Original Article

A Comparative Study Between Orobuccal Melatonin And Nasal Midazolam When Used As Anaesthetic Premedication

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Introduction:

Administration of premedication came in to vogue in the middle of the 19th century, when the anaesthetics such as ether& chloroform used at that time were irritants causing nausea, vomiting and was very unpleasant to the patients. Today, the important objective of premedication drugs isto decrease anxiety. Benzodiazepines have been the mainstay of premedication. Since the last couple of years, melatonin has also been added to the armamentarium of the anaesthesiologists and has been found to be a safe and effective anxiolytic.In this study we will compare orobuccal melatonin with intranasal midazolam when they are used as premedication drugs.

Aim of the study:

To establish the anxiolytic effect, onset of sedation, depth of sedation, change in orientation and adverse effects of Orobuccal Melatonin compared with intranasal midazolam, when administered as pre anaesthetic medication before surgery.

Materials and Methods:

Institutional ethical committee approval was taken. This is a double blinded randomized controlled clinical trial. We included Patients of 18 – 60 years of age, of ASA I and II status, posted for elective surgeries such as Hemorrhoidectomy, Lateral sphincterotomy, fibroadenoma excision, tonsillectomy or Herniorrphy under anaesthesia.Patients who were unwilling to join,patients taking anti-psychotic drugs, on treatment for sleep disorders, with allergy to melatonin or midazolam were not included in the study.The sample size of the study was calculated from a prior placebo-controlled trial by Edwin Seet et al[1] on preoperative anxiety who determined that a sample size of 33 patients per group was prerequisite.

The patients were randomized to 2 groups of 33 each using a computer for generating randomnumbers. Group A – orobuccal melatonin & Group B – intranasal midazolam.Initial assessment of anxiety was done by a trained

anesthesiologist who was blinded to the group that the patient belongs to. Anxiety was assessed using the NRS - 'numerical rating scale' with score starting from 0 to 10. Score 0 means no anxiety, 1,2,3,4,5……9 indicates increasing levels of anxiety and a score of 10 indicates worst or highest level of anxiety.

The drug was administered to the patient 90 min before induction of anaesthesia. Orobuccal Melatonin strip in the dose of 0.1mg/kg body weight or intranasal midazolam sprays, according to the group. Patient was shifted to a quiet corner of the preoperative holding room, asked to relax on the bed after taking the drug and monitored throughout. After 60min, patient was reassessed again.

Anxiety score, onset of Sedation, depth of sedation, orientation, adverse effects such as nausea, vomiting, visual disturbancesincludingchanges in the importantvariables of heart rate, Blood Pressure, SPO2 and Respiratory rate were assessed. Sedation was calculated by "The Observer's Assessment of Alertness/Sedation (OAA/S) Scale Score"[2] from 5 to 0. 5 - Fully awake, 4 –slow response to name calling in normal tone, 3 - Rise only after name is called loudly or repeatedly called, 2 - Responds only after mild prodding or shaking, 1 - Responds only after squeezing the trapezius and 0 - Does not respond after compressing the trapezius. Orientation was scored from 3 to 0. 0 = none, 1 = orientation to either space or time or person, 2 = orientation to 2 of the 3 parameters space/time/person and 3 = orientation to space, time and person. All scores were converted to percentage for analysis.

Statistical analysis: The parameters were subjected to Statistical analysis using statistical software STATA 11.0. The p value of <0.05 were taken into consideration as significant. Continuous variables wereillustrated as Mean (SD), and categorical variables were represented as Frequency (percentage). Chi-square test, Wilcoxon sign rank test, Mann Whitney U test and Kruskal Wallis test were used as required.

Table 1: Analysis of Demographics

		Group A – Orobuccal Melatonin	Group B – Intranasal midazolam	P value
Gender	Female	16(48.48%)	20(60.61%)	0.323
	Male	17(51.52%)	13(39.39%)	
Age	18-40 years	16(48.48%)	16(48.48%)	1.000
	41-60 years	17(51.52%)	17(51.52%)	
ASA grade	I	14(42.42%)	19(57.58%)	0.218
	II	19(57.58%)	14(42.42%)	
Anaesthesia	Spinal	19(57.58%)	21(63.64%)	0.614
	General	14(42.42%)	12(36.36%)	

