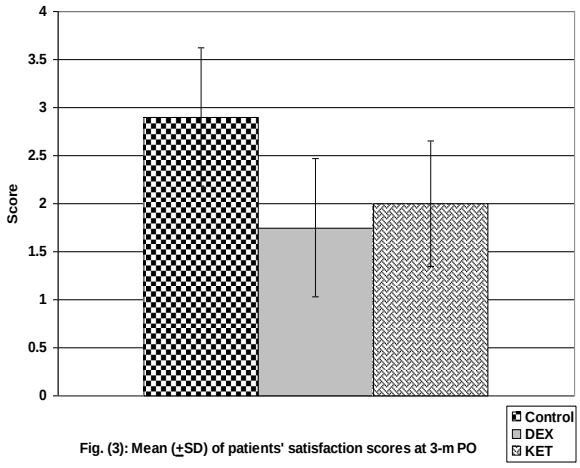

Fig. (3): Mean (±SD) of patients' satisfaction scores at 3-m PO

DISCUSSION

Both of applied analgesic protocols using DEX or KET infusions significantly modulated hemodynamic measures especially in response to induction and intubation with significant difference between patients of the studied groups secondary to increased measures with KET, but decreased measures with DEX infusion. The findings concerning effect of DEX go in hand with previous studies established its hemodynamic depressant effect in separate[19,20] or comparative studies versus placebo[21] or other drugs.[22] Moreover, DEX was experimentally proved to be beneficial for aged patients through its myocardial protective effect.[23] Concerning KET infusion, the reported elevations of hemodynamic parameters coincided with other studies that documented increases in blood pressure after initiation of KET infusion, or on strenuous stimulation and found hypertensive patients being more sensitive and had higher pressure peaks that returned to baseline during monitoring after infusion stoppage.[24,25]

Unfortunately, review of literature detected no comparative studies for both DEX and KET infusions for management of PPP. However, in line with the obtained data concerning the efficacy of KET infusion for management of PPP, **Lavand'homme & Thienpont**[26] documented that patients at risk for chronic pain after TKA would benefit from specific perioperative management including reduction of preoperative opioid intake and perioperative use of antihyperalgesic drugs such as ketamine. Also, **Díaz-Heredia et al.**[27] documented that the use of pre-surgical analgesics especially that used for neuropathic pain (NP) as ketamine decreases the use of PO analgesia, at least for short-term pain management.

In support of perioperative KET infusion for PPP, **Masgoret et al.**[28] found the incidence of PPP at 6 months after open hepatectomies with epidural or IV ketamine analgesia was low with no difference in allodynia/hyperalgesia area that was infrequent and slight. Also, **Rigo et al.**[29] in comparative study of ketamine alone versus methadone or both and reported significant improvement in NP with ketamine alone and despite of reducing pain scores by at least 40% by all treatments and ketamine alone was more effective than both for reduction of allodynia.

On contrary to the obtained results concerning KET versus placebo, **Peyton et al.**[30] considering chronic PO pain as outcome, reported no significant differences in cumulative morphine equivalents consumption or NRS pain scores with ketamine regimen consisted of pre-incision injection (0.5 mg/kg), intraoperative infusion (0.25 mg/kg/hr) and PO infusion (0.1 mg/kg/hr for 24 hours) on comparison versus placebo. However, in hand with the results of current study and against the outcome obtained by **Peyton et al.**[30], **Michelet et al.**[31], in 2018, performed a meta-analysis and found ketamine was efficient in alleviating pain up to 12 weeks after the beginning of treatment and decreased pain intensity at all evaluated points of time, but increased the incidence of psychedelic manifestations compared to placebo.

Concerning the effect of DEX infusion on acute and PPP, the obtained results coincided with multiple previous studies tried DEX infusion for varied types of PPP, where **Patch et al.**[32] found DEX was utilized successfully as a part of a controlled multimodal analgesic plan for patients receiving large amounts of opioids for chronic pain syndrome especially for opioid tolerant patients experiencing opioid induced

hyperalgesia. Also, **Peng et al.**[33] studied randomized controlled trials that compared opioid-DEX combinations with opioid-only for adult surgical patients and found PO strategies with opioid-DEX combinations decreased PO pain, opioid requirement, and opioid-related adverse events, and concluded that DEX is a useful adjuvant to opioid-based PCA.

