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Comparison of Two Sedation Techniques in Patients Undergoing Surgical Procedures under Regional Anaesthesia

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Abstract

Objective: Intraoperative comfort and patient satisfaction during surgical procedures under regional anaesthesia can be improved with the use of supplemental intravenous sedation. The authors conducted a study to compare two sedation techniques for surgical procedures performed under regional anaesthesia, i.e., midazolam and pethidine combination compared with midazolam and tramadol combination.

Methods: Forty adult American Society of Anaesthesiologists (ASA) grade 1-111 patients, aged between 40-65 years undergoing surgery under regional anaesthesia (sub-arachnoid block) were included. The patients were randomly divided into two groups. All patients received standardized premedication, intraoperative monitoring and oxygen therapy. Group A patients received midazolam 0.03 mg/kg followed by pethidine 20 mg intravenously, and group B patients received midazolam 0.03 mg/kg followed by tramadol 20 mg intravenously after the institution of regional anaesthesia. Monitoring included ECG, blood pressure, respiratory rate, oxygen saturation and sedation score. Complications, if any, were recorded. Monitoring was continued during the recovery room stay. All patients were interviewed in the evening and time of ambulation and rating of OR experience was noted.

Results: Data analysis showed no significant difference between pethidine and tramadol for all the haemodynamic variables ($p = >0.05$). There was also no significant difference in patient's and surgeon's assessment of their experience. Complications and recovery characteristics also did not show any significant difference.

Conclusion: Midazolam-tramadol combination may be used as an alternative to midazolam-pethidine combination for sedation during surgical procedures performed under regional anaesthesia (JPMA 57:548:2007).

Introduction

Several surgical procedures are performed under regional anaesthesia. Intraoperative comfort and patient satisfaction during these surgical procedures can be improved with the use of supplemental intravenous sedation.¹ The goal of sedation for surgery under regional anaesthesia is to enhance patient comfort, to preserve protective airway reflexes, to avoid sympathetic stimulation and to help maintain haemodynamic stability during the surgical procedure.² Many single and multiple drug regimes have been used for this purpose with varying degrees of success.^{3,4} Midazolam, propofol and opioids like fentanyl or remifentanyl are often used, either alone or in combination.⁵⁻⁶

While midazolam can be used as the sole supplement to regional anaesthesia, it can prove difficult to titrate and can lead to either undesirably deep sedation or a confused and uncooperative patient.² Therefore other drugs, usually opioids, are often used in combination with midazolam or other sedatives for this purpose so as to prevent undesirable effects of both agents, as a smaller dose of each drug will be required to maintain adequate sedation. Midazolam and fentanyl combination is a popular regime used to enhance patient comfort during regional and local anaesthesia.^{2,6} In

Pakistan fentanyl is often unavailable and other opioid agents like pethidine or morphine are combined with midazolam to provide sedation during regional anaesthesia. However, these combinations of midazolam and opioids can cause significant intraoperative respiratory depression.³

Tramadol hydrochloride is a synthetic atypical opioid with central-acting analgesic properties. When compared with other opioids, it does not induce significant respiratory depression or histamine release.³ The objective of our clinical trial was to study the cardio-respiratory stability, the acceptability to the patient and surgeon, and the incidence of intra-operative and immediate postoperative complications with midazolam-pethidine combination (group P) and midazolam-tramadol combination (group T) in a cohort of patients undergoing regional anaesthesia.

Patients and Methods

Forty American Society of Anaesthesiologists (ASA) 1-111 patients, both female and male, between 40-65 years of age undergoing either inguinal hernia repair or transurethral resection of the prostate (TURP) under sub-arachnoid block (spinal anaesthesia) were included in the study. The patients were randomly divided into two groups

P and T using the opaque sealed envelope method. A total of 20 patients in each group (P and T) were required in order to have a power of 80 percent, level of significance of 5 percent and a change in haemodynamic measures from baseline to the endpoint of 20 percent. Patients with history of renal or hepatic dysfunction, convulsive disorders, and allergy to study drugs were excluded, as were those who were unable to follow instructions, or refused to have surgery under regional anaesthesia or in whom regional anaesthesia was contraindicated. Approval was taken from the institutional ethical review committee and written informed consent was obtained from all patients.

