Effect of Perioperative oral pregabalin in Total Knee replacement for postoperative pain.

INTRODUCTION:

Total knee arthroplasty is among the most common orthopaedic surgeries that is being performed to relieve joint pains in patients who had advanced osteoarthritis and rheumatoid arthritis [(1)]. This procedure is associated with moderate to severe postoperative pain which requires pre-emptive planning of multimodal analgesia. Although Opioids are the mainstay treatment for postoperative acute pain management, they are associated with adverse side effects which limit postoperative rehabilitation, reduce patient satisfaction and overall outcome.

Opioids are well documented for their adverse effects, especially in geriatric patients presenting for Orthopaedic surgeries. The tolerance and physical dependence can develop at prescribed doses even [(2)]. Opioids are associated with sedation, respiratory depression, paralytic ileus, immunosuppression and opioid-induced endocrinopathy to name a few.

Pregabalin is analogue of neurotransmitter gamma-aminobutyric acid (GABA) [(3)] anticonvulsant and has wide range of clinical uses which encompass treatment of not only seizures but also neuropathic pains, adjuvant analgesia in general anaesthesia as part of multimodal analgesia plan, to limit Opioids use. It mainly acts through binding on alpha-2 and delta receptors and act as antihyperalgesic agent [(4)]. Pregabalin delays or offsets the sensitization of dorsal horn neurons, possibly leading to augmentation of surgical stimulation that affects changes in the central and peripheral nervous system. Postoperative pain of Total knee replacement and total Hip replacement has profound effects on patient rehabilitation and satisfaction postoperatively. Mohsen Ziyaeifard et el had studied its effects in patients undergoing CABG that showed its safety profile along with opioid sparing properties. [(5)]

Multimodal analgesia is a term that encompass more than one intervention simultaneously to aim multiple receptors within nociceptive and neuropathic pathways to control postoperative pain by providing opioid-free or opioid-reduced anesthesia. This includes regional anesthesia as core component. Femoral nerve block is one standard intervention which has documented analgesia for lower limb surgeries with wide range of safety profile. It reduces the incident of chronic postoperative pain as well. [6]

In all efforts to develop an opioids free or opioid reduced anesthesia practice, we try to use adjuvants in our practices to improve the outcome without adverse effects. One such practice is addition of Dexmedetomidine in femoral nerve block to enhance the postoperative analgesia duration and quality. Qianchuang Sun et el meta-analysis has shown that dexmedetomidine prolongs the duration of Tap block as well as improve the quality of analgesia [7]. Another study reported 30% increase in duration of ulnar nerve block with IV dexmedetomidine, and 100% increase in duration of ulnar nerve block with perineural treatment[8], compared with an identical dose of ropivacaine alone. Dexmedetomidine is alpha-2 adrenoceptor agonist who act centrally and produce sedative and analgesic effects without respiratory depression or paralytic ileus.

OBJECTIVE: this study aim to determine efficacy and safety of perioperative Oral pregabalin in improving postoperative pain control in patients undergoing total knee replacement surgeries under regional anesthesia.

HYPOTHESIS:

Pregabalin reduces postoperative pain, analgesia and opioid requirement,

MATERIAL AND METHODS:

STUDY TYPE: **Interventional (clinical trial)**

STUDY SETTING: Operation Theatres, Bahrain defence forces

DURATION OF STUDY: 12-18 months after the approval of synopsis

SAMPLING TECHNIQUE: Non probability conservative sampling

OFFICIAL TITLE: Effect of Perioperative oral pregabalin in Total Knee replacement for postoperative pain. A randomized Controlled Single blind trial.

SAMPLE SIZE: sample size of 120 cases (60 in each group) is calculated with 80% power of test, 5% level of significance and taking expected percentage of Pain scores in both groups.

Inclusion criteria:-

1. Age between 18 to 85 year
2. Elective Regional anesthesia.
3. Able to follow study protocol

Exclusion Criteria:

1. ASA -IV
2. Age <18 & > 85 years
3. Patients on pregabalin for chronic neuropathic pain.
4. Patient under General anesthesia
5. Patients with chronic liver failure
6. Patients with chronic renal failure on Hemodialysis
7. Patients on opioid (>3 month)
8. Patient with complicated knee surgery.

DATA COLLECTION PROCEDURE:

After obtaining approval from the institutional ethical committee and informed written consent, 120 patients fulfilling the inclusion criteria will be included in this study. The patients will be randomly assigned into two equal groups; Group P: Pregablain group and Group C: control group. Group P will receive oral capsule pregabalin 75mg one hour preoperatively and Group C will not receive any premedication preoperatively.

Intraoperatively both groups will receive inj. Midazolam 2 mg before subarachnoid block with hyperbaric Bupivacaine 0.5% 2.5-3ml and fentanyl 15mcg in the operation theatre (OT). Both groups will also receive parecoxib 40mg IV and paracetamol 1G Intravenous (IV) as part of multimodal analgesia. Both groups will receive dexamethasone 8mg IV prophylactically.