Despite of improved chronic NP sensation, as judged by ND4 scores, in comparison to preoperative scores, ND4 scores were significantly lower with analgesic infusions than placebo infusion with significantly lower ND4 scores with DEX versus KET infusions. The beneficial effects of analgesic infusion on both acute and chronic pain sensation was also manifested as significantly lower 3-m satisfaction scores of patients of groups D and K than control patients with significantly higher satisfaction scores with DEX than KET analgesia.

These findings go in hand with **Zajonz et al.**[34] found multimodal pain therapy after TKA including pain medication therapy with ketamine is essential element and all patients benefit with regard to pain, function and range of motion. Recently, **Hadlandsmyth et al.**[35] documented that between 6-weeks and 6-months post-TKA improvement of functional category was better than improvement of pain.

In support of the superior outcome of DEX infusion, **Yun et al.**[36] found perioperative intravenous DEX administration decreases pain in patients undergoing unilateral or bilateral TKA. **Li et al.**[37] also, found adding 1 μg/kg DEX to ropivacaine for femoral nerve block (FNB) significantly reduced pain VAS with smaller knee circumference than FNB alone. Moreover, **Packiasabapathy et al.**[38] compared two doses of DEX as adjuvant to FNB for PO analgesia after TKA and detected significantly lower pain VAS scores, longer duration of analgesia and lower PO morphine consumption with DEX and block combination than FNB alone, but DEX showed dose-dependent effect as DEX at 2 μg/kg dose is superior to at 1 μg/kg for providing analgesia after TKA.

Multiple recent experimental studies tried to examine the effect and mechanism of DEX on chronic NP; **Zhang et al.**[39] using chronic compression of dorsal root ganglion rat model suggested that DEX could attenuate NP through depressing the I_h current density and excitability of C- and A_δ-type dorsal root ganglion neurons. Also, **Yang et al.**[40] suggested that in chronic sciatic nerve constriction injury, DEX alleviates NP through inhibition of hyperpolarization-activated cyclic nucleotide-gated channels subtypes; caused a significant decrease in maximal currents. In another animal model, **Dai et al.**[41] found that KCC2-induced shift in neuronal Cl^- homeostasis which is crucial for postsynaptic inhibition mediated by GABAA receptors and suggested that DEX attenuated PPP by restoring KCC2 function through reducing brain-derived neurotrophic factor/TrkB signal in the spinal dorsal horn.

Clinically, **Yun et al.**[36] reported significantly lower serum interleukin-6 (IL-6) levels in patients received perioperative DEX in comparison to placebo and attributed DEX analgesic effect to its anti-inflammatory effect. Also, **Li et al.**[37] found adding 1 μg/kg DEX to ropivacaine for FNB after TKA had a significantly inhibitory effect on local inflammatory response through suppression of local release of IL-6 and prostaglandin E2 and attributed its superior PO pain control than FNB alone to such effect.

CONCLUSION

Pain after total knee replacement is a disastrous condition with serious impact on functional outcome. Perioperative analgesic infusion helped to improve functional outcome through acute and chronic pain alleviation. DEX perioperative infusion did better than KET infusion for pain relieve and improvement of functional outcome and patients' satisfaction. However, wider scale comparative studies are mandatory to evaluate repeated infusion to improve long-term outcome.

ACKNOWLEDGMENT: The authors would like to thank all the staff of the Anesthesia and Orthopedic departments who participated in the conduction of this study.

REFERENCES

1. Turk DC. Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. The Clinical journal of pain, 2002; 18(6): 355.
2. Althaus A, Hinrichs-Rocker R, Chapman O, et al. Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain. 2012 Jul; 16(6): 901-10.
3. Puolakka, P, Michael GF; Roviola M, et al. Persistent pain following knee arthroplasty.European Journal of Anaesthesiology. 2010; 27: 455–460.
4. Wylde V, Hewlett S, Learmonth ID and Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. PAIN., 2011; 152(3): 566-72.
5. Michael E, Michael J, Allan W, et al. Prospective Relation between Catastrophizing and Residual Pain following Knee Arthroplasty: Two-Year Follow-Up. Pain Research and Management. 2008; 13(4): 335-341.
6. Wylde V, Dennis A, Beswick J, et al. Systematic review of management of chronic pain after surgery. Br J Surg., 2017; 104(10): 1293-1306.
7. Ramsay M, Luterman D.Dexmedetomidine as a Total Intravenous Anesthetic Agent. Anesthesiology. 2004; 101: 787-790.
8. Judith E, Uhrich D, Barney MS, et al.Sedative, Amnestic, and Analgesic Properties of Small-Dose

