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Research Article

Mirtazapine premedication: Effect on preoperative anxiety and propofol dose requirements at different stages of hypnosis

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KEYWORDS

Premedication;
Antidepressants;
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Abstract *Background:* Mirtazapine is an antidepressant drug that blocks central 5-HT2 receptors with anxiolytic and sleep-promoting effects and theoretically can be used as a premedication.
Methods: Sixty ASA I-II patients aged 25–50 yr were randomly allocated according to the premedication received 2 h before induction of anesthesia into two equal groups: group M patients received mirtazapine 30 mg tablet mixed with 20 ml of water and group P patients received 20 ml of plain water. Anxiety level was measured by visual analogue scale (VAS) and bispectral index (BIS) electrodes were connected before induction of anesthesia. Intravenous (i.v) infusion of propofol 1% at a rate of 300 ml h^{-1} was started to induce hypnosis till a target BIS value of 45 (BIS45) is reached, and then endotracheal intubation is performed after fentanyl and cis-atracuruim being administered. Propofol dose requirements to achieve loss of response to verbal contact (RVC), loss of eyelash reflex (ELR), and a target BIS45 were recorded. Anesthesia was maintained with sevoflurane titrated to BIS value of 40–50 and oxygen/air mixture. Recovery time was recorded. In postanaesthesia care unit (PACU), VAS for pain and Ramsay sedation score were recorded. Patients were

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discharged from PACU when two consecutive Aldrete scores of 9 or 10 are obtained, and time of PACU stay was recorded.
Results: Preoperative anxiety by VAS and propofol doses required achieving loss of RVC and ELR, and target BIS45 were significantly lower in mirtazapine group. The two groups were comparable with regard to recovery and PACU stay times as well as postoperative pain and anxiety.
Conclusion: Mirtazapine 30 mg oral tablets can be used as a premedication as it reduces preoperative anxiety and hypnotic dose requirements of propofol, and does not prolong recovery time.

1. Introduction

Previous publications have investigated the clinical effect of different drugs used for premedication namely, midazolam, hydroxyzine, clonidine, nimodipine, and melatonin on induction and maintenance doses of propofol using different endpoints [1–5]. Mirtazapine is a novel, dual-acting antidepressant that possesses a potent central α_2-adrenoceptor blocking effect as well as 5-HT_2 and 5-HT_3 receptors antagonism. The antidepressant effect is due to enhancement of serotonergic and noradrenergic systems in the CNS mediated via blocking presynaptic α_2-adrenoceptors with subsequent enhancement of postsynaptic availability of Norepinephrine [6]. In addition, mirtazapine antagonizes α_2-adrenoceptors in the serotonergic nerve terminals, therefore, increasing serotonin release.

Mirtazapine enhances serotonergic transmission only at 5-HT_{A1} receptors. It also blocks 5-HT_2 and 5-HT_3 receptors [7] with subsequent anxiolytic and sleep-promoting effects mediated via blocking central 5-HT_2 receptors [8,9]. Theoretically, mirtazapine can be used as a premedication to provide preoperative anxiolysis and may reduce the induction dose of propofol via sleep-promoting effect.

The goal of the current study is to test the hypothesis that mirtazapine premedication can reduce preoperative anxiety, and induction dose of propofol.

2. Methods

This study was conducted in the period from January 2012 to April 2012 at King Fahd Military Medical Complex (Dhahran, Eastern Province, Saudi Arabia) following approval of the Ethics and Research Committee. Sixty adult patients aged 25–50 years of both sexes, with American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for a variety of elective surgical procedures were included in the study after getting their signed informed written consent. Patients with known hypersensitivity to mirtazapine, taking any other antidepressant drug, receiving monoamine oxidase inhibitor, current prescription of benzodiazepines, renal disease, hepatic disease, or lactating females were excluded from the study.

Patients were randomly allocated (randomization was performed with the help of a computer-generated random number sequence program) to receive either mirtazapine 30 mg chewing tablet which was ground and mixed with 20 ml of water in an opaque cup (Mirtazapine or M group, $n = 20$) or 20 ml of plain water in an opaque cup (Placebo or P group, $n = 20$) 2 h (hrs) preoperatively by an independent ward nurse who was blinded to the study. On receiving the patient in the operating room (OR) and before connecting the monitors, the anxiety level was measured in all patients using visual analogue scale (VAS) for subjective feeling of anxiety by the attending anesthesiologist who was also blinded to the premedication. VAS for subjective feeling of anxiety consists of a 10 cm line anchored at one end by a label such as "not anxious" and at the other end by a label such as "anxious as can be". The use of VAS was explained to each patient in the preoperative visit. Standard monitors were used including electrocardiography (ECG), non-invasive arterial blood pressure monitor (NIBP), pulse oximetry (SpO_2), and capnography. The baseline heart rate (HR) and both systolic and diastolic arterial blood pressures (SBP & DBP) were recorded.

