EAS Journal of Anaesthesiology and Critical Care
Abbreviated Key Title: EAS J Anesthesiol Crit Care
ISSN: 2663-094X (Print) & ISSN: 2663-676X (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-2 | Issue-1 | Jan-2020 | DOI: 10.36349/easjacc.2020.v02i01.002

Research Article

The Effect of Preoperative Oral Melatonin, Duloxetine or Tapentadol on Post Spinal Analgesia and Sedation in Knee Arthroscopic Surgeries: A Comparative Hospital Based Study

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Article History
Received: 04.12.2019
Accepted: 11.12.2019
Published: 03.01.2020

Journal homepage:
https://www.easpublisher.com/easjacc

Quick Response Code

Abstract: ***Background:*** Post-operative pain is a frequent observation in patients undergoing knee arthroscopic surgeries and remains a challenge to anaesthesiologist. The current armamentarium of drugs as multimodal analgesia for post-operative pain utilizes many new medications with different complementary mechanism of action and remains the recommended intervention for the management of post arthroscopic knee pain. ***Aim*****:** We compare the efficacy of preoperative duloxetine, melatonin and tapentadol for post spinal analgesia and sedation in knee arthroscopic surgeries. ***Setting and design*****:** Randomised prospective double blind study. ***Methods***: 124 American Society of Anaesthesiologist 1and II patients undergoing knee arthroscopic surgery requiring spinal anaesthesia were allocated randomly to four groups of 30 each to receive oral Placebo Group 1, 20 mg Duloxetine Group 2, 3 mg Melatonin Group 3, 100 mg Tapentadol Group 4, 90 minutes before surgery. We assessed block characteristics, intraoperative sedation using BIS scores, postoperative pain scores using Numeric Rating Score, time to use of first analgesic, 24 hour analgesic consumption, additional analgesic consumption and any adverse effects. ***Results*****:** Mean duration of post-operativeanalgesia was 477.96±97.85 minutes in Tapentodol Group (P value<0.001). Total 24 hours diclofenac consumption is minimum in Tapentodol Group (P 0.04). No statistical significant differences were present in the onset of the spinal block, BIS and Ramsay Sedation Score among the Groups. ***Conclusion*****:** Preoperative administration of oral tapentadol provides prolonged analgesia with reduced 24 hour analgesic consumption.

Keywords: bispectralindex, tapentadol, melatonin, duloxetine, spinal anaesthesia.

INTRODUCTION

Subarachnoid block is undoubtly a preferred technique for lower limb surgeries. Knee arthroscopy is a common orthopedic surgery on lower limb that has been performed as a day care procedure for more than two decades. Despite advances in understanding pathophysiology of pain, half of the patient still experience post-operative pain. Tissue injury as a result of surgery sensitizes the neuroreceptors present peripherally resulting in Central neuronal sensitization; consequently causing nociceptive pain (Vadivelu N *et al.,* 2010). Pain after arthroscopic procedures such as knee arthroscopic surgeries can be severe which is not only undesirable rather associated with delayed recovery after suboptimal treatment. Pain control after knee arthroscopic surgeries is a challenge to anaesthesiologist .Preemptive analgesia modulates the pain pathway and influences the pain management via multimodal analgesic strategy. Newer concept of multimodal anaesthesia provides superior analgesia with lesser side effect in post-surgical patients (White PF, 2008). The concept of multimodal analgesia currently utilizes many new medications with different complementary mechanism of action to reduce postsurgical pain. Although many therapeutic interventions including oral administration of melatonin, duloxetine and tapentadol as premedicant before spinal anaesthesia have been evaluated in various surgeries to enhance post-operative analgesia .Studies published on the mechanism of synergistic effect of these drugs with spinal anaesthesia is still unclear. Melatonin is reported to mediate analgesic action via action on receptors inside dorsal horn of spinal cord and gabaergic receptors (Shavali S *et al.,* 2005). Duloxetine a newer antidepressant inhibits serotonin and norepinephrine reuptake which are responsible for modulating descending inhibitory pain pathway in CNS (Ho K Y *et al., 2010*). Tapentadol is centrally acting opoid inhibits norepinephrine reuptake and activates α2 receptors and hence responsible for its analgesic properties (Kleinert R *et*

