Print ISSN: 2958-3675 | Online ISSN: 2958-3683
International Journal of Medical and Pharmaceutical Research
Available Online at https://ijmpr.in/
ORCiD ID: 0000-0002-3849-6959
Volume 4, Issue 1; (2023); Page No. 193-198
Original Article Open Access

Comparative Oral Duloxetine, Melatonin And Tapentadol For Post Spinal Analgesia And Sedation In Knee Arthroscopic Surgeries

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ABSTRACT

Background: Arthroscopic knee surgeries are very common procedures as ambulatory day case surgeries and are preferred by most patients. Many patients complain of moderate to severe pain 24 h after surgery and pain affects the patient's activity level and satisfaction. Post-operative pain is a frequent observation in patients undergoing knee arthroscopic surgeries and remains a challenge to anaesthesiologist. **Objective:** To assess the efficacy of preoperative duloxetine, melatonin and tapentadol for post spinal analgesia and sedation in knee arthroscopic surgeries. **Methods:** This prospective, randomized study was conducted at Anesthesia Department, Rahat Anwar Hospital, Band Road, Chandmari, Barishal, Bangladesh from June-2021 to December 2022. After Institutional Ethical Committee clearance and written informed consent in 106 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. Patients undergoing knee arthroscopic surgery requiring spinal anaesthesia were allocated randomly to four groups of oral Placebo Group A, 20 mg Duloxetine Group B, 3 mg Melatonin Group C, 100 mg Tapentadol Group D, 90 minutes before surgery. We assessed block characteristics, intraoperative sedation using Ramsay sedation scores, postoperative pain scores using Numeric Rating Score, time to use of first analgesic, 24-hours analgesic consumption, additional analgesic consumption and any adverse effects. **Results:** Total 106 patients Spinal anaesthesia was successfully performed. No significant difference in age, sex, 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±50.78mg) was significantly longer in Group D compared to Group A. Although post-operative pain assessed by NRS (numerical rating scale) was significantly lower in Group D as compared to Group A, B and C at 2 hours after surgery, no significant difference was observed at any time point among groups. Mean duration of post-operative analgesia 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 and Ramsay Sedation Score among the Groups. **Conclusion:** Preoperative administration of oral tapentadol provides prolonged analgesia with reduced 24-hours analgesic consumption.

Keywords: *Tapentadol, Melatonin, Duloxetine, Spinal Anaesthesia.*

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INTRODUCTION

Arthroscopic knee surgeries are very common procedures as ambulatory day case surgeries and are preferred by most patients [1]. Many patients complain of moderate to severe pain 24 h after surgery [2,3], and pain affects the patient's activity level and satisfaction [4]. 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. Activation of a specialized nerve ending "nociceptor" initiates pain in response to various stimuli (mechanical chemical, or thermal) directly through trauma or indirect via biochemical mediators from tissue damage; Arachidonic acid, histamine, prostaglandins, serotonin, and bradykinins are the common mediators that

stimulate and upregulate nociceptors and augment pain process, so long duration of the stimulus leads to more mediators release, more receptors stimulation, and more pain sensation [5,6]. 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 [7]. Multimodal analgesia uses the synergistic effects of different pain-relieving drugs to decrease postoperative pain with fewer narcotic requirements and fewer adverse effects [8,9]. Different adjuvants are utilized to extend the duration of spinal anesthesia, reduce postoperative pain, and decrease analgesic needs after surgery [10,11]. 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. 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.Melatonin is reported to mediate analgesic action via action on receptors inside dorsal horn of spinal cord and gabaergic receptors [12]. Duloxetine a newer antidepressant inhibits serotonin and norepinephrine reuptake which are responsible for modulating descending inhibitory pain pathway in CNS [13]. Tapentadol is centrally acting opoid inhibits norepinephrine reuptake and activates α2 receptors and hence responsible for its analgesic properties [14]. Although studies suggest 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 postoperative pain in orthopedic surgery.

MATERIALS AND METHODS

This prospective, randomized study was conducted at Anesthesia Department, Rahat Anwar Hospital, Band Road, Chandmari, Barishal, Bangladesh from June-2021 to December 2022. After Institutional Ethical Committee clearance and written informed consent in 106 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. 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 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-A	Placebo Empty capsule
Group-B	20 mg Duloxetine
Group-C	3mgMelatonin
Group-D	100mgTapentadol Group

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

Ramsay sedation: 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. Ramsay sedation 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 were 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 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 usingRamsay sedation monitoring.

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).The Kruskal Wallis test was used for variables that were not distributed normally and further comparisons done using Mann Whitney U Test Categorical variables were analysed using the chi square test.

RESULTS

Table-1: Demographic profile of the study patients.

	Group-A (n=28)	**Group-B (n=24)**	**Group-C (n=26)**	**Group-D (n=28)**	**p value**
Gender M:F	3:25	8:16	6:20	6:22	
Age (in years)	29.35±10.35	29.35±10.35	31.25±11.11	30.87±11.19	0.881
ASA (I:II)	26:2	22:2	25:1	27:1	
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 B, C and D.

Total 106 patients Spinal anaesthesia was successfully performed. No significant difference in age, sex, 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 D compared to Group A (Table-1). Although post-operative pain assessed by NRS (numerical rating scale) was significantly lower in Group D as compared to Group A, B and C at 2 hours after surgery, no significant difference was observed at any time point among groups (Table-2).