All patients were premedicated with oral midazolam 7.5mg given one hour prior to surgery. On arrival in the operating room a dorsal hand vein was cannulated with an 18 gauge cannula and infusion of Ringer's lactate solution was started. A continuous electrocardiogram (ECG-lead 11), the finger probe of a pulse oximeter and a non-invasive blood pressure (BP) monitor set to take readings at five minute intervals were attached to the patient. Datex Ohmeda AS/5 monitors were used for all patients. After a resting period of five minutes a baseline reading of heart rate, systolic, diastolic and mean blood pressure, oxygen saturation on room air and respiratory rate was recorded. Monitoring was continued during the performance of the regional block and throughout surgery. All patients were given oxygen 4L/minute via Hudson facemask.

After performance of a successful spinal block, sedation was started with midazolam 0.03 mg/kg body weight intravenous (IV) bolus given over ten seconds. This was followed two minutes later with pethidine 20 mg IV bolus (group P) or tramadol 20 mg IV bolus (group T). The study drugs were administered over 20 seconds. Both pethidine and tramadol were diluted to a concentration of 10 mg/ml and drawn in a 5 ml syringe which was labeled as "study drug". Blinding was done by ensuring that the anaesthetist concerned with giving the drug (Anaesthetist A) was different from the one observing the patient and recording the parameters (Anaesthetist B). Anaesthetist A prepared the study drug.

The criteria for administering additional boluses of pethidine 10 mg IV in group P patients and tramadol 10 mg IV in group T patients included an increase in blood pressure of more than 30% above the control values and patient's request if he/she experienced pain, discomfort or anxiety. Intraoperative monitoring included ECG, non-invasive blood pressures (systolic, diastolic and mean [SAP, DAP, MAP]), heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation (SpO₂). Level of sedation throughout the procedure was assessed using the Ramsay Sedation Score (RSS) (1 = anxious, agitated, restless; 2 =

cooperative, tranquil, oriented; 3 = drowsy but responsive to verbal commands; 4 = asleep, responsive to light stimulation, sound; 5 = asleep, slow response to stimulation; 6 = asleep, no response to stimulation). The aim was to keep the RSS between 2 and 4 throughout the procedure so that the patient remained responsive to commands. The readings were charted every ten minutes on a pre-designed study form. The lowest value of oxygen saturation and the highest and lowest pulse rate recorded during the procedure were also charted. Any other problems like snoring, vomiting, or restlessness were also noted. Administration of any additional bolus was recorded alongwith the time and the reason for the administration. At the end of the surgery the surgeon was asked to assess the operating conditions as poor, fair or good.

Patients were followed up in the post-anaesthesia care unit (PACU) and their haemodynamic status and respiratory rate were monitored every 15 minutes by the PACU nurses who were blinded to the study group. The presence of complications like nausea or vomiting, hypertension or hypotension, bradycardia or tachycardia was also noted. The patient was visited in the ward on the same evening, four hours after discharge from the PACU, by one of the researchers and asked about any nausea or vomiting after discharge from the recovery room. Patient's assessment of his operating room experience and his willingness to have the same anaesthetic technique again, if required, was also asked.

The data was entered and verified using the statistical software SPSS version 13.0. Means and standard deviations were computed for group P and T separately for continuous variables and comparison of means at the baseline for the two groups were made using independent samples student's t-test. Mann-Whitney test was used to compare intra-operative sedation score at baseline for the two groups. Repeated Measures ANOVA was used to compare systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate and oxygen saturation at different time points between the two groups. Chi-square test was used for categorical data. Repeated Measures ANOVA for ordinal measures was used to compare sedation scores at different time points between the two groups. A p-value of less than 0.05 was taken as statistically significant.