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al.,2008). Although studies suggests that these drugs play a role in central and peripheral pain modulation mechanism, existing literature is sparse in assessing the best agent among the three for decreasing the post-operative pain in orthopedic surgery. With the aim that administration of preemptive analgesia to efficiently manage post-operative pain we planned to compare oral Melatonin, Duloxetine or Tapentadol, in patients undergoing arthroscopic knee surgeries.

METHODS

This prospective, randomized study was conducted after Institutional Ethical Committee clearance and written informed consent in 124 American Society of Anesthesiologists (ASA) I and II patients of either sex between 18-60 years of age, posted for knee arthroscopic surgery under spinal anesthesia over a period of 12 months (July 2017 to July 2018) The Consolidated Standards of Reporting.

Trials (CONSORT) recommendation forreporting randomized trial was adopted (Fig. 1). Exclusion Criteria's included patient refusal for the spinal block, Known allergy and contraindication to study drugs. Contraindication to spinal anesthesia, BMI >30 kg/m 2, history of preoperative intake of with SNRI or analgesics (excluding acetaminophen and non-steroidal anti-inflammatory drugs), patients requiring bilateral surgery, history of alcohol or drug abuse, Pregnant patients. All patients fulfilling inclusion criteria were thoroughly assessed and examined in the preanesthetic clinic. The patients were explained the study protocols along with 11 point numeric rating scale (NRS).

The patients were randomly allocated by sealed envelope technique into four equal groups to receive The drugs were dispensed in identical gelatin capsules prepared by anaesathesia consultant after consulting hospital pharmacist and supplied in opaque envelopes marked 1,2,3 and 4.The drugs were administered according to group allocation by assigned nurse in ward with no further involvement in the study. Drug was administered 90 min prior to surgery with sips of water as-

- (Group I), Placebo Empty capsule,
- (Group 2), 20 mgDuloxetine (Tab Duloxee-20, Talent India)
- (Group 3). 3mgMelatonin (Tab Meloset- 3, Aristo Pharmaceuticals Pvt Ltd)
- (Group 4). 100mgTapentadol Group (Tab Tydol-100, SUN Pharmaceuticals Industries Pvt Ltd

Patients in all the groups were kept fasting for solids for 6-8 h and received oral alprazolam 0.25 mg night. In the operating room,routine monitors such as Non Invasive Blood Pressure (NIBP), Pulse oximetery (SpO2), Electrocardiogram (ECG), Bispectral index (BIS) monitor were attached and baseline vitals noted.

After securing the intravenous line the patients were preloaded with 500 ml Ringer Lactate followed by administration of spinal anesthesia with 3 ml of 0.5% heavy bupivacaine mixed with 25 µg fentanyl utilizing 25G Quincke's needle in L3-L4 intravertebral space. Time taken to achieve the sensory and motor block height of T10 or above was noted. Bromage score was used for assessing motor blockade and pin prick sensation for sensory blockade. Initial values of Ramsay sedation scores were noted .BIS values ,NIBP, HR were recorded every 2 min for first 15 minutes of spinal administration and thereafter every 10 minutes up to 105 mins then every 15 mins till the end of surgery by anaesthesia consultant not involved in the study. At the end of surgery, the level of sensory and motor blockade was checked by pin-prick method and the Bromage scale. The patients was shifted to post anaesthesia care unit(PACU).The pain was assessed on a 11 point by Numeric Pain Rating Scale(NRS) and analgesic was administrated when NRS>4 in the form of inj. Diclofenac 75 mg (Dynapar AQ, Troika) intravenous as a bolus over 10 sec for next 24 hours. In the PACU, NRS, sensory level and motor blockade checked at 0 hours, 2 hours, 4 hours, 12 hours, 24 hours postoperatively by the anesthesiologist posted in post anaesthesia care unit who was blinded to the drugs given as a part of study. The time of bromage 0/1, for demand of the first dose of analgesia in PACU was noted. Additional analgesic in form of injection tramadol was given if pain still not relieved or NRS>4 after 15 minutes with injection diclofenac.

