Original Article

Comparison of Ramelteon with Clonidine as an Adjuvant to Anesthesia: A Placebo-controlled, Randomized, Double-blinded Trial

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Abstract

Context: We have evaluated the effect of ramelteon, clonidine, and a placebo on perioperative sedation, anxiety, cognition, and postoperative analgesia in cases of laparoscopic cholecystectomies. **Aims:** To study the comparative efficacy of ramelteon and clonidine on sedation and in reducing anxiety perioperatively. **Settings and Design:** Prospective, randomized, double-blinded, placebo-controlled trial. **Materials and Methods:** Ninety patients undergoing laparoscopic cholecystectomies were randomized into the following three groups; the control group (placebo), the clonidine group, and the ramelteon group. The sedation, anxiety, orientation scores, psychomotor functions, the hemodynamic parameters, and the recall and total analgesic consumption postoperatively for 24 h were assessed. **Statistical Analysis Used:** Statistical analysis was done with Student's *t*-test for the quantitative data and Chi-square test for the categorical data. **Results:** The anxiety scores were significantly lower in both the clonidine group and the ramelteon group in comparison to the placebo group. Higher level of sedation was noted in the clonidine and ramelteon groups compared to the placebo group. Patient satisfaction score was significantly higher in the clonidine group. Analgesic consumption was noted to be significantly less in the clonidine group. Statistically significant reduction in the mean arterial pressure (MAP) and heart rate were observed in the clonidine group. **Conclusions:** We observed that oral premedication of ramelteon and clonidine resulted in a significant level of sedation and reduction of anxiety score with no significant impairment of the psychomotor functions compared to the placebo. The clonidine group, in addition, showed significant analgesic sparing effect in the first 24 h and reduction in the MAP and heart rate pre- and postoperatively.

Key words: Clonidine, melatonin, perioperative sedation, ramelteon

Introduction

Perioperative anxiety leads to significant discomfort, adverse cardiovascular effects, increased pain scores, and recall. A relatively new drug melatonin has emerged in this role with anxiolytic and sedative properties. Ramelteon is a U.S. Food and Drug Administration (FDA)-approved congener of melatonin sharing similar profile as that of melatonin. Melatonin (*N*-acetyl-5-methoxytryptamine) is a hormone secreted from the pineal gland with several properties including sedative, analgesic, anti-inflammatory, antioxidative, and chronobiotic effects.[1] Ramelteon's hypnotic effects are mediated through activation of the MT_1 and MT_2 melatonin receptors and selective affinity for the MT_3 receptors. It has no appreciable affinity for γ-aminobutyric acid (GABA) receptor complex or neuropeptides, noradrenaline, and opiates.[2] Melatonin has been studied in comparison to benzodiazepines as premedicants. In this study, we aim to evaluate ramelteon's clinical efficacy in comparison to clonidine (α_2 agonist) with sedative, anxiolytic, analgesic sparing, reduction in the anesthetic requirement and favorable cardiovascular properties.

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Materials and Methods

Ninety patients (30 in each group) aged 18-45 years undergoing laparoscopic cholecystectomy surgeries were chosen. The patients were randomized into three groups, namely, the control group receiving placebo orally, the clonidine group receiving 300 μg of clonidine orally, and

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the ramelteon group receiving 8 mg of ramelteon orally 60 min before the operation.

All the patients with pregnancy, significant hepatorenal impairment, on psychiatric drugs, with drug abuse, chronic pain syndrome, epileptic patient, patients with significant cardiac disease or rhythm disturbance, and patients with allergy to the said drugs were excluded from the study.

The day before surgery, the anesthesiologist explained the procedure involved and the scales used in the study to the patients.

The patients were brought to the preoperative holding area and their baseline blood pressure, heart rate, peripheral capillary oxygen saturation (SpO_2), and baseline scores were recorded. The abovementioned drugs were then administered. The patients and the anesthesiologist administering the drugs were blinded to the drug used in the study.

A separate psychiatrist evaluated the patients before premedication and thereafter at 30 min, 60 min, and then again after the completion of the operation at 30 min and 60 min. The psychological parameters evaluated were the visual analogue scale (VAS) for anxiety scale, Ramsay score for sedation, orientation score, digit symbol substitution test (DSST), and Trieger dot test (TDT) for the assessment of psychomotor performance. Recall was assessed with a picture shown to the patients before premedication and the patients were asked about the picture.

In the operating room, the patients were premedicated with fentanyl (2 μg/kg) and induced with propofol (2 mg/kg), the muscle relaxant vecuronium bromide (0.01 mg/kg) was administered and the patient was intubated. The patients were maintained with 70% nitrous oxide in oxygen and isoflurane. Standard monitoring was done with pulse oximetry, capnography, and electrocardiography. Intraoperative mean arterial pressures (MAPs) and heart rates were recorded at 15-min intervals. Postoperative pain was managed with incremental doses of tramadol. Postoperative pain was assessed with VAS score and patients with a score more than 4 received additional tramadol. The total analgesic consumption in 24-h period was noted.