Bispectral index (BIS) monitor (BIS version 3.2, Aspect Medical Systems Inc., Newton, MA, USA) was connected to all patients prior to induction of anesthesia. After preoxygenation, anesthesia was induced by continuous intravenous (i.v) infusion of propofol solution 1% mixed with 2 ml of lignocaine 1% at a rate of 300 ml h^{-1} by a syringe pump till a target BIS value of 45 is reached (BIS_{45}), then, propofol infusion was stopped. The total dose of propofol required achieving loss of response to verbal communication (RVC), loss of eyelash reflex (ELR), and a target BIS_{45} as well as the time needed for propofol achieving a target BIS_{45} ($Propofol_{BIS45}$) were recorded in all patients. Also, the HR, SBP, and DBP at BIS_{45} were recorded by the same attending anesthesiologist. After that, 2 $\mu g\ kg^{-1}$ of fentanyl was given and 0.15 $mg\ kg^{-1}$ of cis-atracuruim to facilitate intubation of the trachea. Anesthesia was maintained with sevoflurane and oxygen/air mixture ($FiO_2 = 0.6$). Sevoflurane concentration was titrated to maintain BIS value between 40 and 50 (BIS_{40-50}) and was turned off at the end of surgery. Recovery time was defined as the time from discontinuation of sevoflurane till the patient can grasp his or her hand on command. To reverse residual neuromuscular block, 50 $\mu g\ kg^{-1}$ of i.v neostigmine and 20 $\mu g\ kg^{-1}$ of atropine were given.

In post-anesthesia care unit (PACU), VAS for pain and Ramsay sedation score were recorded by the PACU nurse who was also blinded to the study. When two consecutive Aldrete scores [10] of 9 or 10 are obtained, patients are discharged from the PACU and time of PACU stay is recorded in all patients.

In a preliminary unpublished pilot study conducted on 50 unpremedicated patients who received i.v infusion of propofol 1% at a rate of 300 ml h^{-1} to reach our endpoint of a target BIS_{45}, we found that propofol dose requirement to reach BIS_{45} was 141 ± 28. Based on that, the group size necessary to detect a clinically relevant difference of 25% in propofol dose requirements to reach BIS_{45} was estimated to be 27 patients per group to give a power of 0.8 at a level of $P = 0.05$ (α error = 0.05; β error = 0.1). To overcome potential dropouts, 30 patients per group were enrolled. Secondary outcomes were preoperative anxiety level, induction time by propofol infusion, hemodynamics, recovery and PACU stay times, and postoperative pain and anxiety scores.

Data were presented as mean ± SD, median (range), or number (percentage) as appropriate. Numerical demographic data, propofol dose requirements, propofol induction time, hemodynamics, durations of anesthesia and surgery, and recovery and PACU stay times were compared using unpaired student's *t*-test, while categorical data were compared using Chi-square (χ^2) or Fischer's exact test as appropriate. Preoperative anxiety score (VAS), and postoperative pain (VAS) and sedation (RSS) scores were compared using Mann–Whitney *U*-test. A *P*-value <0.05 was considered as statistically significant. Statistical software package (Graph Pad In Stat® version 3.00 for Windows, Graph Pad Software Inc., San Diego, California, USA) was used for data analysis.

3. Results

In this randomized, placebo controlled, double blinded study, sixty patients were randomly allocated into to two groups: group M (n = 30) and group P (n = 30). No patient was excluded from the study.

Table 1 Demographic data, and duration of surgery and anesthesia.

	Group M (n = 30)	Group P (n = 30)	*P* value
Patient demographics			
Age (years)	43.4 ± 6.7	44.1 ± 8.2	0.719
Gender (male/female)	18 (60)/12 (40)	21(70)/9 (30)	0.589
Weight (kg)	83.6 ± 18.1	81.4 ± 18.7	0.645
Duration of surgery (min)	44.6 ± 17.3	43.8 ± 19.2	0.866
Duration of anesthesia (min)	67.3 ± 18.2	72.1 ± 20.4	0.340

Group M = mirtazapine group; Group D = midazolam group; Group P = placebo group; n = number; min = minutes.
Data are expressed as mean ± SD, or number (percentage).

Table 2 Effect of mirtazapine on preoperative anxiety, propofol requirements, propofol induction time, recovery time, and PACU stay.