The time to first rescue anaelgesic, total consumption of tramadol and the presence of side effects such as if any were noted and managed. The primary outcome measure was the total diclofenac requirements in 24h after surgery. The secondary outcome measures was post-surgery pain score in form of NRS scoring noted at 0,2,4,12,and 24 hrs and intraoperative sedation using BIS monitoring.

Sample size calculation was based on previous study (Atef HM, 2014). The sample size was calculated 25 subjects in each group, using power analysis (α =0.05, β=0.8)to detect 50% difference in analgesic consumption at 24 hours post-surgery. To prevent possible data loss, we took 31 subjects per group.

Statistical analysis

The data generated in the study is presented as Mean ± standard deviation (SD), median and range, frequency, ratio and percentage. The data was analysed for statistical analysis using Microsoft Office Excel 2010 and SPSS IBM version 22. Normally distributed continuous variables were compared using analysis of variance ANOVA (analysis of variance).If the F value was significant and variance was homogeneous, Bonferroni multiple comparision test was used to assess the differences between the individual groups .The Kruskal Wallis test was used for variables that were not

distributed normally and further comparisions done using Mann Whitney U test Categorical variables were analysed using the chi square test.

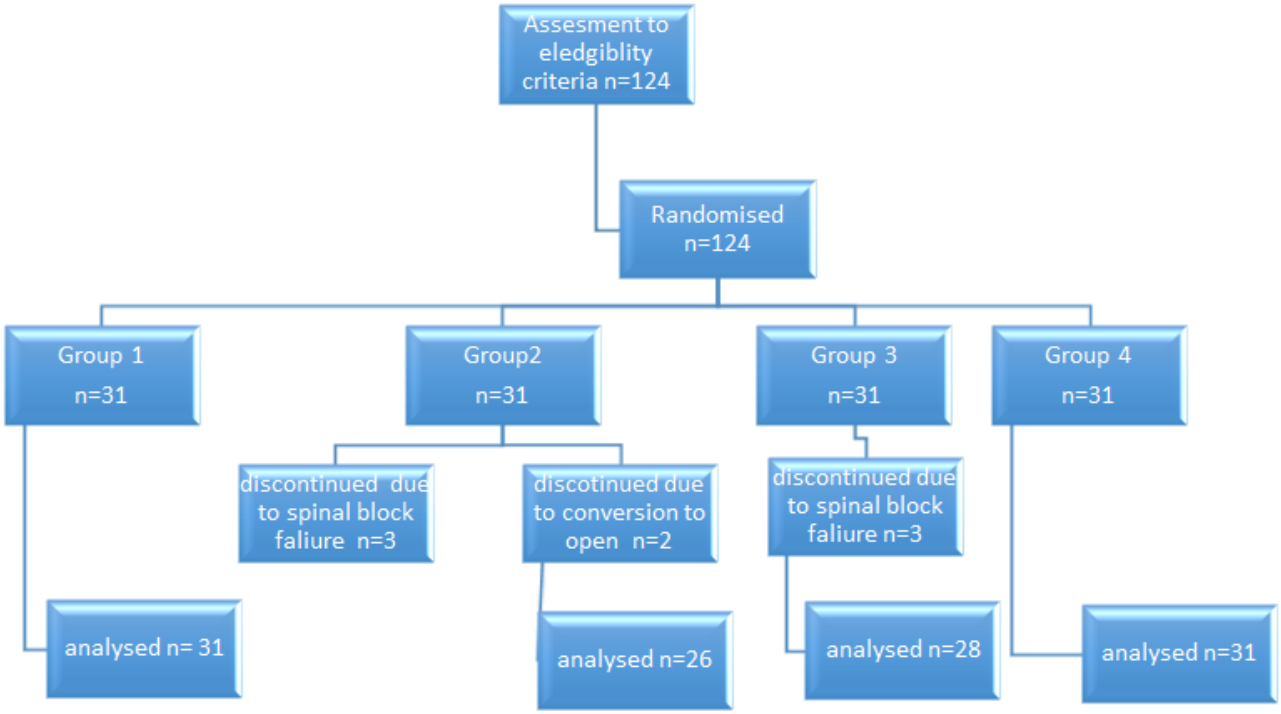

Figure-1: Consort Diagram

RESULTS

Spinal anaesthesia was successfully performed in 124 patients. Inadequate block after successful intrathecal injection was seen in five patients and three patients in Groups 2 and Group 3 respectively and thus excluded from the final analysis [Fig1].

Table 1: Demographic profile, Data Is presented as mean ± Standard deviation or numbers

	Group 1 (n=31)	**Group 2 (n=26)**	**Group 3 (n=28)**	**Group 4 (n=31)**	**P value**
Gender M:F	4:27	8:18	7:21	6:25	
AGE (in years)	29.35±10.35	29.35±10.35	31.25±11.11	30.87±11.19	0.881
