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Melatonin Alprazolam Combination: Evaluation for Hemodynamic Stability during Intubation and Post Operative Analgesia in Patients Undergoing Cholecystectomy

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Abstract

Background: Many drugs have been used for attenuating hemodynamic response to intubation and laryngoscopy during general anesthesia, to provide post operative analgesia and to decrease the analgesic consumption in post operative period. The present study was conducted to evaluate the effects of low dose Melatonin and Alprazolam combination in patients undergoing laparoscopic cholecystectomy under general anesthesia. *Materials and Methods:* Fifty adult patient of either sex, aged between 20-50 years with American Society of Anesthesiologist (ASA) grade I and II presenting for laparoscopic cholecystectomy were divided into two groups. Group I (Gp I, n=25) acted as a control group and received placebo as tablet B complex and Group II, (test group Gp II, n=25) received Tab. Melatonin (3mg) and Alprazolam (0.25mg) combination one hour before surgery. The primary objectives were to assess the sedation score, effect on induction dose of Propofol and hemodynamic response to laryngoscopy and intubation. Secondary objectives were to assess the post operative Fentanyl consumption in first 24 hours. *Statistical Analysis:* The data thus obtained was analyzed using Epi-info and SPSS 16 software and various suitable statistical tests like Student t test, ANOVA, Chi-square test, Mann Whitney test etc. were applied. P-values > 0.05 were considered to be not significant, p-values < 0.05 were considered to be significant and p-values < 0.001 were considered to be highly significant. *Results:* The level of sedation in Gp II was significantly higher as compared to Gp I at one hour of giving the test drug(0.88±0.332 vs. 0.00±0.00, p value <0.001). The mean dose of Propofol for induction of general anesthesia was significantly reduced in Gp II (109.20±17.540 in Gp I and 87.60±17.388 in Gp II respectively, p value< 0.001). Both groups showed rise in heart rate and mean blood pressure following laryngoscopy and intubation up to three minutes but the rise was significantly more in Gp I as compared to Gp II at all time intervals . Significant decrease in total number of doses (5.12 ±0.833 vs. 4.12±0.332, p<0.001) as well as mean total fentanyl consumption (316.88 vs. 246.86, p<0.001) was noted in Gp II. No adverse effect was noted during the study which can be attributed to test drug. *Conclusion*: Low dose melatonin and alprazolam combination when given one hour before the surgery provides many advantages. It produces sedated patients which are easily arousable, decrease dose of induction agent, decrease the increase in heart rate and mean arterial blood pressure following laryngoscopy and intubation. It also reduces the post operative fentanyl consumption in first twenty four hours following surgery.

Keywords: Alprazolam; Melatonin; Post Operative Analgesia; Sedation.

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Introduction

Preoperative anxiety and stress are common in patients awaiting surgery and is described as unpleasant state of uneasiness secondary to concerned about a disease, hospitalization, anesthesia, surgery and also fear of unknown [1,2]. If anxiety is sufficiently marked then it leads to

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sympathetic stimulation with resultant increase in heart rate and blood pressure, ventricular ectopic beats or ischemic features in ECG and is associated with slower and complicated postoperative recovery [3,4].

Laryngoscopy and intubation is associated with several unwanted hemodynamic responses such as tachycardia, hypertension, arrhythmias and increased circulating catecholamines [5]. Hypertension and tachycardia are two dynamic predictors of peri-operative cardiac morbidity, so prevention of these responses during laryngoscopy and intubation remains an important clinical goal for the patients with cardiac or cerebral disease [6]. These effects are deleterious in susceptible individuals culminating in peri-operative myocardial ischemia, acute heart failure and cerebro vascular accidents [7]. Several methods have been used to attenuate hemodynamic response to laryngoscopy and intubation such as pretreatment with beta blockers, calcium channel blockers, opioids , nitroglycerine, dexmedetomidine etc. [8,9,10].

Melatonin (5-methoxy-N-acetyltryptamine) is a hormone found in all living organisms, from algae to humans [11]. In humans melatonin is produced mainly by pineal gland (acts as endocrine hormone) and to lesser extent by GIT and retina (acts as paracrine hormone). Melatonin is synthesized from amino acid tryptophan via 5-hydroxyindole-O-methyl transferase enzyme pathway [12,13]. The biological effects are produced via melatonin receptors MT1 and MT2. Clinical applications of melatonin include its use for insomnia, jet lag and other types of misalignments in the circadian rhythm [14,15,16].

