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ANXIOLYTIC EFFECT OF MIDAZOLAM PREMEDICATION ASSESSED BY CLINICAL AND PLATELET AGGREGATION PROFILES

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Background: It is well documented that surgery is associated with increased anxiety, which has an adverse impact on patient's outcome. This study was designed to assess the anxiolytic effect of midazolam in pre-anaesthetic medication by using clinical and platelet aggregation profiles. **Methods:** Sixty ASA I and II female patients aged between 35 and 60 years undergoing elective abdominal hysterectomy were randomly divided into two equal groups. Group I received placebo as pre-medication while group II received 0.15 mg/kg midazolam as pre-medication 1 hour preoperatively. They were monitored for visual analogue scale (VAS) for anxiety, observer's anxiety criteria, sedation score, blood pressure, heart rate and platelet aggregation profile immediately before and 1 hour after pre-medication. **Results:** There was statistically significant difference with respect to VAS of anxiety, observer's anxiety criteria, sedation scores, systolic and diastolic blood pressure ($p<0.05$). Heart rate was higher in the midazolam group but this was not statistically significant. There was no statistical significant difference in platelet aggregation profile in the two groups. **Conclusion:** Findings of the study suggest midazolam is a good anxiolytic for pre-medication and its effect on platelet aggregation profile needs to be further evaluated.

Keywords: Pre-medication, Widazolam, Anxiolysis, Platelet aggregation

INTRODUCTION

Preoperative anxiety is a challenging concept in the preoperative care of patients and almost all patients undergoing surgery experience varying level of anxiety.[1] Anxiety is dependant upon the perceived threat and danger of the surgical procedure, pain, anaesthesia, outcome of surgery and worries about the family. Patients undergoing major surgery, i.e., major abdominal, thoracic and cardiac surgery and women have higher levels of anxiety.[2] It has been demonstrated that women undergoing invasive radiological or surgical procedures for gynaecological disorders experience higher levels of state anxiety, express more worry, display greater heart rate and blood pressure changes before and during surgery, are more difficult to anaesthetise and are more likely to experience headache, vomiting and pain in the postoperative period.[3,4] Relief of anxiety is thus a humane goal and should be attempted in every patient.

Benzodiazepines are widely used as anxiolytics prior to surgery.[5] Midazolam, a water soluble benzodiazepine is a useful agent for pre-medication and sedation. It has a short onset time and duration of action when compared to other benzodiazepines. In addition to anxiolysis, it also possesses hypnotic, anticonvulsant, muscle relaxant and antegrade amnestic properties.[6]

Blood platelets, numbering $1.8–3.5\times10^5$/ml, circulate within the vasculature as disc shaped cells that are normally non-adherent to each other and to the endothelial cells that line the blood vessel wall. 'Platelet aggregation' is a term used to denote the adherence of one platelet to another. Adding aggregating agent, e.g., adrenaline, noradrenaline, etc. to platelet rich plasma, which is being continually stirred, can induce this phenomenon. Induction of platelet aggregation by adrenaline presumably occurs through binding to specific receptor, suggested to be α-type, on platelet membrane.[7]

Preoperative anxiety is associated with a rise in plasma catecholamine (adrenaline, noradrenaline) levels. This rise in adrenaline would result in enhanced platelet aggregation in anxiety states. Midazolam, an anxiolytic agent, would reduce the anxiety levels and corresponding catecholamine secretion. This will prevent the platelet aggregation in patients receiving midazolam as pre-medication.

The objective of this study was to examine the anxiolytic effects of midazolam in a homogenous group of patient undergoing elective hysterectomy using cardiovascular variables, subjective anxiety and sedation scores and objectively by platelets aggregation profiles.

MATERIAL AND METHODS

After approval from Ethics Review Committee of the Aga Khan University and obtaining informed consent, a double blinded, randomized, placebo controlled trial was conducted on 60 ASA I and II female patients, aged between 35 and 60 years, scheduled for elective abdominal or vaginal hysterectomy. Patients with history of psychiatric illness, alcohol abuse, hypertension, ischemic heart disease, diabetes mellitus, patients receiving β-blockers and Ca^{++} channel blockers and those taking benzodiazepines since admission to hospital were excluded from the study. Patients were equally divided into two groups with patients in group I receiving placebo and group-II receiving midazolam 0.15 mg/kg orally as pre-medication 1 hour prior to the anaesthetic. The

pre-medication drug, either placebo or midazolam, was grinded and dissolved in sweet syrup to make the drug palatable. The final concentration of midazolam was 1 mg/ml and the mixture was prepared fresh for every patient. Appropriate amount of drug was given to the patient in the ward by a person not involved in taking observations.