ASA (I:II)	29:2	24:2	27:1	30:1	
WEIGHT (in Kgs)	62.35±6.68	58.81±6.88	60.75±9.43	62.19±9.24	0.342
Duration of surgery(min)	118.12±40.02	116±32.08	122±28.16	120±24.16	0.802
Time to First post op analgesia(min)	377.25±52.58	430.65±84.84	410.71±65.20	477.96±97.85	**<0.001**
Diclofenac consumption (mg)	150 ± 64.2	115.7 ± 43.3	128.5± 64.0	111.25±50.78	**<0.001**

- Data are presented as mean ±SD. : Statistically significant difference (p-value<0.05)
- High statistically significant difference (p-value <0.005)
- Duration of post-operative analgesia and diclofenac dosage used were comparable among Group 2, 3 and 4.

No significant difference in age,s ex, weight and duration of surgery were found among the groups .Time to first post-operative analgesic request (477.96±97.85 min) and total diclofenac consumption (111.25±50.78 mg) was significantly longer in Group 4 compared to Group 1[Table1].

Although post-operative pain assessed by NRS(numerical rating scale)was significantly lower in Group 4 as compared to Group 1, 2 and 3 at 2 hours after surgery, no significant difference was observed at any time point among groups [Table2].

Table 2: NRS Score

	Group 1 (n=31) Median(IQR)	Group 2 (n=26) Median(IQR)	Group 3 (n=28) Median(IQR)	Group 4 (n=31) Median(IQR)	P value
T'0	3(3-4)	2.5(2-3)	3(2-3)	1(0-2)	0.624
T'2	3(3-4)	3(2-3)	3(2-3)	2(2-3)	**0.001**
T'4	2(2-3)	2(2-3)	2(2-3.75)	3(2-3)	0.861
T'12	3(2-4)	3(2-3)	2(2-3)	3(2-4)	0.939
T'24	2(2-3)	3(2-3)	3(2-3)	3(2-3)	0.607

*IQR = Interquartile Range The above table shows post-operative NRS at 0hr,2hr,4hr,12hr,24hr respectively

Comparision of means of BIS score is shown among the groups. No significant difference was observed among the groups [Figure: 2].

Tramadol as additional analgesic was needed in different groups.No patient required 200 mg tramadol except in Group 1 were one patient required [Table 3] .

Intraoperative complications observed are shown in Table 4.

Hypotension was the commonest complication observed in Group 1.