Melatonin has been used as premedication drug for anxiolysis. When used alone in higher doses, it provides sedation, reduction in dose of induction agent, post operative analgesia resulting in fewer requirements of post operative analgesics [17]. The present study was carried out to determine the effectiveness of low dose melatonin in combination with alprazolam in decreasing anxiety and attenuating hemodynamic response to laryngoscopy /intubation. The post operative analgesic requirement in first twenty four hours was also evaluated.

Material and Methods

After approval of institutional research ethics committee, the study was conducted in prospective randomized double blind manner in patients undergoing laparoscopic cholecystectomy under general anesthesia. The patients willing to participate in this study were informed about the purpose of this study, procedure details, and their informed consent in writing were obtained. The patients were also informed that they can opt out of the study any time without assigning any reason.

The target sample of 50 patients was divided into two groups of 25 patients in each group using random allocation software. The random number was kept in envelope under custody of consultant in charge and the envelope was opened one hour before surgery and the patient was assigned to respective group. Post premedication observations during laryngoscopy and intubation and follow up were made by independent anesthetist not associated with first team thus making it blind to trial participants, data collectors and analyzers.

The inclusion criteria included patients between 20-50 years of age, of either sex, ASA grade I and II, undergoing laparoscopic cholecystectomy under general anesthesia

Exclusion criteria included known hypersensitivity to any of drug used, ASA grade III or above, patient refusal to participate in study, pregnancy and lactation, use of psychotropic drugs or drug abuse, any language and communication difficulties, hemorrhagic diathesis, on anti platelet/anti coagulant therapy, history of Diabetes, Asthma, Renal or hepatic insufficiencies and any psychiatric illness.

Procedure

All the patients were visited one day before the surgery. The general physical examination was carried out and routine investigations were noted**.** Informed consent for participation in the study was taken from all patients after explaining the procedure in detail. All patients were given premedication with 7.5mg Tab. Midazolam (Tab. Mezolam by Neon Laboratories Limited) at bedtime prior to the day of surgery. Next day, one hour before the surgery the patients were assessed for Sedation Score: (grade 0 - Alert, conversant, grade 1- Awake but drowsy, grade 2- Asleep but arousable and grade 3 - Asleep and not arousable).

The patients were assigned to one of the groups using random allocation software.

Group I (Gp I, n=25) acted as a control group and received placebo as tablet B Complex (Cobadex forte by Glaxo Smith Kline Pharmaceuticals Ltd.)

Group II, test group, (Gp II, n=25) received Tab. Melatonin (3mg) and Alprazolam (0.25mg) combination (Tablet Stresnil by Aristo Pharmaceuticals Pvt. Ltd.)

Heart Rate, SpO_2, MAP and ECG were recorded before giving premedication as per the allocated group. They were assessed again at 30 minutes and 1 hour later for the same parameters with continuous monitoring in between. On arrival in the operating room, intravenous line was secured with 18G intravenous cannula. Monitoring of noninvasive blood pressure (NIBP), heart rate, electrocardiogram and arterial oxygen saturation (SpO2) was carried out and the basal readings were noted. A uniform anesthetic technique was used. Pre induction analgesia was given with Inj. Fentanyl at dose of 2µg/kg followed by pre-oxygenation for 3 minutes with 100% oxygen. Anaesthesia was induced by slowly injecting Inj. Propofol and the dose at which eyelash-reflex/verbal response was lost was noted, followed by administration of Inj. Atracurium at a dose of 0.6 mg/kg for muscle relaxation for intubation of trachea. Intubation was done 3 minutes after administering Inj. Atracurium. Vital parameters were recorded post intubation every one minute for the first five minutes and then every five minutes. Analgesic top-up was provided with Inj. Fentanyl (0.5µg/kg) as and when required. The patients were also observed for any special event during the surgery. General Anaesthesia was maintained with oxygen (33%), Nitrous Oxide (66%) and Isoflurane (0.1-1.5%).

During the Post Anesthesia Care, the patients were observed for adverse effects, if any, and requirement for analgesics every 1 hour during the first four hours and then every four hours for the next 20 hours. Analgesic requirement of the patient were met on demand basis with Inj. Fentanyl (1µgm/kg i/v), the response was awaited and if required, a further top up with Inj. Fentanyl (0.5µgm/kg i/v) was given after 10 minutes.

Statistical Analysis

The data thus obtained was analyzed using Epi-info and SPSS 16 software and various suitable statistical tests like Student t test, ANOVA, Chi-square test, Mann Whitney test etc. were applied. p-values > 0.05 were considered to be not significant, p-values < 0.05 were considered to be significant and p-values < 0.001 were considered to be highly significant.

