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# Prophylactic Administration of Low Dose Midazolam and Ketamine in Prevention of Profound Hypotension in Severely Anxious Females Undergoing Cesarean Section

**Chaudhry Amjad Ali, Fatima Sharif Khan*, Akhtar Hussain, Kaswar Sajjad Ansari**, Kaukab Majeed, Sajjad Qureshi**

Department of Anesthesiology, Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan, *Department of Obs & Gynae, Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan, ** Department of Medicine, Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan

## ABSTARCT

***Objective:*** To compare the efficacy of a combination of Midazolam and Ketamine in providing anxiolysis to prevent profound hypotension in severely anxious patients undergoing cesarean section.

***Study Design:*** Quasi-Experimental Study

***Place and Duration of Study***: Combined Military Hospital Quetta, Pakistan from Mar to Apr 2023.

***Methodology:*** The study population included female patients of reproductive age group undergoing lower segment cesarean section under spinal anesthesia. A total of 100 patients were recruited. The study sample was divided into two sets. The first set of patients was labeled Group-A and second was labeled as Group-B. Visual Analogue Scale for Anxiety (VAS-A) was used to assess the anxiety in all patients. Group-A received premedication (Ketamine and Midazolam) and Group-B patients didn't receive the premedication and they were only given Verbal Reassurance. The primary outcome was frequency of hypotension in patients of moderate-severe anxiety.

***Results:*** The frequency of the adverse outcomes was higher in Group-B as compared to Group-A. The frequency of tachycardia was 1(2%) versus 17(34%), hypotension was 1(2%) versus 17(34%), nausea/vomiting was 2(4%) versus 9(18%), shivering was 2(4%) versus 9(18%), and Diaphoresis was 2(4%) versus 5(10%) in Group-A versus Group-B respectively.

***Conclusion:*** The combination of low dose Midazolam (0.03mg/kg) and Ketamine (0.2mg/kg) prevents anxiety related hypotension in gravid female undergoing cesarean section under spinal anesthesia.

**Keywords:** Anxiety, Ketamine, Midazolam, Pregnancy, Visual Analogue Score (VAS).

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## INTRODUCTION

Anxiety is a manifestation of fear. It is a multitude of cognitive, behavioral, affective and neurophysiologic responses aimed at preparing body for fight or flight. It's an appraisal and awareness of existing or impending danger which is either actual or professed[1].It's an intra-psychic conflict which can be regarded as tension, worry or apprehension[2].The level of anxiety within a physiological range is expected and accepted in patients before surgery and it prepares them to embrace the danger associated with surgical experience but if it is out of proportion or exaggerated then it becomes pathological and does more harm than good. Anxiety is insufficiently acknowledged, underrated and untreated in operative settings although its prevalence is as high as forty-seven percent[3].The somatization of pre-operative anxiety is associated with an aggravated hypotensive response after spinal anesthesia[4].It has also been reported to cause transient seizures in a patient undergoing cesarean delivery under subarachnoid block[5]. Increased levels of anxiety are linked to vaso-vagal syncope and bradycardia before and during execution of regional anesthesia[6].

Somatization of anxiety can therefore effect peri-operative anesthetic management of a patient and present clinical challenge to anesthetists and gynecologists in operation theatre. The maternal anxiety not only potentiates spinal hypotension[7], but it also culminates in post-partum hemorrhage and pre-eclampsia[8]. There are a number of studies to support the fact that spinal hypotension and gynecological complications are attributed to high anxiety levels in laboring women. Therefore, alleviation of anxiety should be part of management of these patients. Most of these patients undergo surgery during regional anesthesia and anxiety escalates due to hemodynamic changes, fear of pain, fear of surgical complication and feeling of touch and dragging sensation[9].

This study aimed to study strategies that could alleviate anxiety to counter its adverse effects such as

**Correspondence: Dr Kaukab Majeed,** Department of Anesthesiology, Combined Military Hospital Quetta Pakistan

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hypotension and improve satisfaction levels in laboring women. The local evidence on this topic is scarce and we will be the first ones to provide evidence on pharmacological prevention of anxiety induced hypotension in gravid females undergoing caesarean section in Pakistani population.

## METHODOLOGY

This Quasi-Experimental study was done in the operation theatre complex of Combined Military Hospital Quetta, Pakistan. The ethical committee board approved the research vide (ERC# CMH QTA-IERB/12/2023). The study was joint venture of Anesthesiology along with Obstetrics & Gynecology Department of CMH Quetta. The study spanned over a period of six months, from March 2023 to April 2023. Sample size of 100 patients (50 patients in each group) was estimated by using expected percentage of hypotension in both groups i.e non-anxious 28%10 and anxious patients as 47%[10]. Patients were recruited through non-probability, consecutive sampling.