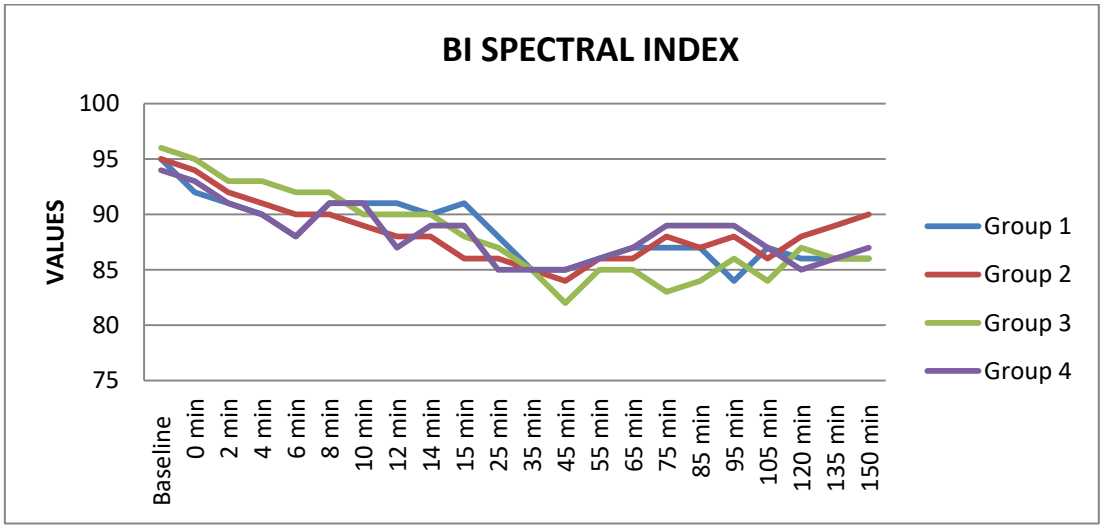

Figure 2: Comparison of means of BIS values at different time intervals among the groups

Table 3: Tramadol Consumption in 24 Hours as Additional Analgesic

		GROUPS				Total
		Group 1	Group 2	Group 3	Group 4	
No of tramadol used in 24 hrs (in mg)	0mg	27	23	26	30	106
	100mg	3	3	2	1	9
	200mg	1	0	0	0	1
Total		31	26	28	31	116

Table 4: Incidence of Intraoperative Complications

	Group 1	Group 2	Group 3	Group 4
Bradycardia	2	0	0	0
Hypotension	8	0	2	0
Nausea	2	0	0	2
Vomiting	0	0	3	1
Respiratory depression	0	0	0	0
Pruritis	0	1	0	0
Shivering	3	2	2	0

DISCUSSION

The results of our study demonstrated that a single dose of 100 mg oral tapentadol preoperatively is more effective in decreasing the pain severity and post-operative analgesic requirement without adverse effects in patients undergoing knee arthroscopic surgery.

Orthopedic procedures such as arthroscopic surgeries are associated with moderate to severe pain along with psychological distress in the post-operative period (Obasuyi BI *et al.,* 2013) hence necessitating active intervention. The preemptive analgesic effect of oral melatonin, duloxetine and tapentadol has been previously studied independently in a variety of surgical procedures. To the best knowledge, this is the first study to compare these drugs in a single setting. In our study, drugs dosage, and timing of drug administration were selected as per previous studies to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery. Our study drugs had no effect on block characteristics in terms of onset and height of block but enhanced motor block is observed significantly in tapentodol group. Role of preemptive analgesia has been documented in attenuation of post-operative pain (Woolf CJ & Chong MS, 1993).