Results

The two groups were comparable demographically [Table 1]. There were no statistically significant differences between the two groups with regards to the systolic blood pressure (group P 120 versus group T 130; P-value = 0.18), diastolic blood pressure (group P 75 versus group T 77; P-value = 0.5) and the mean blood pressure (group P 90 versus group T 97; P-value = 0.5) [figure 1] at any point in time.

Table 1. Patient Characteristics: (Mean, Standard deviation or absolute numbers); P = Pethidine, T = Tramadol.

Demographic Data	Group P (n=20)	Group T (n=20)
Age (Yr)	54 (29 - 65)	58 (33-65)
Weight (Kg)	70.3 (10.4)	69.2 (11.7)
Gender (Male / Female)	11/9	10/10
ASA I/II/III (n)	5/11/4	6/9/5
TURP/Inguinal hernia repair	8/12	8/12

Table 2. Intra-operative Sedation Scores.

Time	Group P						Group T							
	m	Sedation Score					n	Sedation Score						
		1	2	3	4	5	6	1	2	3	4	5	6	
10 mins	20	0	5	11	3	0	1	20	1	5	7	6	1	0
20 mins	20	0	5	7	5	0	3	20	1	4	7	4	4	0
30 mins	20	0	7	5	5	0	3	20	0	4	9	4	3	0
40 mins	20	0	7	4	6	0	3	20	0	4	11	3	1	1
50 mins	17	0	5	5	5	1	1	19	0	8	7	2	2	0
60 mins	13	0	4	5	3	1	0	16	0	5	6	4	1	0

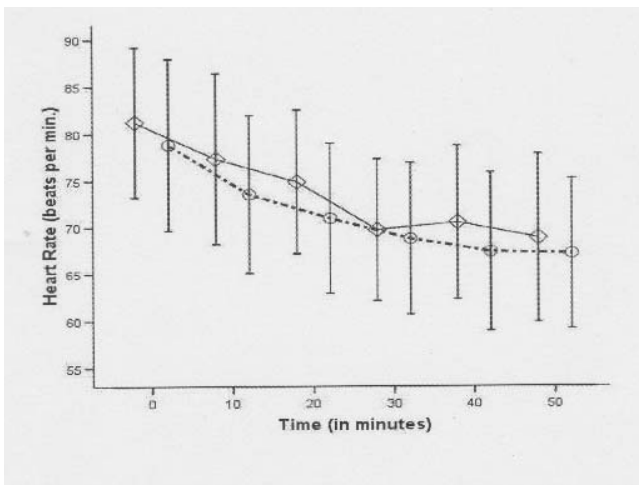
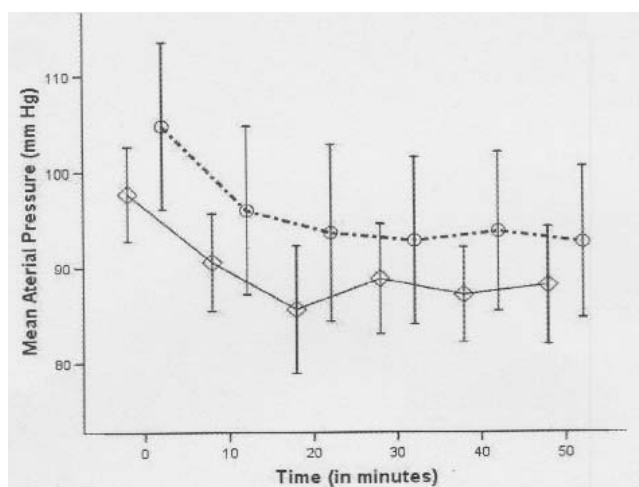


Figure 1. Intraoperative mean arterial pressure and heart rate in the two groups at different time points. P = patients given Pethidine T = patients given Tramadol

The mean heart rate was also not statistically different between the groups [Figure 1] (group P 71 versus group T 67; P-value = 0.43), however, a decline in HR and arterial pressure was observed with time in each group [Figure 1], although all readings were within 20% of baseline. The maximum decline was observed in group P, i.e. 13 percent from the baseline in a time period of 50 minutes, while it was under 12 percent in group T. None of the patients in either group displayed any episode of significant tachycardia or bradycardia, the heart rate remaining within 20% of baseline at all times.