Patient satisfaction with regard to premedication was assessed with a three-point satisfaction score.

Statistical analysis was done with Student's *t*-test for the quantitative data and Chi-square test for the categorical data. For an 80% power of study and an alpha error of 95%, the sample size was kept 30 in each group. *P* value < 0.05 was considered significant.

Results

The age, weight, and height of the patients were not significantly different and the demographic profile was comparable between the three groups.

The anxiety scores were significantly lower in both the clonidine and ramelteon groups in comparison to the placebo group (<0.001) [Chart 1 and Table 1]. There was a significant difference between the clonidine and ramelteon groups at 60 min, [2.56 ± 0.5 for the clonidine group (group C) and 2.01 ± 0.01 for the ramelteon group (group R), $P < 0.001$] and postoperatively at 60 min (3.03 ± 0.18 for group C and 2.02 ± 0.01 for group R, $P < 0.05$).

At 30 min from the administration, a significantly higher level of sedation was noted in the clonidine and ramelteon groups compared to the placebo group and similar results were obtained at 60 min postoperatively [Chart 2 and Table 2].

The DSST scores were first explained and practiced in all the patients of all the three groups. The DSST scores at 30 min (13.6 ± 1.4 for the control group, 13.5 ± 1.43 for the clonidine group, and 13.2 ± 1.45 for the ramelteon group, $P > 0.05$) and postoperatively at 60 min were also comparable and no statistical significance was noted [Chart 3 and Table 3].

The TDT time was noted in all the groups that was also comparable at 0 min, 30 min, and postoperatively at 60 min.

All the patients were able to recall the picture shown to them before the operation.

Patient satisfaction score was significantly higher in the clonidine group (1.3 ± 0.7 for group C and 0.83 ± 0.06 for group R, $P < 0.001$) compared to the placebo and ramelteon groups [Chart 4]. The total number of rescue analgesics needed in the 24-h period was noted and it was significantly less in the clonidine group compared to the ramelteon and placebo groups (3.06 ± 0.52 for group C and 3.7 ± 0.59 for group R, $P < 0.001$) [Chart 4 and Table 4].

The hemodynamic parameters were comparable at 0 min. Significant hypotension was noted in the clonidine group at 60 min and postoperatively at 30 min and 60 min ($P < 0.05$) [Chart 5 and Table 5].

Heart rate was significantly lower in the clonidine group compared to the placebo and ramelteon groups at 60 min after administration and postoperatively ($P < 0.05$) [Chart 6 and Table 6].

Discussion

Various drugs have been used to allay anxiety preoperatively and reduce the fear of the operating room. Among them the most widely used orally are benzodiazepines, α_2 agonists, etc., In this study, we observed that oral premedication of 8 mg of ramelteon and 300 μg of clonidine resulted in a significant level of sedation and reduction of anxiety score with no significant impairment of the psychomotor functions and orientation score compared to the placebo. The clonidine group in addition showed significant analgesic sparing effect and reduction of the total opioid consumption in the first 24 h and reduction in MAP and heart rate pre- and postoperatively.

The dose used in our study was 8 mg of ramelteon. It is comparable to a dose of 0.2 mg/kg of melatonin that is a dose