As depth of sedation is not easy to measure, we utilized BIS monitor which gives an EEG derived parameter related to sedation level (Billard V, 1997; Rosow C, 1995). BIS score dropped to around 85 in all groups after 30 minutes of subarachnoid block although we did not find any significant difference in BIS values between different groups. The use of lower dosages of drugs could have the reason attributed to this finding. (Ben et al., 1995) concluded in their study that patients under spinal anaesthesia show significant sedation only after achieving high sensory block. This is in correlation with study by (Evagelidis P *et al*., 2009*)* who did not find any difference in BIS values even with sublingual 9 mg melatonin. The other reason may be the same median and anaesthetic block height achieved in the groups . Our study showed decreased 24 hour diclofenac consumption in all study drugs groups compared to placebo. Significantly reduced in tapentodol group. (p value 0.04) Tapentadol, an opioid owing to its dual mode of action (μ-receptor agonist/ norepinephrine reuptake inhibitor) increased time to first analgesic use, reduced postoperative analgesic consumption without any side effects of opioids. Tapentodol decreased induction dose requirement, post-operative analgesic requirement in surgical patients (Singh DR *et al.,* 2013). Similarly, reduced postoperative dose requirement was observed by (Daniels SE, 2009; Hatrick, 2009). Yadav G *et al* (2016) reported significant decrease inpain score and analgesic requirement in laparoscopic cholecystectomy patients. Antinociceptive actions of melatonin have been well demonstrated in various studies (Acil M, Basgul E *et al.,* 2004). The anxiolytic action of melatonin is directly correlates to its pharmacokinetics, time required to reach peak plasma concentration of drug ranged from 0.25 h to 13 h. The postoperative analgesic effect of melatonin has been proved with cataract surgery under topical anaesthesia and with laparaoscopic cholecystectomy (Khezri MB et al., 2013). Melatonin impact on pain may be due to interplay between the melatonergic and GABA-ergic systems, enhancement of endorphin levels and the antinociception induced by opioid receptor agonists, and activation of MT2 melatonin receptors in the dorsal horn of the spinal cord (Brydon L *et al.,* 1999*;*

Marseglia L *et al.,* 2015). Ionescu D *et al*., (2008) reported reduced post-operative fentanyl requirement after melatonin. Yousaf *et al.,* (2010) in studies showed an opioid-sparing effect or reduced pain scores with melatonin premedication whereas three studies were contradictory.

Majority of studies of duloxetine are done in spine patients with drug started preoperatively one to two week prior to surgery and continued post-operatively.

Ours is first study done with single preoperative administration in subarachnoid block, short term administration of duloxetine elevated extra cellular monoamine levels and in this way exerts the modulating effect on spinal pain circuits. Studies by Castro LJ, Hyer L reported decreased analgesic requirement and consequently improved quality of recovery with duloxetine (Castro-Alves LJ,2016; Hyer L,2016).

In our study none of the patients had respiratory depression, 8 patients had hypotension, 2 patients had bradycardia and 3 patients had shivering in Group 1 where as in 2 patients hypotension was observed in Group 3. Pruritis was seen in 1 patient where as shivering was observed in 2 patients each in Group 2 and Group 3 .Nausea was found in 2 patients receiving Tapentadol and vomiting was seen in 3 patients of Group 3 and 1 patient in Group 4.

This study had few limitations such as smaller sample size and unequal distribution of patient in the groups .As it was not the crossover study the influence of inter patient variably could not be avoided during the comparison. Secondly, we did not measure the serum level of study drugs, as existing literature mentions that smoking lowers duloxetine serum levels thus requiring high dose to achieve therapeutic level, but we did not look into this aspect in our study.

Conclusion our study showed that preoperative administration of oral tapentadol is more efficacious than duloxetine and melatonin in reducing post-operative pain severity and prolonging duration of

post-operative analgesia without sedation as a multimodal approach in knee arthroscopy surgery. Although these findings cannot be extrapolated to all the patients, the present study provides additional evidence that oral tapentodol administration in preoperative period may cause reduction in analgesic consumption without significant side effects. Further studies are required to see dose response on block characteristics and sedation scores.

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