	Group M (n = 30)	Group P (n = 30)	*P* value
Preoperative anxiety (VAS)	3 (1–5)**	8 (5–9)	<0.001
Propofol requirements (mg)			
Loss of RVC	104 ± 15*	118 ± 19	0.003
Loss of ELR	107 ± 16*	123 ± 22	0.002
BIS_{45}	112 ± 19**	139 ± 25	<0.001
$Propofol_{BIS45}$ (min)	2.1 ± 0.26*	2.5 ± 0.30	<0.001
Recovery time (min)	10.3 ± 2.6	10.8 ± 2.9	0.485
PACU stay (min)	31.8 ± 6.8	30.1 ± 6.5	0.326

Group M = mirtazapine group; Group P = placebo group; VAS = visual analogue scale; RVC = response to verbal contact; ELR = eyelash reflex; $Propofol_{BIS45}$ = time needed for propofol achieving BIS_{45}; n = number; min = minutes.
Data are expressed as mean ± SD, or median (range).
* $P < 0.05$.
** $P < 0.001$.

Table 3 Hemodynamics before and after propofol induction at BIS_{45}.

	Group M (n = 30)	Group P (n = 30)	*P* value
HR			
Baseline	77 (60–93)	79 (64–94)	0.263
At BIS_{45}	72.5 (56–93)	76 (60–89)	0.510
SBP			
Baseline	116 (105–143)	121 (108–152)	0.184
At BIS_{45}	110 (100 – 133)	115.5 (105–136)	0.214
DBP			
Baseline	73 (60–94)	79 (62–92)	0.469
At BIS_{45}	72 (58–83)	71.5 (60–87)	0.663

Group M = mirtazapine group; Group P = placebo group; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; n = number.
Data are expressed median (range).

Table 4 Postoperative pain and anxiety scores.

Time points	Group M (n = 30)	Group P (n = 30)	*P* value
PACU			
VAS	3 (0–5)	3 (0–6)	0.434
RSS	3 (1–5)	3 (1–4)	0.060
6 h			
VAS	3 (1–5)	3 (0–5)	0.719
RSS	3 (1–3)	2 (1–3)	0.176
12 h			
VAS	3 (0–6)	3 (0–5)	0.823
RSS	2 (1–3)	2 (1–2)	0.651
24 h			
VAS	2.5 (0–4)	3 (0–4)	0.925
RSS	1 (1–3)	1 (1–2)	0.124

Group M = mirtazapine group; Group P = placebo group; n = number; h = hours; PACU = post-anaesthesia care unit; VAS = visual analogue scale; RSS = Ramsay sedation score.
Data are expressed median (range).

The two groups were comparable with regard to the demographic data (age, gender, and weight) and durations of surgery and anesthesia (Table 1). Also, the two groups were comparable with regard to the recovery time and PACU stay (Table 2). Preoperative anxiety level measured by VAS was significantly lower in mirtazapine group (group M) compared to placebo (group P) [3(1–5) vs. 8(5–9), respectively, $P > 0.001$] (Table 2). Moreover, the propofol doses required to achieve loss of RVC, loss ELR, and a target BIS_{45} were significantly lower in mirtazapine group (group M) compared to placebo (group P), and the time needed for propofol achieving a target BIS_{45} at a fixed infusion rate of 50 mg min^{-1} in all patients in both groups was significantly shorter in mirtazapine group (group M) in comparison to placebo group (group P) being 2.1 ± 0.26 *vs.* 2.5 ± 0.30 min, respectively, with estimated *P* value >0.001 (Table 2).

The HR, SBP, and DBP before propofol induction of anesthesia and at a target BIS_{45} were comparable between both groups (Table 3).

The two groups were comparable with regard to postoperative pain (measured by VAS) and anxiety (measured by Ramsay sedation score) recorded in the PACU (Table 4).

4. Discussion

The main finding in the current study is that orally administered mirtazapine 2 h before induction of anesthesia is effective in reducing the preoperative anxiety level and induction dosing of propofol without prolonging recovery or PACU stay times.

A previous study had investigated the effect of a single oral dose mirtazapine (30 mg) on sleep demonstrated that mirtazapine has a sleep-promoting effect when given 2 h before bedtime [11]. Some preliminary studies of mirtazapine in anxiety disorders have been published. One previous study [12] compared the effect of diazepam 10 mg and mirtazapine 5, 15, or 30 mg with placebo on preoperative anxiety in female patients undergoing gynecological surgery on the following day. Both diazepam and mirtazapine reduced insomnia and preoperative anxiety more than placebo. The anxiolytic and sleep-promoting effects of mirtazapine are likely to be mediated via blocking central 5-HT_2 receptors. These findings are consistent with the results of the current study as patients in mirtazapine group exhibited significantly less preoperative anxiety in comparison to who received placebo. Mirtazapine is rapidly absorbed after oral administration, and the peak plasma concentration is reached within about 1.65 ± 0.7 h for fasting patients versus 2.4 ± 1.2 h for fed patients with elimination half-life of 20–40 h [13]. The onset time of 5-HT_2 receptors blocking effect of mirtazapine matches its peak plasma concentration after oral administration. The patients in the current study were fasting before oral administration of mirtazapine and this explains the fast onset of anxiolysis. Despite of long half-life of mirtazapine, it did not prolong recovery time in the current study. These results are consistent with a previous study conducted by Chen et al. [14] on 80 female patients who had undergone laparoscopic gynecologic procedures, and demonstrated that a single oral dose of 30 mg of mirtazapine received 1 h before surgery reduced preoperative anxiety level and promoted sleep in 45% of patients without prolonging recovery time.