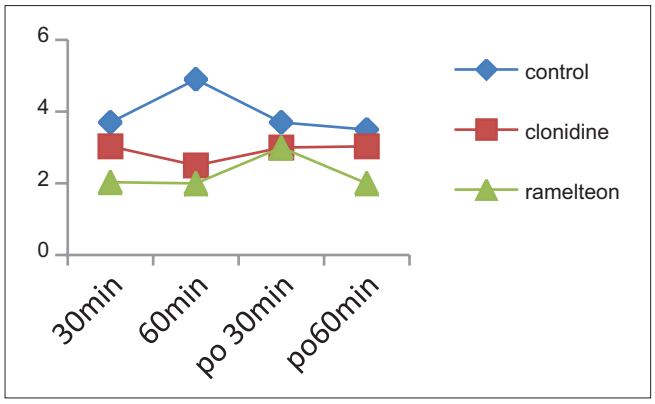

Chart 1: Anxiety scores at different time points

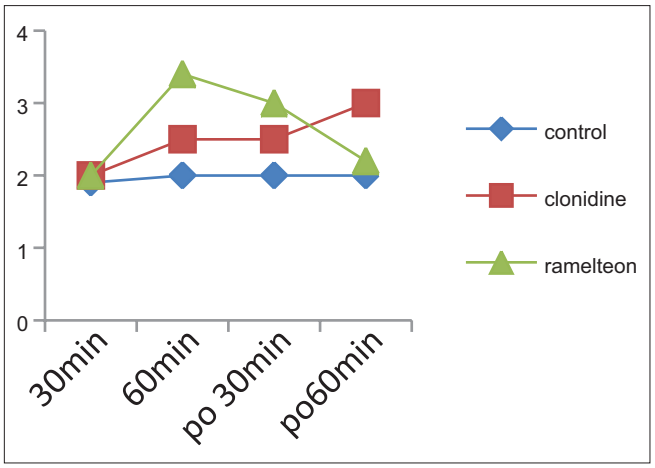

Chart 2: Sedation scores at different time points

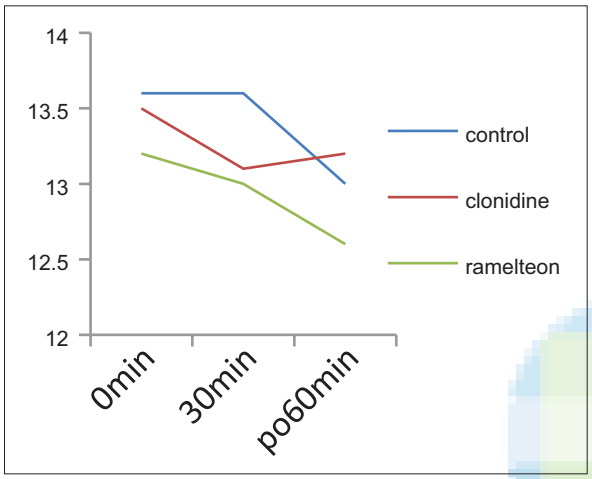

Chart 3: DSST scores at different time points

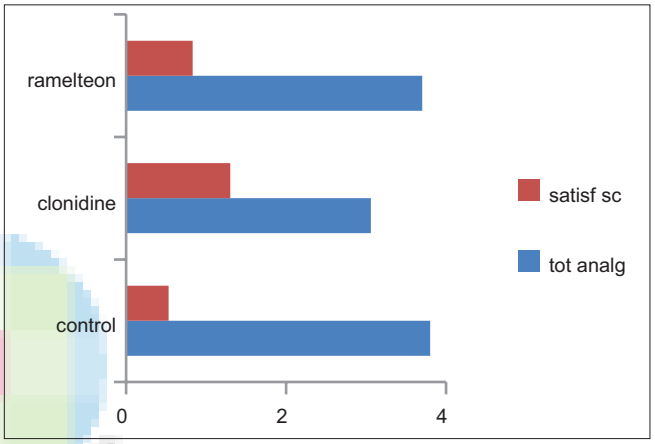

Chart 4: Satisfaction and total analgesic scores at different time points

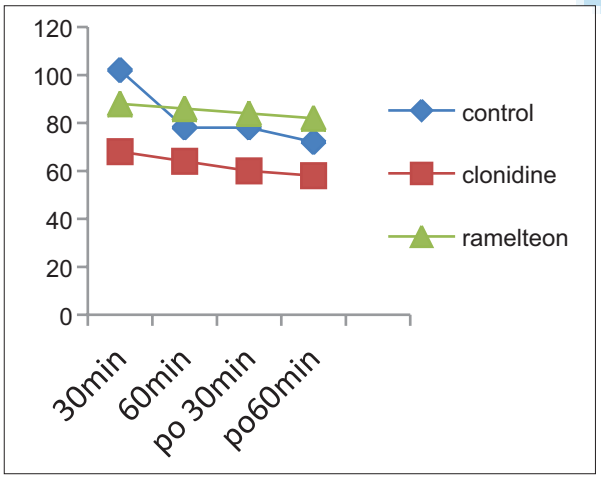

Chart 5: MAP at different time points

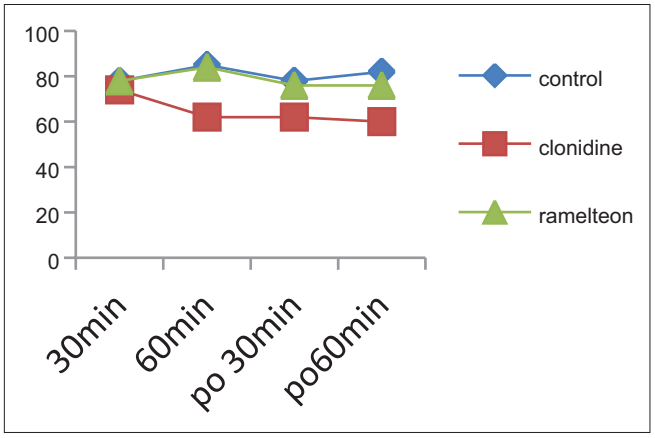

Chart 6: Heart rate at different time points

well within the safe therapeutic range,[3] although significant sedation and anxiolysis with different doses of oral/sublingual melatonin (0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg) without any impairment of psychomotor skills was observed.[3] Similarly, 5 mg of oral melatonin the night before and 1 h before the surgery reduced pain and anxiety scores in the first 24 h.[4] Melatonin has a vast therapeutic window with safety profile even with doses of up to 300 mg/day taken orally.[5] In most of the studies, significant anxiolytic effect was observed at 90 min after administration,[2] so the timing was done accordingly.

The anxiety scores were significantly lower in both the clonidine and ramelteon groups in comparison to the placebo group ($P < 0.001$). Patients who received premedication with either midazolam or melatonin had a significant decrease in

Table 1: Anxiety scores at different time points

Anxiety score	30 min	60 min	po30 min	po60 min
Control	3.7	4.9	3.7	3.5
Clonidine	3.03	2.5	3	3.03
Ramelteon	2.03	2	3	2

Table 2: Sedation scores at different time points

Sedation score	30 min	60 min	po30 min	po60 min
Control	1.9	2	2	2
Clonidine	2	2.5	2.5	3
Ramelteon	2	3.4	3	2.2

Table 3: DSST scores at different time points

DSST score	0 min	30 min	po60 min
Control	13.6	13.6	13
Clonidine	13.5	13.1	13.2
Ramelteon	13.2	13	12.6

Table 4: Satisfaction and total analgesic scores at different time points

	Total analgesic consumption	Satisfaction score
Control	3.8	0.53
Clonidine	3.06	1.3
Ramelteon	3.7	0.83

Table 5: MAP at different time points

MAP	30 min	60 min	po30 min	po60 min
Control	102	78	78	72
Clonidine	68	64	60	58
Ramelteon	88	86	84	82

Table 6: Heart rate at different time points

Heart rate	30 min	60 min	po30 min	po60 min
Control	78	85	78	82
Clonidine	74	62	62	60
Ramelteon	78	84	76	76

the anxiety levels and increase in the levels of sedation before operation compared with the controls.[3] Similar results were observed on pain and anxiety scores in the first 24 h.[4,6-8] At 30 min from administration, a significantly higher level of sedation was noted in the clonidine and ramelteon groups compared to the placebo group ($P < 0.0001$) and similar results were obtained at 60 min postoperatively; however, no significant difference was noted between groups C and R (2.53 ± 0.62 for group C and 3.4 ± 0.67 for group R, $P > 0.05$). All the patients were oriented to time and place.