Observations and Results

Demographic Data

Both groups were comparable in age, weight and sex distribution (p value > 0.05). Incidentally, majority of patients in both groups were females. The ratio of female versus male in Gp I was 20:5, and in Gp II was 21:4 which was not statistically significant (Table 1).

Baseline Vitals and Sedation Score

The patients were continuously monitored and HR, MAP, SpO_2 and ECG were recorded twice at an interval of half an hour each. In both groups, the changes in the vitals were found to be insignificant at half an hour (T30) and one hour (T60) after giving premedication (p-values > 0.05).

All the 25 patients in Gp I had a sedation Score of 0 at T30 and T60. At time T30 the mean sedation score in Gp II was 0.24±0.436 and at time T_{60} the mean sedation score in Gp II was 0.88±0.332 (p-value < 0.05). There was a significant difference in sedation score in two groups at one hour after administering the test drug as most of patients in Gp II were awake but drowsy (Table 3).

Anesthetic Drugs

The dose of Fentanyl and Atracurium administered in the both groups were comparable as doses were based on body weight. The mean dose of Propofol required in Gp II was significantly lower than in Gp I. Mean dose of Propofol consumed in Gp I was 109.20±17.540 and in Gp II was 87.60±17.388 (p-value < 0.05) (Table 3).

Vitals (HR, SpO_2, MAP and ECG) were recorded just before and after intubation and post intubation every 1minute for the first 5 minutes and then every 5 minutes till completion of surgery.

The values of mean heart rate before intubation were taken as baseline value and were compared with the mean heart rate post laryngoscopy/intubation, using student t-test within each group. In both groups it was observed that there was a significant difference in the heart rate till three minutes post intubation.

Table 1: Demographic data

	Gp I	Gp II	
Mean age (yrs)	39.4±10.5	39.12±9.6	> 0.05
Mean weight(Kg)	61.56±9.23	59.92±8.25	0.787
Number of females	20/25(80%)	21/25(88%)	> 0.05
Number of males	5/25(20%)	4/25 (16%)	> 0.05

Table 2: Post laryngoscopy/intubation hemodynamic changes (T-bi-before intubation,Tai- after intubation, T1-T5 minutes after intubation)

		Gp 1	p-value intragroup Gp I	Gp II	p-value intragroup Gp II	Intergroup p-value Gp I & II
Heart rate	T bi	81.24±14.684		76.04±7.855		0.315
	T ai	103.32±16.703	Tbi-ai- 0.000	86.16±9.428	Tbi-ai- 0.000	0.000
	T 1	101.40±17.732	Tbi-T_1-0.000	85.88±10.600	Tbi-T_1-0.000	0.001
	T2	96.52±17.176	Tbi-T_2-0.000	84.04±10.002	Tbi-T_2-0.001	0.005
	T 3	92.48±15.524	Tbi-T_3- 0.003	83.72±10.04	Tbi-T_3- 0.007	0.047
	T4	89.72±15.350	Tbi-T_4-0.051	82.96±9.489	Tbi-T_4-0.066	0.146
	T5	86.84±14.389	Tbi-T_5-0.598	81.68±9.344	Tbi-T_5-0.056	0.282
MAP	T bi	74.64±11.554		77.44±11.181		0.651
	T ai	110.68±17.902	Tbi-ai- 0.000	86.80±11.218	Tbi-ai- 0.000	0.000
	T 1	103.48±5.796	Tbi-T_1-0.000	87.24±9.951	Tbi-T_1-0.000	0.000
	T2	94.80±12.777	Tbi-T_2-0.000	85.76±9.351	Tbi-T_2-0.009	0.011
	T 3	88.48±11.211	Tbi-T_3- 0.001	82.20±8.578	Tbi-T_3- 1.000	0.069
	T4	84.20±11.053	Tbi-T_4-0.046	81.48±7.235	Tbi-T_4-1.000	0.565
	T5	83.20±11.737	Tbi-T_5-0.279	82.16±8.320	Tbi-T_5-1.000	0.932

Table 3: Mean sedation score, Propofol dose and post operative analgesic requirement in first 24 hours

	Gp I	Gp II	p value
Mean sedation score T_0	0.00±0.00	0.00±0.00	NA
T_{30}	0.00±0.00	0.24±0.436	0.078
T^{60}	0.00±0.00	0.88±0.332	0.000
Propofol requirement	109.20±17.54	87.60±17.38	0.000
Total fentanyl doses in post op period (24 hrs)	5.12±0.833	4.12±0.332	
Total fentanyl consumed in first 24 hrs (µgm)	316.88	246.86	0.000

The heart rate before intubation in both groups was comparable. In Gp I heart rate after laryngoscopy/intubation increased significantly and lasted up to three minutes post intubation (p-value <0.003). In Gp II there was significant increase in heart rate in post intubation period and it remained elevated till three minutes (p-value 0.007). The intergroup comparison of mean heart rate at different time intervals shows that increase in heart rate was more in Gp I as compared to Gp II (Table 2).