In October 1996, bispectral index (BIS) achieved approval by the Food and Drug Administration as the first electroencephalogram (EEG)-based monitor of hypnotic component of anesthetic state. BIS reduces complex EEG processing to a simple number ranging from 100 (awake) to 0 (isoelectric EEG), and decreasing values indicate more sedation and hypnosis. BIS ranging from 40 to 60 correctly predicts absence of consciousness [15]. Published data had demonstrated that BIS correlates well with the level of responsiveness and accurately predicts loss of consciousness with propofol [16–18], midazolam [17,19], alfentanil, and isoflurane [17]. It had also been demonstrated that the correlation of BIS to the level of sedation is equal to, or even better than, using measured drug concentration [17]. Moreover, Gan and colleagues [20], in their multicentric study conducted on three hundred two patients at four institutions who received a propofol–alfentanil–nitrous oxide anesthetic, concluded that titrating propofol with BIS monitoring during balanced anesthesia reduced propofol use with faster emergence and significantly improved recovery. Based on these previous data, BIS monitor was used in the current study to evaluate adequate hypnosis induced by i.v propofol infusion. A BIS value of 45 (BIS_{45}) was determined in the current study as a target value for adequate hypnosis with no recall based on previous published data correlating the BIS values with the level of sedation and hypnosis by various sedatives and anesthetics. Glass et al. [17] in their multicentric study evaluating the relation between BIS and increasing level of sedation for propofol, midazolam, isoflurane, and alfentanil concluded that BIS levels less than 50 indicate adequate hypnosis with no recall. Furthermore, Lallemand et al. [21] in their prospective, double blind study to test three currently used induction doses of etomidate against both BIS values and clinical criteria for adequate depth of general anesthesia have concluded that a BIS value of 50 or less was associated with absence of purposeful movements during orotracheal intubation and the absence of recall following administration of etomidate.

Varying the rate of infusion induction of anesthesia with propofol in healthy adults does not result in major differences in changes in arterial pressure. However, induction by slow infusion can be recommended because of the reduced dose requirements, the lower incidence of apnea, and good patient acceptance [22]. At induction of anaesthesia with propofol, administration rates of approximately 50 mg min^{-1} seem likely to provide improved titration to effect without excessively prolonging induction and therefore, this rate of propofol infusion during induction of anesthesia is suggested to be close to the optimal rate in humans [23]. Consequently, in the current study, at induction of anesthesia propofol infusion was fixed at a rate of 300 ml h^{-1} (50 mg min^{-1}) in all patients.

In the current study, it was found that mirtazapine administered orally in a dose of 30 mg 2 h before surgery was effective in reducing propofol dose requirements to produce loss of RVC, loss of ELR, and to achieve a target BIS value of 45 and shortened the propofol induction time needed to achieve target BIS value of 45. Also, there were not statistically or clinically significant reductions in arterial blood pressure in all studied patients. The synergistic effect of mirtazapine can be explained by its blocking effect to central 5-HT_2 receptors enhancing anxiolysis and promoting sleep. The onset time of 5-HT_2 receptors blockade was matching the peak plasma concentration of mirtazapine after oral administration in fasting patients which was synchronous with the time of propofol induction of anesthesia providing synergistic effect to propofol with ultimate effect of reducing propofol dose requirements. Conflicting with our results, Chen et al. [14] in their study found that a single oral dose of 30 mg of mirtazapine 1 h prior to surgery did not reduce induction dose of propofol, however, in mirtazapine group, the auditory evoked potential index at loss of consciousness during induction was significantly less than in placebo group. The lack of reduction of propofol dosing can be explained by the earlier time of propofol induction in Chen et al. study which was not synchronous with the peak plasma concentration of mirtazapine with insufficient synergistic effect of mirtazapine to propofol.

In conclusion, a single oral dose of mirtazapine 30 mg administered 2 h before induction of anesthesia significantly reduces preoperative anxiety level and propofol induction dose requirements at different stages of hypnosis with shorter induction time and without prolonging recovery time, and therefore, it can be used as a premedication due to its anxiolytic and sleep–promoting effects.

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