Following parameters were monitored immediately before and 1 hour after the administration of study drug:

1 Visual analogue scale for anxiety in which patients were asked to grade their level of anxiety on a scale of 0–10 (0 being totally calm and 10 being extremely anxious).
2 Observer's anxiety criteria, in this, the patient's anxiety was assessed by the observer who was blinded to the type of medication given to the patient and was assessed on the following scale:
   Grade 1- Calm
   Grade 2- Mild anxiety
   Grade 3- Moderately anxious
   Grade 4- Extremely anxious.
3 Sedation score was also assessed by the blinded observer who rated the patients sedation as:
   Grade 0: Fully awake,
   Grade 1: Awake but with signs of drowsiness,
   Grade 2: Asleep but responsive to spoken words,
   Grade 3: Asleep and unresponsive to spoken words and
   Grade 4: Asleep and unresponsive to gentle shaking.
4 Systolic and diastolic blood pressure and heart rate was measured by using automated blood pressure and heart rate monitors.
5 For platelet aggregation profile, the method used to quantitatively assess platelet aggregation was introduced by Born[8] in 1962 and is based on the principle of light transmission through platelets rich plasma (PRP) caused by the formation of platelet aggregates and the volume occupied by the platelets in a photoelectric cell. In this study, 4.5 ml of venous blood was collected in a 5 ml syringe with a 21 gauge needle. Blood was then gently transferred into a tube containing 0.5 ml of 3.8% sodium citrate which was mixed by gentle inversion and vigorous shaking was avoided. This process was done before and one hour after the pre-medication. The sample was taken to the pharmacology laboratory and PRP was prepared by centrifuging the sample at a speed of 1,100–15,000 RPM for 15 minutes (DYDAC II Clay Adams). PRP was withdrawn with a siliconised plastic pipette into a glass tube and was capped and labelled PRP. The platelet poor plasma (PPP) was prepared by re-centrifuging the remaining blood specimen at 4,000 RPM for 5 minutes. The PPP was transferred into a plastic tube and was labelled platelet poor plasma. To study platelet aggregation Lumi Aggregometer model 400 was used. Epinephrine 200 μmol was added to 0.45 ml of PRP, which was continually being stirred. As aggregation proceeded, platelet clumping occurred. This reduced the optical density of the PRP allowing more infrared light to pass through. The process was repeated for PPP. The Lumi Aggregometer developed voltage proportional to the difference between the PRP and PPP and this difference was recorded on the strip chart. Test was performed within an hour after the blood was drawn from the patient and efforts were made to keep the plasma at ambient temperature of 37 ºC.

All values given in the results are presented as mean with standard deviation (SD). Numerical data were analysed using the analysis of variants (ANOVA) and chi-square test where appropriate. A *p*-value of less than 0.05 was considered statistically significant in each case.

RESULTS

Both the groups were comparable for demographic data (Table-1). The objective variables for anxiety which included VAS for anxiety, observer's anxiety criteria and sedation score were all significantly better ($p<0.05$) in patients who received midazolam when compared to the placebo group (Table-2). When systolic and diastolic blood pressures were compared between the two groups, they were significantly lower in the midazolam group after pre-medication ($p<0.05$) whereas there was no statistically significant change in the heart rate after pre-medication in either group (Table-3). Platelet aggregation profile was also similar among the two groups before and after pre-medication (Table-2).