Dexmedetomidine Infusions. Anesthesia & Analgesia. 2000; 90(3): 699–705.
9. Gertler R, Mitchell H and Silvius E. Dexmedetomidine: A Novel Sedative-Analgesic Agent. Baylor University Medical Center Proceedings Journal. 2001; 14(1): 13-21.
10. Bennett G. Update on the Neurophysiology of Pain Transmission and Modulation: Focus on the NMDA-Receptor. Journal of Pain and Symptom Management. 2000; 19(10): 2-6.
11. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. The journal of pain. 2009; 895-926.
12. WolfgangKoppert, Martin Schmelz. The impact of opioid-induced hyperalgesia for postoperative pain. Best Practice & Research Clinical Anaesthesiology. 2007; 21(10): 65-83.
13. Georges Mion.History of anaesthesia,The ketamine story – past, present and future. European Journal of Anaesthesiology (EJA). 2017; 34(9): 571–575.
14. Vissera E, Schugab SA. The role of ketamine in pain management. Biomedicine & Pharmacotherapy. 2006; 60(7): 341-348.
15. Zorumski C, Izumi Y and Mennerick S. Ketamine: NMDA Receptors and Beyond. J Neurosci., 2016; 36(44): 11158–11164.
16. Hawker G, Mian S, Kendzerska T and Melissa F. Measures of Adult Pain. Arthritis Care & Research. 2011; 63(11): S240-S252.
17. Macintyre PE, Jarvis DA. Age is the best predictor of postoperative morphine requirements. Pain. 1996; 64(2): 357-64.
18. Harifi G, Ouilki I, El Bouchti I, et al. Validity and Reliability of the Arabic Adapted Version of the DN4 Questionnaire (Douleur Neuropathique 4 Questions) for Differential Diagnosis of Pain Syndromes with a Neuropathic or Somatic Component. Pain Practice j. 2011; 38(1): 139-147.
19. Yildiz M, Tavlan A, Tuncer S, et al. Effect of Dexmedetomidine on Haemodynamic Responses to Laryngoscopy and Intubation, Perioperative Haemodynamics and Anaesthetic Requirements. Drugs in R & D. 2006; 7(1): 43–52.
20. Ickeringill M, Shehabi Y, Adamson H and Ruettimann u. Dexmedetomidine Infusion Without Loading Dose in Surgical Patients Requiring Mechanical Ventilation: Haemodynamic Effects and Efficacy. Anaesth. and Intensive Care 2004; 32: 741-745
21. Ferdi Menda, Ozge Koner, Murat Sayin, Hatice Ture, Pinar Imer, Bora Aykac. Dexmedetomidine as an adjunct to anesthetic induction to attenuate hemodynamic response to endotracheal intubation in patients undergoing fast-track CABG. Annals of cardiac anaesthesia. 2010; 13(1): 16-21.
22. Gunalan S, Venkatraman R, Sivarajan G and Sunder P. Comparative Evaluation of Bolus Administration of Dexmedetomidine and Fentanyl for Stress Attenuation During Laryngoscopy and Endotracheal Intubation. Clin Diagn Res. 2015; 9(9): UC06–UC09.
23. Jianjun Ren Huijun Zhang Lining Huang Yue Liu Fengqin Liu Zhenming Dong. Protective effect of dexmedetomidine in coronary artery bypass grafting surgery. Experimental and Therapeutic Medicine. 2013; 12(1): 497-502.
24. Raeder, Johan C.; Stenseth, Liv B.Ketamine: a new look at an old drug. Current Opinion in Anaesthesiology. 2000; 13(4): 463-468.
25. Zielmann S, Kazmaier S, Schnüll S, Weyland A. S-(+)-Ketamine and circulation.Europe PMC.1997; 46 (1): S43-S46.
26. Irina Grosu, Patricia Lavand'homme, Emmanuel Thienpont. Pain after knee arthroplasty: an unresolved issue. Knee Surgery, Sports Traumatology, Arthroscopy. 2014; 22(8): 1744–1758.
27. Hernández C, Díaz-Heredia J, Berraquero ML, Crespo P, Loza E, Ruiz Ibán MÁ. Pre-operative Predictive Factors of Post-operative Pain in Patients With Hip or Knee Arthroplasty: A Systematic Review. Reumatología Clínica. 2015; 11(6): 361-380.
28. Paula Masgoret, Carmen Gomar, Beatriz Tena, Pilar Taurá, José Ríos and Miquel Coca. Incidence of persistent postoperative pain after hepatectomies with 2 regimes of perioperative analgesia containing ketamine. Medicine.2017; 96(15): e6624.
29. Godoy, Maria Celoni de Mello de; Dalmolin, Gerusa Duarte, et al. Management of chronic neuropathic pain of different causes with the combination of oral methadone along with ketamine: A report of 18 cases. European Journal of Anaesthesiology. 2013; 30 (10): 638–640.
30. Schug S and Peyton P. Does perioperative ketamine have a role in the prevention of chronic postsurgical pain: the ROCKet trial. British Journal of Pain. 2017; 11(4): 166–168.
31. Souhayl Dahmani, Daphné Michelet, Paer-Selim Abback and Chantal Wood. Ketamine for perioperative pain management in children: a meta-analysis of published studies. The Clinical Journal of Pain. 2011; 31(12): 112-119.
32. Richard K. Patch III,1 Jason S. Eldrige,2 Susan M. Moeschler,2 and Matthew J. Pingree. Dexmedetomidine as Part of a Multimodal Analgesic Treatment Regimen for Opioid Induced Hyperalgesia in a Patient with Significant Opioid Tolerance. Case Reports in Anesthesiology. 2017; 230-235.
33. Peng, Ke; Liu, Hua-Yue; Wu, Shao-Ru; Cheng, Hao; Ji, Fu-Hai. Effects of Combining Dexmedetomidine and Opioids for Postoperative Intravenous Patient-controlled Analgesia. The Clinical Journal of Pain. 2015; 31(8): 1097-1104.
34. Dirk Zajonz, Johannes K. M. Fakler, Anna-Judith Dahse, Fujiaoshou Junping Zhao, Melanie Edel, Christoph Josten and Andreas Roth. Evaluation of a multimodal pain therapy concept for chronic pain