Table 2: NRS Score.

	Group-A (n=28) Median(IQR)	**Group-B(n=24) Median(IQR)**	**Group-C (n=26) Median(IQR)**	**Group-D (n=28) 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.

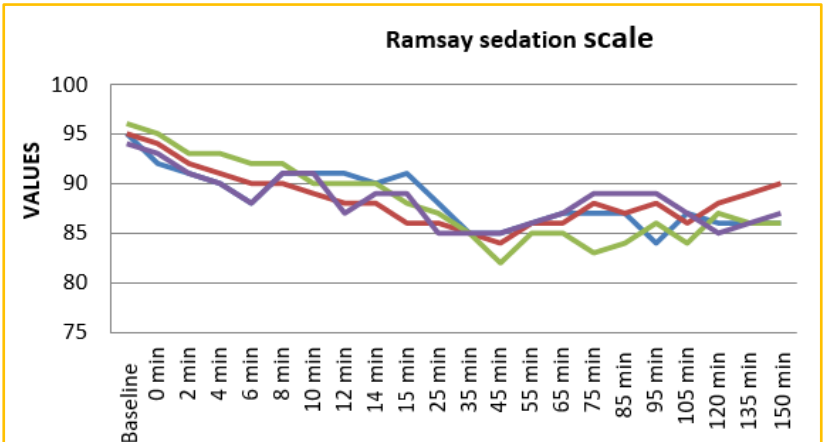

Figure 2: Comparison of means of Ramsay sedation values at different time intervals among the groups.

Comparison of means of Ramsay sedation score is shown among the groups. No significant difference was observed among the groups (Figure-2).

Table-3: Tramadol Consumption in 24 Hours as Additional Analgesic.

		GROUPS				Total
		Group-A	Group-B	Group-C	Group-D	
No of tramadol used in 24 hrs (in mg)	0mg	25	22	24	27	98
	100mg	2	2	2	1	07
	200mg	1	0	0	0	01
Total		28	24	26	28	106

Table-4: Incidence of intraoperative complications.

	Group-A	Group-B	Group-C	Group-D
Bradycardia	2	0	0	0
Hypotension	6	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

Tramadol as additional analgesic was needed in different groups. No patient required 200 mg tramadol except in Group A were one patient required (Table 3). Intraoperative complications observed are shown in Table 4. Hypotension was the commonest complication observed in Group A.

DISCUSSION

Our results showed that the effect of duloxetine on the onset (as primary outcome) and duration of the spinal blockade were statistically non-significant; also, duloxetine delayed the time to the first dose of rescue analgesia request about double the time and maintained VAS score in the lower range in comparison to control group; frequency and total morphine consumption (half the dose) were less in duloxetine group when compared to placebo up to 24h as a secondary outcome. No significant differences in adverse effects were observed between the duloxetine group and placebo with consideration of prophylactic ondansetron for postoperative nausea and vomiting (PONV). Our study demonstrated that a single dose of 100 mg oral tapentadol preoperatively is more effective in decreasing the pain severity and postoperative analgesic requirement without adverse effects in patients undergoing knee arthroscopic surgery. Total 106 patients Spinal anaesthesia was successfully performed. No significant difference in age, sex, 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 D compared to Group A. Although post-operative pain assessed by NRS (numerical rating scale) was significantly lower in Group D as compared to Group A, B and C at 2 hours after surgery, no significant difference was observed at any time point among groups. Orthopedic procedures such as arthroscopic surgeries are associated with moderate to severe pain along with psychological distress in the post-operative period hence necessitating active intervention [15]. 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 [16]. Ramsay sedation score dropped to around 85 in all groups after 30 minutes of subarachnoid block although we did not find any significant difference in Ramsay sedation values between different groups. The use of lower dosages of drugs could have the reason attributed to this finding. Ben et al [17] 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 [18] who did not find any difference in Ramsay sedation 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 hours 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, postoperative analgesic requirement in surgical patients [19]. Similarly, reduced postoperative dose requirement was observed by Daniels SE, 2009; Hatrick[20,21]. Yadav G et al [22] reported significant decrease inpain score and analgesic requirement in laparoscopic cholecystectomy patients. Antinociceptive actions of melatonin have been well demonstrated in various studies [7]. The anxiolytic action of melatonin is directly correlates to its pharmacokinetics, time required to reach peak plasma concentration of drug ranged from 0.25h to 13h. The postoperative analgesic effect of melatonin has been proved with cataract surgery under topical anaesthesia and with laparaoscopic cholecystectomy [23]. 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 [24,25]. Yousaf et al [26] in studies showed an opioid-sparing effect or reduced pain scores with melatonin premedication whereas three studies were contradictory. 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 A where as in 2 patients hypotension was observed in Group C. Pruritis was seen in 1 patient whereas shivering was observed in 2 patients each in Group B and Group C. Nausea was found in 2 patients receiving Tapentadol and vomiting was seen in 3 patients of Group C and 1 patient in Group D. 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. Majority of studies of duloxetine are done in spine patients with drug started preoperatively one to two week prior to surgery and continued postoperatively.

CONCLUSION

Our study showed that preoperative administration of oral tapentadol is more efficacious than duloxetine and melatonin in reducing postoperative 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.

Conflict of Interest: None.
Source of Fund: Nil.

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