The mean arterial pressure just before laryngoscopy and intubation in both groups was comparable. The mean post intubation values of MAP were significantly increased in Gp I till 4 minutes post intubation, while in Gp II the values were significantly increased until 2 minutes after intubation. The values of mean MAP with standard deviation in two groups are depicted and the intra group and inter group comparison of mean MAP is given in Table. 2

The mean oxygen saturation was found to be comparable between both groups at all the times with a p-value more than 0.05.

During the first 24 hours of Post operative period, the analgesic requirement of the patients were met on demand basis with Inj.fentanyl (1µgm/kg i/v), and if required, a further top up with Inj.fentanyl (0.5µgm/kg) was given after 10 minutes. The number of doses and amount administered, on demand basis, were recorded for the next 24 hours. The mean number of inj.fentanyl doses required in Gp I was 5.12 while in Gp II it was 4.12. The amount of fentanyl required in Gp I was 316.88µgm and in Gp II was 246.86 µgm in first 24 hours post operatively. There was a highly significant decrease in requirement for postoperative analgesia in the patients of Group II as compared to Group I. (p <0.001) (Table 3).

Discussion

It is evident from various studies that pre operative anxiety and stress are common in patients awaiting surgery and also leads to increased requirement of anaesthetic induction agents and post operative analgesic drugs. Laryngoscopy, intubation and post operative pain are associated with sympathetic

stimulation leading to hypertension, tachycardia and even arrhythmias. These effects are deleterious in susceptible individuals like the patients with cardiac or cerebral disease culminating into peri operative complications. Melatonin has a sedative, anxiolytic, hypnotic, analgesic, anti-inflammatory properties and is gaining popularity as premedication drug. Alprazolam possesses anxiolytic, sedative, skeletal muscle relaxant and amnesic properties.

In present study we compared the low dose Melatonin / Alprazolam combination with placebo on the basis of their ability to sedate, to alter dose of inducing agent, attenuating hemodynamic response during laryngoscopy / intubation and post operative analgesic requirement. The two groups were comparable on the basis of age, weight, sex distribution and base line vitals one hour before surgery. The females formed the majority in both groups.

While no sedation was noted in Gp I after giving placebo drug at any time, there was significant sedation present in Gp II at one hour of giving the test drug (0.88± 0.332, p value < 0.05) with most of patients awake but drowsy. Similar results were obtained by Pokharel et al. in their study showing that Melatonin and Alprazolam when used alone or in combination causes sedation.

The mean dose of Propofol required to induce sleep was significantly lower in Gp II (87.60±17.388) as compared to Gp I (109.20±17.540). Similar results were obtained by Pokharel et al. and Turkistani and coworkers in their study [18,19].

In both groups it was observed that there was a significant difference in heart rate and MAP when post intubation values were compared to before intubation values within the group. This increase was significantly more in Gp I as compared to Gp II (p-value <0.05). Similar results were reported by Mohamed and co worker but in their study the attenuation of MAP lasted for ten minutes when compared with control group [20].

The mean number of doses and total fentanyl drug used in Gp I was 5.12 and 316.88µgm and in Gp II was 4.12 and 246.86µgm respectively. There was a significant reduction in number of doses required and total consumption of fentanyl in Gp II as compared to Gp I in first 24 hours of post operative period. Similar results were reported by Radwan and associates when they used melatonin in dose of 6 mg [21]. Borazan and associates also reported similar results but in their study they used melatonin in dose of 6 mg night before and one hour before surgery [22].

No side effect was noted during observation period.

Conclusion

Low dose combination of Melatonin (3 mg) and Alprazolam (0.25 mg) is effective in reducing preoperative anxiety, decreasing the dose of induction agent, attenuating the hemodynamic response to laryngoscopy and intubation and also reducing the number of doses and total dose of fentanyl required in post operative period for pain relief. The above combination produces less unwanted side effects like increased sedation which is seen when melatonin is used in higher doses of 6 mg or more. This combination can be safely prescribed for patients undergoing surgery under general anesthesia.