after total knee arthroplasty: a pilot study in 21 patients. Patient Safety in Surgery. 2017; 11-22.
35. Hadlandsmyth, Katherine; Zimmerman, M.Bridget, Wajid, Roohina, Sluka, et al. Longitudinal Postoperative Course of Pain and Dysfunction Following Total Knee Arthroplasty. The Clinical Journal of Pain. 2018; 34(4): 332-338.
36. Yun SH, Park JK,Kim, Sang R, et al. Effects of Dexmedetomidine on Serum Interleukin-6, Hemodynamic Stability, and Postoperative Pain Relief in Elderly Patients under Spinal Anesthesia. Acta Medica Okayama. 2016; 70(1): 37-43.
37. Li J, Wang H, Dong B, et al. Adding dexmedetomidine to ropivacaine for femoral nerve block inhibits local inflammatory response. Minerva Anestesiologica , 2017; 83(6): 590-597.
38. Packiasabapathy S, Lokesh K, Arora M, et al. 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. 2017; 11(3): 293–298.
39. Zhang J,Le Yang Ning, Xiao-Ming D, et al. Evidence for suppression of spinal glial activation by dexmedetomidine in a rat model of monoarthritis. Clinical and Experimental Pharmacology and Physiology.2010; 37: P158-166.
40. Yang B,Yuan-Chang, XiongaYu-Qiu, et al. Involvement of spinal microglia and interleukin-18 in the anti-nociceptive effect of dexmedetomidine in rats subjected to CCI. Neuroscience Letters. 2014; 560: 21-25.
41. Dai Z, Jiang L, Hu M, et al. The protective effects of dexmedetomidine on ischemic brain injury: A meta-analysis. Journal of Clinical Anesthesia. 2017; 40: 25-32.