There was no statistically significant difference in the intraoperative peripheral oxygen saturation (SpO₂) within the groups or between the two groups at any point in time (group P 98 [SD 1.2] versus group T 99 [SD 1.16]; P-value = 0.88). The SpO₂ did not drop below 95% in any patient at any time. There was also no statistically significant difference in the respiratory rate within the groups or between the two groups at any point in time (group P 17 [SD 3.7] versus group T 17 [SD 3.4]; P-value = 1). There was no incidence of airway compromise or fall in respiratory rate to below 10/minute in any patient.

Ten minutes after administration of the study drugs, 19 patients in group P and 18 patients in group T showed the desired levels of sedation, i.e., sedation score of 2, 3 or 4. One patient in group P was oversedated having a score of 6 and one patient in group T had a sedation score of 5 at 10 minutes, whereas one patient in group T had a score of 1 showing inadequate sedation. At 30 minutes three patients in group P had a sedation score of 6 and three in group T had a score of 5, whereas all the other patients in both groups had achieved desired levels of sedation, whereas at 60 minutes only one patient in each group showed sedation score of 5 [Table 2]. Surgical procedure finished within 60 minutes in seven patients in group P and four patients in group T. In the remaining patients, surgery finished within the next 30 minutes. No significant difference was observed in the sedation scores between the two groups at any point of assessment (p=0.1035), although a significant difference was observed in the sedation scores within the group with time, the score increasing with time. This difference was most significant between time 0 minute and time 50 minutes (p<0.0001).

Two patients in group P needed additional boluses. One patient developed shivering during TURP and was given 10 mg bolus of pethidine twice, after which the shivering settled. The second patient in group P was given a bolus because he became restless towards the end of left inguinal herniorrhaphy as the procedure became prolonged. Only one patient in group T required an additional bolus as he was feeling some discomfort near the end of the

procedure. There was no incidence of intraoperative complications (tachycardia, bradycardia, hypoxia, vomiting, snoring etc) in either group.

Similar to the intraoperative parameters, no statistically significant difference was found between the two groups in the PACU with regards to the blood pressure (MAP: group P 92.5 [SD 13.4] versus group T 97.8 [SD 17]; P-value = 0.25), heart rate (group P 72 [SD of 21] versus group T 67 [SD 15]; P-value = 0.46), respiratory rate (group P 19 [SD 3] versus group T 19 [SD 2]; P-value = 0.52) and the SpO₂ (group P 98.95 [SD 1] versus group T 98.49 [SD 1.5]; P-value = 0.33). One patient in group P and two in group T had nausea and vomiting in the PACU which responded to intravenous metoclopramide. There was no incidence of complications like hypertension, hypotension, tachycardia or bradycardia in any patient during their stay in the recovery room. There was no statistically significant difference in the length of PACU stay with the two techniques with all patients discharged within two hours in both groups.

All patients except one in each group were willing to have the same anaesthesia technique in any subsequent procedure, although the two patients who refused reported satisfaction with their operating room stay and did not report of any complaints during the procedure. All the surgeons expressed satisfaction with the technique.

Discussion

Our study shows that both midazolam-pethidine combination or midazolam-tramadol combination, when used for intraoperative sedation during regional anaesthesia, are satisfactory in terms of cardio-respiratory stability, acceptable sedation, acceptability to the patient and surgeon, and the incidence of intraoperative and immediate postoperative complications.