Table-1: Demographic data

	Group-I	Group-II	*p*-value
Age	42.67±5.64	44.24±6.33	NS
Weight	63.69±9.39	60.37±16.26	NS
Height	153.57±11.27	156.22±14.06	NS

NS= not significant

Table-2: Visual analogue, observers anxiety, sedation score and platelet aggregation profile

	Before drug	After drug	*p*–value
Visual Analogue Scale for Anxiety			
Group I	3.49±1.51	3.50±1.33	NS
Group II	3.06±1.34	2.01±1.38	<0.05
Observer's anxiety Criteria			
Group I	1.92±0.97	1.94±0.92	NS
Group II	1.74±0.73	1.13±0.69	<0.05
Sedation Score			
Group I	0.36±0.18	0.47±0.15	NS
Group II	0.67±0.31	1.72±0.56	<0.05
Platelet aggregation profile			
Group I	14.51±5.68	13.75±5.96	NS
Group II	15.35 ± 7.92	14.02 ± 6.53	NS

Table-3: Haemodynamics

	GROUP I	GROUP II	*p*–value
SBP Before drug	130.83±13.74	127.31±11.97	N.S
SBP After drug	134.71±15.49	112.83±11.39	<0.05
DBP Before drug	81.25±8.64	82.52±8.77	N.S
DBP After drug	84.17±8.66	72.13±6.74	<0.0
HR Before drug	78.24±6.54	80.87±8.29	N.S
HR After drug	78.31±6.32	82.32±6.58	N.S

SBP= Systolic blood pressure, DBP= Diastolic blood pressure, HR= Heart Rate

DISCUSSION

Pre-medication traditionally has been used to achieve several goals including reduction of anxiety, preamptive analgesia, antisialogogue effect, provision of sedation etc, but the primary purpose of prescribing these drugs in the immediate preoperative period is to allay patient's anxiety. Midazolam is an imidazobenzodiazepine that is rapidly and almost completely absorbed after oral administration.[12] It has important hypnotic with anxiolytic properties that makes it very useful as a pre-medication drug.[5] We have performed a double blind, randomized, placebo controlled study to assess the anxiolytic effect of midazolam as pre-medication subjectively, objectively and biochemically. The significant reduction in subjective assessment of anxiety level, both by the patient and the observer, after the administration of midazolam is in consistence with the previous studies.[9,10] Sedation was also significantly better in the midazolam group as also shown in previous studies. We also measured the haemodynamic parameters including systolic blood pressure, diastolic blood pressure and heart rate as objective indicators of anxiolysis. In this study, there was a statistically significant reduction in both the systolic and diastolic blood pressures in the midazolam group whereas the heart rate increased clinically, but not statistically, in patients premedicated with midazolam. Midazolam have distinct effect on the cardiovascular system including a decrease in myocardial contractility, systemic vascular resistance and venodilation, all of which result in a fall in arterial blood pressure. This fall in systemic vascular resistance and venodilation leads to reduction in cardiac filling pressure, which further reduces the cardiac output. In response the baroreceptor reflex arc is activated which causes the heart rate to increase proportionately to compensate for the fall in cardiac output.[11] The results of our study are consistent with previous studies[6] but there is a difference in the magnitude of heart rate effect. In our study the rise in heart rate was less as compared to these studies which have quoted a rise in heart rate of up to 18%. The probable reason for this difference could a difference in patient population and low preoperative anxiety levels. Further studies are required to evaluate this effect in detail. There was no statistically significant difference in the platelet aggregation profile among the groups in our study which is contrary to the results of previous studies done on other drugs of benzodiazepine group. They all showed an increase in platelet aggregation when exposed to exogenous epinephrine.[13,14] There are several factors which influence the platelet aggregation profile including age of plasma after venipuncture, *p*H of plasma, platelet count of platelet rich plasma, drugs ingested by patients, quality of reagent and patient's age and sex.[15] Many of the above mentioned variables were not standardised in our study which might have affected the platelet aggregation profile in our study. We also used sweet syrup to dissolve placebo and midazolam which could have resulted in a rise in serum glucose levels. It is known that increased level of glucose increases spontaneous platelet aggregation, independent of other factors, therefore the results obtained in our study may not be reflecting the true picture of platelet aggregation.[13] In this study, platelet aggregation profile was obtained within an hour of collection of venous blood. Hardeman[14] showed transient aggregation resistance of human blood platelets in fresh plasma if the test is done within an hour of venipuncture, this being another factor responsible for adverse platelet aggregation profile.

CONCLUSION

In conclusion midazolam 0.15 mg orally one hour before surgery is a suitable pre-medication to allay anxiety when clinical and objective criteria are used. The effect of midazolam on platelet aggregation needs to be further evaluated with better controlled trials attempting to maintain most of the variables constant.

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