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Conflicts of Interest: Nil

Permissions: Nil

References

1. McCleane GJ, Copper R. The nature of preoperative anxiety. Anaesthesia. 1990;45:153-55.
2. Ramsay MAE. A survey of preoperative fear. Anaesthesia. 1972;27:396-402
3. Clarke RS. Premedication. In: T Cecil Gray Ed Nunn, Utting, Brown. General Anaesthesia. 5th edition. London: Butterworth's; 1989:412-418.
4. Mathews A, Ridgeway V. Personality and surgical recovery: A review. Brit J of Clin Psychol. 1981;20: 243-260.
5. Fassoulaki A, Melemeni A, Paraskeva A, Petropoulas G. Gabapentin attenuates the presser response to direct laryngoscopy and tracheal intubation. Br J of Anaesth. 2006;96:769-773.
6. Salman E, Celik C, Candan S. Premedication with single dose pregabalin 150 mg attenuates Hemodynamic response to laryngoscopy and endotracheal intubation. Scientific Reports 2012; 1:297.
7. Rathore A, Gupta H K, Tanwar GL, Rehman A. Attenuation of the pressure response to laryngoscopy and endotracheal intubation with different doses of Esmolol. Indian J Anaesth. 2002;46(6):449-52.
8. Liao X, Yang QY, Xue FS, Luo MP, Xu YC, et al. Bolus dose Remifentanil and Sufentanil blunting cardiovascular intubation response in children: a randomized double blind comparison. Eur. J Anesthesiol. 2009;26:73-80.

9. Basar H, Akpinar S, Doganci N, Buyukkocak U, Kaymac C, et al. The effect of pre anaesthetic single dose dexmedetomidine on induction, hemodynamic and cardiovascular parameters. J of Clin Anesth. 2008; 20:431-436.
10. Sun HL, Wu TJ, Ng C, Chien C, Chie W, et al. Efficacy of oro pharyngeal lidocaine instillation on hemodynamic response to orotracheal intubation. J of Clin Anaesth. 2009;21:103-107.
11. Melatonin. Sleepdex. Retrieved 2011-08-17.
12. Hardeland, Rüdiger, Pandi –Perumal SR, Cardinali, Daniel P. Melatonin. The International journal of Biochemistry and Cell Biology. 2006;38(3):313-316.
13. Tan DX, Zheng X, Kong J, Manchester L, Hardeland R, Kim S. et al. Fundamental issues related to origin of Melatonin and Melatonin isomers during evolution: Relation to their biological functions. International journal of molecular Sciences. 2014 Sept; 15(9):15858-90.
14. Ardura J, Gutierrez R, Andres J, Agapitos T. Emergence and evolution of the circadian rhythm of melatonin in children. Horm. Res. 2003;59(2)66-72.
15. Carrillo –Vico A, Guerrero JM, Lardone PJ , Reiter RJ. A review of the multiple actions of melatonin on the immune system. Endocrine 2005 July;27(2):189-200.
16. Lemoine P, Zisapel N. Prolonged release formulation of melatonin (Circadian) for the treatment of insomnia. Expert Opin Pharmacother. 2012;13(6): 895-905.
17. Wilhelmsen M, Amirian I, Russell J, Reiter, Rosenberg J, Gçgenur I. Analgesic effect of melatonin : A review of current evidence from experimental and clinical studies. J Pineal Res 2011 Apr;51:270-71.
18. Pokharel K, Tripathi M, Gupta PK, Bhattarai B, Khatiwada S, and Subedi A. Premedication with oral alprazolam and melatonin combination: A comparison with either alone- A randomized controlled factorial trial. Bio Med Research International Volume 2014; Article ID 356964.
19. Turkistani A, Abdullah KM, Al Shaer AA, Mazen KF, K Alkatheri. Melatonin premedication and the induction dose of Propofol. European Journal Of Anaesthesiology. 2007;24:399-402.
20. Mohamed AA, Hosam H, Atef HM, Alaa El-in M, El Kassaby, Ismail SAAM, Helmy. Effects of melatonin premedicationon the hemodynamic responses and perfusion index during laryngoscopy and endotracheal intubation. A M, Med .J. Cairo Univ.2013 Dec ;81(1):859-867.
21. Radwan K, Youssef M, El-TYawdy A, Zeidman M, Kamal N. Melatonin versus Gabapentin. A comparative study as pre-emptive premedications. The Inter. Journal of Anaesthesiology 2010;23(1).
22. Borazan H, Tuncer S, Yalein N, Erol A, Otelcioglu S. Effects of pre operative oral melatonin on post operative analgesia, sleep quality and sedation in patients undergoing elective prostatectomy:A randomized clinical trial. J Anaesth. 2010;24:155-60.