Table 2: Analysis of parameters after drug administration

	Group A– Orobuccal Melatonin	Group B– Intranasal midazolam	P-value
Anxiety	3.72±1.17	3.48±1.48	0.4968
Sedation Onset (In mins)	14.87±1.49	9.45±1.45	<**0.001***
Sedation Score Depth in %	4.69±0.58 3.8%	3.66±0.47 26.8%	<**0.001***
Orientation score Decrease in orientation as %	3±0 0%	2.84±0.36 5.33%	<**0.0198***
Nausea/ vomiting	2(6.06%)	0	0.151
Blurred vision	0	2(6.06%)	0.151
Inability to concentrate	0	3(9.09%)	0.076
Bitter taste	0	27(81.82%)	<**0.001***
ECG rhythm changes	0	0	
Vital Parameters			
Heart Rate	77.60±4.40	74.75±5.55	<**0.0188***
Blood Pressure (MAP)	82.69±0.23	80.25±0.51	<**0.001***
SpO2	99.39±0.49	97.95±0.66	<**0.001***
Respiratory Rate	13.36±0.65	11.93± 0.82	<**0.001***

Figure 1: Analysis of parameters after drug administration

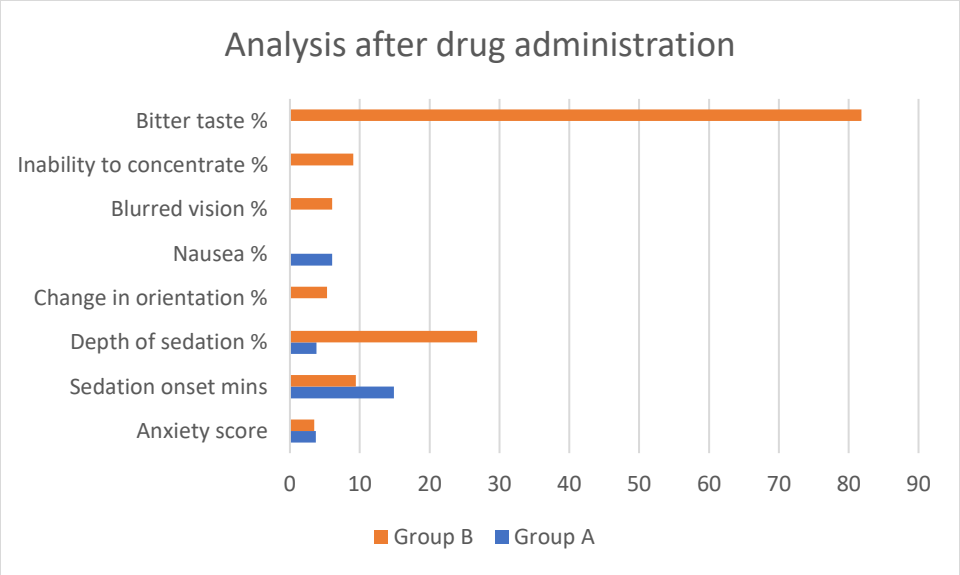
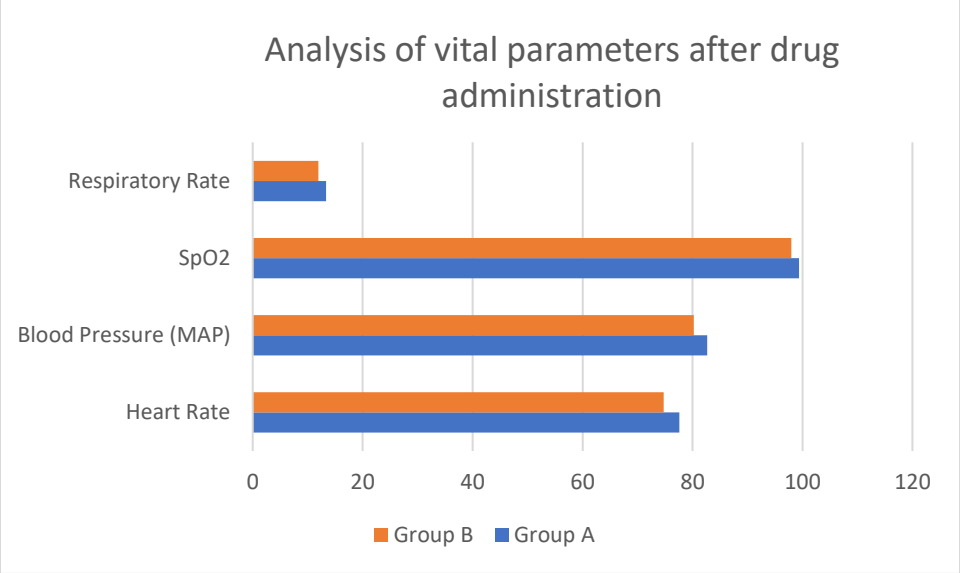


Figure 2: Analysis of vital parameters after drug administration



Results:

	Group A vs Group B
Demographics	No statistically significant difference among the groups.
Anxiety	No statistically significant difference among the groups. Both equally effective.
Sedation Onset (In mins)	Statistically significant faster onset of sedation in Group B compared to Group A

Sedation Score	Statistically significant with deeper sedation in Group B compared to Group A
Orientation	Statistically significant difference with poorer orientation in Group B and no change in orientation in Group A
Adverse effects	Of all adverse effects such as nausea, blurred vision, inability to concentrate and bitter taste, only statistically significant was bitter taste in group B
Vital Parameters	Statistically significant changes between the groups with more pronounced effects in Group B. But clinically insignificant as the changes from baseline recordings were less than 30%.