No significant impairment of the psychomotor skills was noted in either group. The DSST score improved in the first 10 min due to learning behavior; therefore, the patients were explained the DSST test and practiced before operation.[3] No significant difference was noted in both the groups in comparison to the placebo group in psychomotor functions (TDT and DSST). Similar results were observed in other studies.[3,9] DSST was impaired in the midazolam group compared to the melatonin and placebo groups at 30 min.[3] The verbal fluency scores were observed to be poor in both the midazolam and melatonin groups.

The total number of rescue analgesics needed in the 24-h period was noted and this was significantly less in the clonidine group compared to the melatonin and placebo groups (3.06 ± 0.52 for group C and 3.7 ± 0.59 for group R, $P < 0.001$). The total opioid consumption in the ramelteon group was observed not to be statistically significant in our study compared to the control group. The analgesic action of melatonin is possibly linked to G protein-coupled opioid mu receptors or GABA-B $\mu\iota$ receptors; however, ramelteon has no observed effects on them.

Although no significant decrease in MAP was noted in the ramelteon group, melatonin has a mild hypotensive effect due to the direct action on vascular melatonin receptors and the reduction of the adrenergic outflow and catecholamine levels.[5] On the other hand, 10 mg melatonin taken orally 90 min before the operation in cataract surgery patients provided significant sedation and lowering of intraocular pressure.[10] In this study, there was a significant decrease in the MAP and heart rate in the clonidine group compared to the ramelteon group.

Patient satisfaction score was significantly higher in the clonidine group (1.3 ± 0.7 for group C and 0.83 ± 0.06 for group R, $P < 0.001$) compared to the placebo and ramelteon groups. It was observed that anesthesia and surgery suppressed the release of melatonin and disrupted the normal circadian rhythm in patients.[11]

The scope of further research on ramelteon includes the use of ramelteon in higher doses and postoperative continuation of ramelteon, and its effects on the sleep pattern and analgesia can be studied.

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Conflicts of interest

There are no conflicts of interest.

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