Postoperatively both group will receive Ultrasound guided Adductor canal saphenous Nerve block in the PACU with 0.2% Bupivacaine 20-30ml & dexmeditomidine1.0mcg/kg. Group P will receive oral capsule pregabalin 75 mg Q12hrly from the 1st dose for next 60 hrs. Group C will not receive any medication. Both groups will receive paracetamol 1G IV Q6Hrly for 24 hrs and rescue Analgesia will be provided with oral oxycodone 5mg TDS as PRN and Morphine PCA, in escalating manner as per patient requirement.

After 24 hrs both group will continue with paracetamol 1G Q6Hourly and tab Ibuprofen 400mg Q8 Hourly along with oxycodone or PCA morphine as per requirement.for 72 hrs.

DATA ANALYSIS: SPSS

Outcome measure:

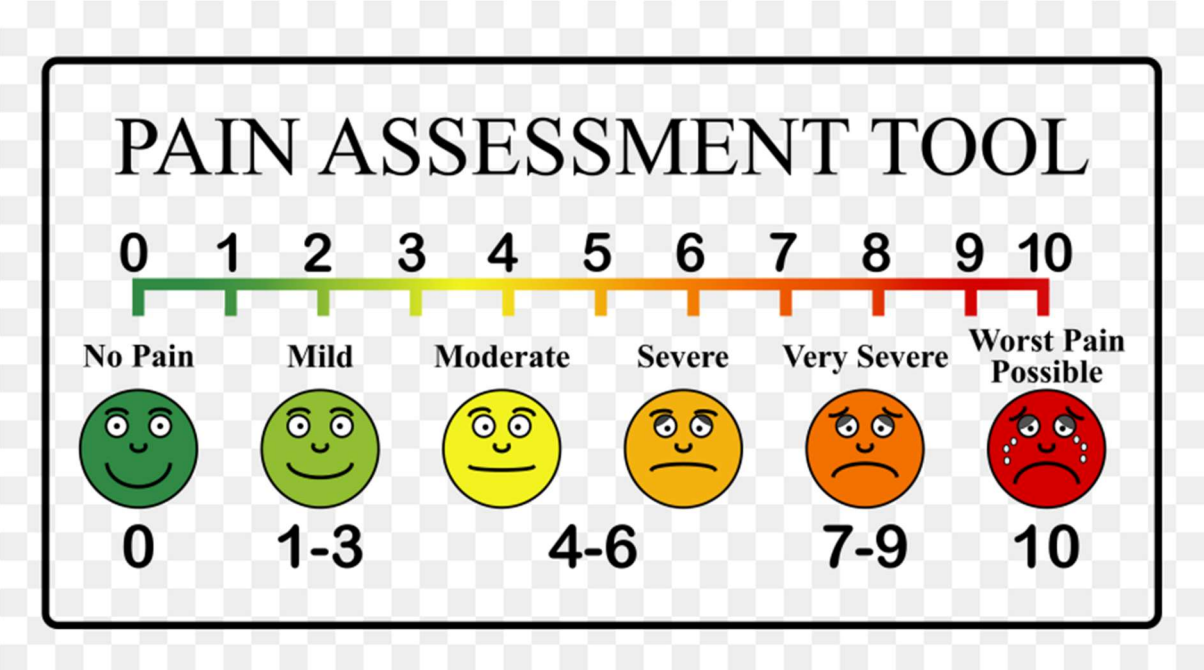
Primary outcome:

- VAS score at 4hrs, 8hrs, 12hrs, 24hrs, 36 hrs, 48hrs, 60hrs, and 72hrs. Annexure attached

Secondary outcome:

- Sedation score: RASS score at 4hrs, 8hrs, 12hrs, 24hrs, 36 hrs, 48hrs, 60hrs, 72hrs. Annexure attached
- VAS at 1st CPM :
- Time of 1st analgesia request
- Incident of bradycardia in 1st 24 Hrs
- Incident of Hypotension in 1st 24 Hrs
- Total opioid consumption in 72hrs: Oxycodone/Morphine
- Patient satisfaction at 72 hrs : rated as numeric 1-5 (1=not satisfied, 5=fully satisfied)

ANNEXURE FOR VAS score



ANNEXURE FOR RASS score

The Richmond Agitation–Sedation Scale		
Score	**Term**	**Description**
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff
+2	Agitated	Frequent non purposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

REFERENCES:

1. Jing-wen Li, MSc1,2, Ye-shuo Ma, PhD3 , Liang-kun Xiao, MSc: Postoperative Pain Management in Total Knee Arthroplasty: review article
2. Anesth Analg. 2017 November ; 125(5): 1733–1740. doi:10.1213/ANE.0000000000002458.
3. https://reference.medscape.com/drug/lyrica-cr-pregabalin-343368
4. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol.* 2010;17(9):1113–e88. doi: 10.1111/j.1468-1331.2010.02999.x. [PubMed] [CrossRef] [Google Scholar]
5. Mohsen Ziyaeifard, Mohammad Javad Mehrabanian, Seyedeh Zahra Faritus, Mehrdad Khazaei Koohpar, Rasool Ferasatkish, Heidar Hosseinnejad, and Mohammadreza Mehrabanian: Premedication With Oral Pregabalin for the Prevention of Acute Postsurgical Pain in Coronary Artery Bypass Surgerysatkish,1 Heidar Hosseinnejad,3 and Mohammadreza Mehrabanian:
6. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic postoperative pain: a narrative review: Y.-Y.K. Chen,1 K.A. Boden,2 and K.L. Schreiber, Assistant Professor3: Anaesthesia. 2021 Jan; 76(Suppl 1): 8–17.