**Inclusion Criteria**: The study population included female patients of reproductive age group, booked cases undergoing lower segment cesarean section under spinal anesthesia.

**Exclusion Criteria**: The gravid ladies with neuropsychiatric disorders or emergency surgery were excluded from the study.

All the patients undergoing elective surgery were included and their written consent was taken. the recruited patients were divided into two groups (Figure). The first set of patients was labeled Group-A and second was labeled as Group-B. All patients had routine gynecological and anesthesia assessment before shifting to operation theatre. Intravenous line (16 G) was passed with local anesthesia (subcutaneous administration of 1ml of 2% lignocaine).No pre-medication was given to patients in wards. All patients were given 15ml/kg lactated ringer solution to counteract hypotension due to dehydration. Standard monitoring was attached. Visual Analogue Scale for Anxiety 11 was used to assess the anxiety in all patients. The Visual Analogue Scale for Anxiety is a hundred millimeter line with zero on one extreme signifying no anxiety and 10 on the other extreme signifying maximum anxiety. On the basis of Visual Analogue Scale for Anxiety, Visual Analogue score for anxiety (VAS-A) was obtained for all study participants. Three categories of patients were devised as: Mildly anxious (VAS-A 0-3), moderately anxious (VAS-A 4-6) and severely anxious (VAS-A 7-10). All patients with moderate to **severe** anxiety were included in the study. Group-A received premedication for anxiety (Ketamine and Midazolam) and Group-B patients didn't receive the premedication for anxiety and they were only given verbal reassurance.

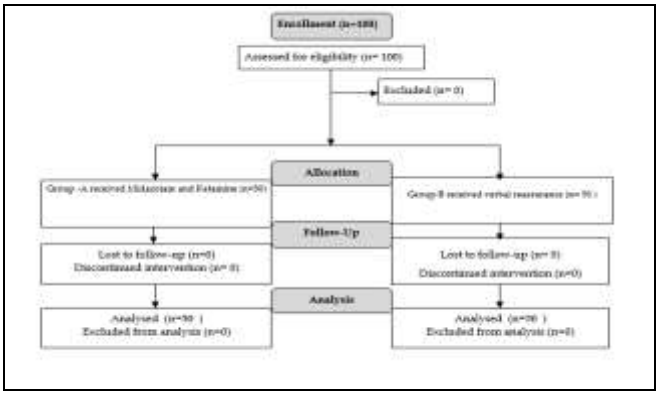


**Figure: Patient Flow Diagram**

All Group-A patients were given 8mg of Ondansetron intravenous 2 minutes before spinal anesthesia. Spinal anesthesia was given in sitting position with 27G (B.Braun, Quinke) spinal needle and 1.5 milliliter of 0.75%hyperbaric Bupivacaine (Brooks pharma) at interspace between lumbar vertebra four and five and they were laid supine with a wedge under right hip causing a visible left uterine tilt. The dermatomal spread was checked after 7 minutes with Ethyl Chloride spray and surgery was initiated after satisfactory block (T5 level and Bromage 1). 20mg of intravenous Ketamine and 2mg of Midazolam were given after that. Any episode of hypotension and tachycardia was recorded during operative period. The boluses of Phenylephrine (50ug) were given in case of hypotension. Similarly, All Group-B patients were given spinal anesthesia in similar fashion. The patients were observed for any episode of hypotension and tachycardia. The boluses of Phenylephrine (50ug) were given in case of hypotension. Following variables were recorded: Age, BMI, parity, gestational age, baseline mean arterial pressure (MAP), baseline heart rate (HR), surgical time, presence and absence of hypotension, total dose(mg) of Phenylephrine used, presence or absence of nausea/vomiting, shivering and diaphoresis, VAS-A (pre-operative, intraoperative and post-operative) and maternal satisfaction after surgery (30min post-operatively). The satisfactory block was signified by two indices: The achievement of T5 dermatomal spread and Bromage score 12 of one. The primary outcome was frequency of

hypotension in patients of moderate-severe anxiety. Secondary outcomes were mean VAS-A preoperatively, VAS-A intra-operatively or mean VAS-A in post-operative period , maternal satisfaction and adverse outcomes( tachycardia, nausea/vomiting , shivering and diaphoresis).

The data was analyzed using statistical package of social sciences (SPSS) version[26]. Qualitative variables were analyzed through means and standard deviation while qualitative variables were processed to get frequency and percentages. Independent samples T-Test was applied to compare mean visual analogue score for anxiety (VAS-A) and compute significance while Chi-square analysis was used to compare frequencies. *p*-value of less than 0.05 was considered statistically significant.