The aim of sedation during regional anaesthesia is to permit the patient to tolerate the procedure with minimal anxiety and discomfort.⁷⁻¹⁰ Ideally during sedation, the patient should be relaxed, comfortable and cooperative throughout the procedure.^{2,11} An ideal sedation technique should produce a rapid and smooth onset of action with minimal cardiorespiratory depression and fast recovery.² Benzodiazepines tend to have prolonged duration of action and even midazolam when used as a sole agent, may cause prolonged memory impairment and delayed recovery.¹² Propofol has ideal pharmacokinetic properties for this purpose, but its cost is still a limiting factor in a developing country like ours. In our hospital, it is a common practice to use midazolam alongwith pethidine or fentanyl, when available, for sedation during regional anaesthesia. The addition of opioids to the sedation regimen allows for a

smaller dose of midazolam to achieve the desired effect, thus avoiding delay in recovery besides adding an element of analgesia to the sedation, but can lead to an increase in the incidence of respiratory depression and other side effects like nausea and vomiting.^{10,13}

Tramadol hydrochloride has been shown to be safe and reliable with a low incidence of side effects when used as an adjuvant to regional anaesthesia for sedation and analgesia without loss of cooperation in patients of all ages.¹⁴ An outstanding aspect of tramadol is its extremely low ability to produce clinically relevant respiratory depression, which is claimed to be negligible in comparison with other opioids.¹³⁻¹⁶ The most common adverse effects of tramadol include dizziness, incoordination, nausea, vomiting and dry mouth¹⁶, but the dose required for sedation in combination with midazolam is low enough to prevent most of these side effects.

The results of this study have shown that both midazolam-pethidine combination and midazolam-tramadol combination produce satisfactory sedation in patients undergoing surgical procedures under regional anaesthesia. The two groups did not show any significant cardiorespiratory depression, and all patients in both groups remained haemodynamically stable throughout their surgical procedures. Patients in group T demonstrated a slight rise in systolic, diastolic and mean arterial pressures soon after administration of tramadol, which settled down within 10-15 minutes. This rise was not clinically significant. Such haemodynamic effects have earlier been recorded after intravenous administration of tramadol¹⁷, where during anaesthesia systolic arterial pressures were found to rise 14-16 mm Hg and diastolic pressures 10-12 mm Hg after I.V injection of tramadol for 4-6 minutes, returning to baseline within 15 minutes.

All other parameters including heart rate, respiratory rate and oxygen saturation remained stable in both groups, which is consistent with other authors' reports on tramadol.^{3,13,16,17} In general, the heart rate showed a lower value in group T patients compared to those in group P, both during surgery (Figure 1) and in the PACU (Table 1), but this difference was not statistically significant. The frequency of side effects (tachycardia, bradycardia, hypoxia, vomiting, snoring etc) was low in both groups, both during the operation and in the recovery period. Only three patients, two in group P and one in group T, required additional boluses. One patient in group P developed shivering during TURP and was given 10 mg bolus of pethidine twice, after which the shivering settled. Both pethidine and tramadol are known for their efficacy in the treatment of postoperative shivering and shivering during spinal anaesthesia¹⁸, therefore the available study drug

(pethidine in this case) was utilized to manage this problem intraoperatively. The two other patients who received one additional bolus each, both required it towards the ends of their procedures, when they felt discomfort and were getting restless. As in most of the other patients included in the study, surgical procedures were of shorter duration, this problem was not seen in them. Further studies designed to include patients undergoing procedures of longer duration (two hours or more) need to be undertaken to determine the time when most patients receiving these drug combinations would require a repeat bolus.

All the surgeons showed satisfaction with the operating conditions in all patients in both groups. As tramadol, unlike pethidine, is not a controlled drug in Pakistan, its ease of availability is an added advantage to its use for the purpose of sedation during regional anaesthesia. Thus, our results suggest that midazolam-tramadol combination can be used as an alternative to midazolam-pethidine combination as an adjunct to regional anaesthesia. The authors believe that this combination would be of particular advantage in elderly patients who are at an increased risk of respiratory depression with opioid agents, but further research needs to be done, using this combination in elderly and high risk patients, before any recommendations could be made.

Conclusion

Both techniques appeared satisfactory in terms of physiological stability, acceptable sedation, and patient and surgeon acceptability. Thus our results suggest that midazolam-tramadol combination may be used as an alternative to midazolam-pethidine combination for sedation during surgical procedures performed under regional anaesthesia.

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