7. Dexmedetomidine as an Adjuvant to Local Anesthetics in Transversus Abdominis Plane Block: A Systematic Review and Meta-analysis: Qianchuang Sun 1, Shuyan Liu 2, Huiying Wu 3, He Ma 1, Wei Liu 1, Meidan Fang 1, Kexiang Liu 4, Zhenxiang Pan : Clin J Pain 2019 Apr;35(4):375-384.doi: 10.1097/AJP.0000000000000671.
8. Andersen JH, Jaeger P, Grevstad U, et al. Systemic dexmedetomidine is not as efficient as perineural dexmedetomidine in prolonging an ulnar nerve block. Reg Anesth Pain Med. 2019;44:333–40.

PERFORMA: Effect of Perioperative oral pregabalin in Total Knee replacement for postoperative pain.

Serial N0: _____ Hospital Record NO: _____

Date: _____ Patient Age: _____

Gender: _____ ASA Status: _____

Preoperative Oral capsule pregabalin time: _____.

Subarachnoid block given (Bupivacain+fentanyl) (Start point time) _____

Postoperative USG guided femoral nerve block (Bupivacaine + dexmedetomidine): start point time. _____

VAS SCORE: (0-10)

Time:Start point	At 4Hrs	8Hrs	12Hrs	24Hrs
	36 Hrs	48Hrs	60Hrs	72Hrs

Sedation score: RASS attached {0- (-5)}

+4	+3	+2	+1	0	-1	-2	-3	-4	-5

Time:Start point	At 4Hrs	8Hrs	12Hrs	24Hrs
	36 Hrs	48Hrs	60Hrs	72Hrs

VAS at 1st CPM :

Time of 1st analgesia request:_____

Incident of bradycardia in 1st 24 Hrs: Y/N _____

Incident of Hypotension in 1st 24 Hrs: Y/N _____

Total opioid consumption in 72hrs: Oxycodone: _____mg Morphine: _____ mg.

Patient satisfaction (1-5): at 72 Hrs(1: Not satisfied, 5: fully satisfied)

1	2	3	4	5

ANNEXURE FOR ASA STATUS

ASA I
Patients are considered to be normal and healthy. Patients are able to walk up one flight of stairs or two level city blocks without distress. Little or no anxiety. Little or no risk

ASA II
Patients have mild to moderate systemic disease or are healthy ASA I patients who demonstrate a more extreme anxiety and fear toward dentistry. Patients are able to walk up one flight of stairs or two level city blocks, but will have to stop after completion of the exercise because of distress. **Examples**: History of well-controlled disease states including non-insulin dependent diabetes, prehypertension, epilepsy, asthma, or thyroid conditions; ASA I with a respiratory condition, pregnancy, and/or active allergies. May need medical consultation.

ASA III
Patients have severe systemic disease that limits activity, but is not incapacitating. Patients are able to walk up one flight of stairs or two level city blocks, but will have to stop enroute because of distress. If dental care is indicated, stress reduction protocol and other treatment modifications are indicated. **Examples:** History of angina pectoris, myocardial infarction, or cerebrovascular accident.

ASA IV
Patients have severe systemic disease that limits activity and is a constant threat to life. Patients are unable to walk up one flight of stairs or two level city blocks. Distress is present even at rest. Patients pose significant risk since patients in this category have a severe medical problem of greater importance to the patient than the planned dental treatment. **Examples**: History of unstable angina pectoris, myocardial infarction or cerebrovascular accident within the last six months, severe congestive heart failure.

ASA V
Patients are moribund and are not expected to survive more than 24 hours with or without an operation. These patients are almost always hospitalized, terminally ill patients. Elective dental treatment is definitely contraindicated; however, emergency care, in the realm of palliative treatment may be necessary.

ASA VI

Clinically dead patients being maintained for harvesting of organs.

ASA-E: Emergency operation of any variety (used to modify one of the above classifications, i.e., ASA III-E).

* Status can change as medical history changes; adapted by Margaret J. Fehrenbach, RDH, MS, from the American Society of Anesthesiologists, *Medical Emergencies in the Dental Office* (Malamed, Mosby, 2008), and included in *Saunders Review of Dental Hygiene* (Fehrenbach and Weiner, Elsevier, 2009).