## RESULTS

The primary outcome was frequency of hypotension which was hypotension was 1(2%) versus 17(34%), in Group-A versus Group-B with *p*-value of <0.001. The demographics of both groups were similar. The mean age in Group-A was 28.14±6.2 years, BMI was 28.26±2.6 kg/m2, gestational age was 38.52±1.19 weeks. Similarly mean age in Group-B was 28.20±6.52years, BMI was 29.0±6.52 kg/m2 and gestational age was 38.08±1.04 weeks. The baseline vitals were comparable in both study groups. The baseline mean arterial blood pressure was 84.96±6.40 mm of Hg versus 84.50±7.06 mm of Hg, mean baseline pulse rate was 112.22±8.45 bpm in Group-A versus 105.46±9.02 bpm in Group-B. The mean surgical time was 38.30±0.97 minutes in Group-A and 38.20±0.80 minutes in Group-B. 9(18%) patients in Group-A were primigravida, 21(42%) patients were para one, 12(24%) patients were para two and 8(16%) patients were three.7(14%) were primigravida in Group-B, 21(425) were para one, 13(26%) were para two and 9(18%) were para three. The demographics are displayed in Table-I.

The frequency of the adverse outcomes was higher in Group-B as compared to Group-A. The frequency of tachycardia was 1(2%) versus 17(34%), nausea/vomiting was 2(4%) versus 9(18%), shivering was 2(4%) versus 9(18%), and Diaphoresis was 2(4%) versus 5(10%) in Group-A versus Group-B respectively. The adverse outcomes are presented in Table-II

The mean Visual Analogue Scale for Anxiety before induction was comparative in both groups that is 8.12±0.84 in Group-A and 8.00±0.85 in Group-B (p equals 0.483). However, there was a substantial decrease in Visual Analogue Scale for Anxiety intraoperatively in Group-A patients with mean VAS-A of 0.28±0.45 and almost no decrease in Group-B patients with mean VAS-A of 8.48±0.61 in Group-B with p value of <0.001. The difference remained noteworthy in post-operative period with mean VAS-A in Group-A patients to be 1.19±0.80 and 4.64±0.94 in Group-B patients (*p*-value <0.001) which shows that our intervention was successful in alleviation of stress during cesarean section. (Table-III).

The maternal satisfaction was found in 49(98%) patients in Group-A versus 36(72%) patients in Group-B with *p*-value of <0.001 as shown in Table-IV.

**Table-I: Demographic Characteristics of the Study Groups (n=100)**

| Variables | | Group-A Mean±SD n=50 | Group-B Mean±SD n=50 |
|---|---|---|---|
| Age (Years) | | 28.14±6.24 | 28.20±6.52 |
| Body Mass Index (kg/m2) | | 28.86±2.61 | 29.00±2.79 |
| Gestational Age (weeks) | | 38.52±1.19 | 38.08±1.04 |
| Baseline Mean Arterial Pressure (mm of Hg) | | 84.96±6.40 | 84.50±7.06 |
| Baseline Pulse Rate (bpm) | | 112.22±8.45 | 105.46±9.02 |
| Surgical Time (Minutes) | | 38.30±0.97 | 38.20±0.80 |
| | | Frequency(%) | Frequency (%) |
| Parity | 0 | 9(18) | 7(14) |
| | 1 | 21(42) | 21(42) |
| | 2 | 12(24) | 13(26) |
| | 3 | 8(16) | 9(18) |

**Table-II: Frequency of adverse outcomes among the study groups (n=100)**

| Adverse outcomes | | GROUP-A Frequency (%) (n =50) | GROUP-B Frequency (%) (n =50) | *p* value |
|---|---|---|---|---|
| Tachycardia | YES | 20(40.0) | 19(38.0) | 0.50 |
| | NO | 30(60.0) | 31(62.0) | |
| Hypotension | YES | 1(2.0) | 17(34.0) | <0.005 |
| | NO | 49(98.0) | 33(66.0) | |
| Nausea/Vomiting | YES | 2(4.0) | 10(20.0) | <0.031 |
| | NO | 48(96.0) | 40(80.0) | |
| Shivering | YES | 20(40.0) | 19(38.0) | <0.247 |
| | NO | 30(60.0) | 31(62.0) | |
| Diaphoresis | YES | 0(0) | 2(4.0) | <0.495 |
| | NO | 50(100.0) | 48(96.0) | |

## DISCUSSION

In our study, the administration of anxiolytics improved the hemodynamic profile of the moderate to severely anxious patients having similar

demographics and clinical parameters as compared to verbal reassurance. This signifies the fact that anxiety should be treated and mental health of the patient should also be a pre-anesthetic concern. This is of particular importance in patients who undergo surgery under regional anesthesia as they are awake and are exposed strange and unfamiliar environment of operation theatre.