Discussion:

The importance of premedication has been well understood as it prevents a host of perioperative problems such as hemodynamic changes, delayed wound healing etc, that arise from anxiety. Post operative pain is said to increase due to anxiety as the pain threshold is lowered.[3]Hence premedicant drugs should be administered.

The role of melatonin as an effective premedicant has been documented by studies, which have concluded that it possesses anti-inflammatory and analgesic properties.[4,5,6]Midazolam, a benzodiazepine has been in clinical use as a premedicant for decades. It can be administered by oral, sub-lingual, intranasal, intra-muscular, intra-venous and rectal routes for sedation.[7,8,9] We chose the intranasal route.

In our study, the anxiolysis produced by melatonin was comparable to the midazolam group, both these drugs producing equally effective anxiolysis. The effects of melatonin are due to its activity on melatonin receptors located in the suprachiasmatic nucleus (SCN) of the hypothalamus.[10]Midazolam produces its effect by activating the brain's normal endogenous inhibitory neurotransmitter - Gamma Amino Butyric acid – GABA.[11]

The onset of sedation and depth of sedation was higher in nasal midazolam group. This is due to the fact that midazolam has much elevated systemic availability after intranasal rather than oral route as Intranasal area is rich in blood supply and has the merit of faster absorption of the drug directly into the systemic dissemination, without passing through the portal circulation which can cause a first pass metabolism.[12,13] According to Zetner et al,[14]Bioavailability following oro buccal administration of melatonin was found to be around 55 % and it lacks of first-pass metabolism in this route whereas the bioavailability of intranasal midazolam is around 60–70%.[15]Furthermore, it has been found that once intranasal midazolam is administered in to the physiological pH buffered nasal mucosa, the pH of the formulation immediatelyescalates causing midazolam to revert to its pharmacologically active closed ring structure, leading to a quick onset of action.[16]Onset of action of intranasal midazolam in our study is similar to other studies. In one study by Schrier,[17] onset of action of intranasal midazolam occurred at 7 ± 4.4 min. Another reason for higher depth of sedation with midazolam can be due to its mechanism of action on GABA as compared to melatonin acting on receptors in the suprachiasmatic nucleus and researchers have found that drug mechanisms that focus added neurotransmitters, other than GABA are generally less effective for sedation when used alone.[18]

Orientation was not affected in melatonin Group but was affected in intranasal midazolam group. A study by Wang et al[19]furnishproof that midazolam-induced mild sedation is correlated with reduced connectivity within the dorsal attention network (DAN) which routinely mediates external processing and attention-demanding cognitive function, thus explaining the cause for change in orientation.

Though there were changes in vital parameters in melatonin and more pronounced in midazolam groups; none of them were more than 30% of baseline readings and therefore not clinically significant. According to Ghali et al,[20] the hemodynamic variations more than 30% of the baseline value is to be considered important.At the given doses, none of our drugs produced ECG changes. Of the adverse effects, only nausea was observed in melatonin groups, and this was statistically insignificant. Melatonin is a drug which is known to cause nausea.[21]No nausea was seen in midazolam groups. It is reported that midazolam reduces the frequency and intensity of Post-operative nausea and vomiting, showing an antiemetic effect.[22,23]

Midazolam is known to cause many adverse effects of which we observed 'blurred vision' and 'inability to concentrate' in our study patients, at the dose of 0.1mg/kg body weight; both being statistically insignificant. But bitter taste with intranasal midazolam in Group D was seen in 27/33 patients (81.81%), which is highly significant. Wilton et al [24]found this to be due to the low pH (approximately 3) and benzoyl alcohol preservative used in the formulation; this effect being eliminated by using a 4% lidocaine topical solution nasally prior to midazolam administration. Karl and Khalil et al[25,26] have reported that this bitter taste is a limiting factor and basis for rejection along with low compliance in pediatric population. Whereas, the Mint flavored orobuccal melatonin strip was well liked by our study population. Overall, the adverse effects were minimal with melatonin group.

Conclusion:

Orobuccal melatonin and intranasal midazolam in the dose of 0.1mg/kg body weight provide equally effective anxiolysis. But orobuccal melatonin is a saferand pleasant premedicant as compared to intranasal midazolam; as intranasal midazolam produced greater depth of sedation, change in orientation and unpleasant bitter taste.

Limitation of the study:

This study was conducted using only one dose and only in 18 – 60years age group, not in pediatric and elderly population.

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