**Table-III: Comparison of Visual Analogue Score (Vas-A) Of Study Groups (n=100)**

| Visual Analogue Score for anxiety (VAS-A) | Group-A (n=50) Mean±SD | Group-B (n=50) Mean±SD | *p*-value |
|---|---|---|---|
| Pre-operative | 8.12±0.84 | 8.00±0.85 | 0.483 |
| Intra-operative | 0.28±0.45 | 8.48±0.61 | <0.001 |
| Post-operative | 1.19±0.08 | 4.64±0.94 | <0.001 |

**Table-IV: Comparison of Maternal Satisfaction between both groups (n=100)**

| Variable | | GROUP-A Frequency (%) (n=50) | GROUP-B Frequency (%) (n=50) | *p*-value |
|---|---|---|---|---|
| Satisfaction | Yes | 49 (98.0) | 36(72.0) | <0.001 |
| | No | 1(2.0) | 14(28.0) | |

According to prospective study by Sklebar *et al*., four out five women develop transient anxiety during peripartum period attributable to apprehensions related to child birth. These anxious women have more propensities to develop late postpartum depression in due course of time[13]. Thus, prevention is better than cure and the continuity of mental health care should be maintained in operative settings as well to avoid such complications. The somatization of anxiety poses problems for anesthetists in operation theatre. The spinal anesthesia is preferred Centro-axial anesthesia for cesarean section but unfortunately it is related to a very high incidence of hypotension (75%). Relief of aorto-caval compression, administration of intravenous fluids, limiting local anesthetic dose and use of vasoactive drugs are some of measures that help in mitigation of spinal induced hypotension[14]. However, despite all these interventions, it is a common observation that hypotension still happens and it is more often seen in anxious patients. In our clinical practice, we waited till the delivery of baby to administer anxiolytics and opioids to alleviate anxiety in gravid ladies. However, according to randomized controlled trial of Mokhtar *et al*.,[14] in 2016 Midazolam can be given to gravid ladies before delivery of baby. They recruited eighty pre-eclamptic partiturens and pre-medicated half of them with Midazolam half an hour prior to subarachnoid block. It was concluded that premedication with Midazolam relieved anxiety, enhanced post-operative satisfaction and preserved hemodynamic stability. The role of Midazolam in prevention of hypotension induced by anxiety couldn't not be established in their study as pre-eclampsia was a confounding factor.

Ketamine modulates NMDA (N-methyl-D-aspartate) receptors of thalamus to induce a dissociative state coupled with analgesia and amnesia. Its role has been highlighted as favorable anxiolytic and anti-depressive agent in refractory anxiety[16]. Ketamine is also used for relieving break through pain during neuroaxial anesthesia. It can be used as both pre-emptive and rescue analgesic but higher doses (> 2mg/kg) are associated with fetal despression[17]. Never the less, low dose of Ketamine(≤5mg/kg) has successfully treated post-partum depression as Monks et al performed a pilot study with almost one-twenty patients and studied effect of subcutaneous and intravenous routes of Ketamine for post-partum depression. They established that it was tolerated well and exerted its anti-depressive effects without any adverse outcomes[17]. The use of Ketamine in perioperative setting also reduces post-operative depression[19]. The relatively lower dose (0.15mg/kg) of Ketamine also mitigate post-dural puncture headache and can be helpful in immediate post-operative period.

The use of combination of Ketamine and Midazolam alleviated anxiety. The post-operative patient satisfaction was more in Group-A patients. The possible mechanism in our patients would be that the antidepressive effect of Ketamine potentiated Midazolam and anti-hypotensive effects of Ketamine also prevented hypotension. The overall result was prevention of hypotension and relief of anxiety.

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Anesthesia and Gynecology Department CMH Quetta.

## LIMITATION OF THE STUDY

The limitation of our study was that we only relied on subjective measure of anxiety. The education of level of patients could have been a confounding factor hindering the proper assessment of anxiety.

## CONCLUSION

The combination of low dose Midazolam and Ketamine prevents anxiety related hypotension in gravid female undergoing cesarean section under spinal anesthesia.

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**Funding Source:** None.

**Authors' Contribution**

The Following authors have made substantial contributions to the manuscript as under:

CAA & FSK: Conception, study design, drafting the manuscript, approval of the final version to be published.

AH & KSA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

KM & SQ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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