A Comparison of Equisedative Infusions of Propofol and Midazolam for Conscious Sedation During Spinal Anaesthesia - A Prospective Randomized Study

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ABSTRACT

Background: Supplemental sedation with an intravenous agent is often required to allay fear and anxiety in patients subjected to spinal anaesthesia .We studied and compared the properties of propofol and midazolam as equisedative continuous infusions.

Patients & Methods: 100, ASA grade 1 and 2 patients, 18 to 60 years of age, undergoing spinal anaesthesia, were randomly allocated to receive either propofol 1mg/ml or midazolam 0.1mg/ml in 50ml syringes through syringe pump. The infusion rates were titrated in order to maintain a desired sedation score of 4 on the Observer's assessment of alertness/ sedation scale. Anxiety score was assessed at regular intervals by a single observer in all cases, using a 100mm visual analog scale.Intraoperative and postoperative amnesia was assessed using visual task of recall of pictures and verbal task of recall of words.

Results: Propofol infusion was found to be superior to that of midazolam as it showed a statistically significant faster onset in achieving the desired sedation score, significantly lower mean anxiety scores, a clear headed, rapid recovery and significantly lesser postoperative impairment of recall, but midazolam infusion was seen to be associated with deeper intraoperative amnesia over the former which was beneficial.

Conclusion: Equisedatine infusion of propofol & midazolam as an adjunct & spinal anaesthesia offer good anxiolysis and cardio respiratory stability. Propofol her faster onset & recovery while midazolam provides better intraoperative annesia.

KEYWORDS: Conscious sedation, Propofol, Midazolam, Spinal anaesthesia, Amnesia, Anxiolysis, Recall.

The use of spinal anaesthesia is often limited by the unwillingness of patients to remain awake during surgery.[1] The operating room is an anxiety provoking environment and chemically induced tranquility improves acceptance of regional techniques. Intravenous sedative medications are also useful for the same as positioning for surgery can be uncomfortable and spontaneous movements by an inadequately sedated patient can cause interference with the surgical procedure.[2] There are some constraints on the choice of these supplemental medications, though, as long acting amnesia is also undesirable.[3] The ambulatory day case surgical patient is expected to remember all the postanaesthetic and post surgical discharge instructions given to him or her. Hence these drugs should be carefully selected.

Conscious Sedation is a minimally depressed level of consciousness that retains the patient's ability to maintain his or her airway independently and continuously, and to respond appropriately to physical stimulation and verbal command, produced by pharmacologic or non-pharmacologic methods alone or in combination.[4] With conscious sedation only some of the centers in the medullary reticular formation and thalamus are depressed in a dose dependent manner.[5] Thus, this level of sedation additionally provides the benefit of preservation of protective airway reflexes, especially in monitored anaesthesia care.

An ideal supplemental sedative should provide, effective anxiolysis, an easily controllable level of sedation, predictable depth of amnesia, a rapid and clear headed recovery, minimal intraoperative side effects, no evidence of cumulation and minimal postoperative side effects. Numerous agents ranging from methohexitone to etomidate and droperidol to dexmedetomidine have been used as sedative adjuvants to spinal anaesthesia, with their very own advantages and disadvantages over one another.

Midazolam, a short acting water soluble benzodiazepine, has a fast onset and short recovery time, because of which it is one of the most widely used sedative in spinal anaesthesia.With a low context sensitive half time (70 minutes for a four hour long infusion and up to 100 minutes for longer infusions), it can be easily titrated as per the need of the user, making its use well suited for ambulatory conscious sedation techniques. Similarly, Propofol, with its early metabolism to inactive metabolites, has a rapid onset

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of action and an extremely short recovery. It has a context sensitive half time of 25 minutes for a three hour long infusion and 50 minute for a prolonged infusion and thus can also be easily titrated for achieving conscious sedation.[6]

The objective of this study was to compare two of the most popularly used sedative drugs, propofol and midazolam, given in equisedative continuous infusions, in spinal anesthesia for their anxiolytic, sedative, amnestic, haemodynamic & recovery characteristics, to find out whether Propofol and Midazolam suffice the need of "Ideal supplemental sedation", and as to which stands superior over the other in the same.

PATIENTS & METHODS

This prospective, randomized study was carried out following approval from the institutional ethics committee. Patients included in this study were informed about the procedure in their own language, and a written informed consent was taken from all of them.

100, ASA grade 1 & 2 patients, between 18 to 60 years of age, weighing 40 to 70kgs,of both genders, scheduled for either elective or emergency lower limb or lower abdominal surgical procedures, which were anticipated to complete within 2 hours, were included. They were initially assessed in the preoperative checkup room, where along with general and systemic examinations, baseline measurements of heart rate, mean arterial pressure by noninvasive sphygmomanometer, pulse oximetry, respiratory rate, and baseline anxiety score on a 100mm visual analog scale were made by a single observer. Anxiety Score was recorded as 100 for those who were extremely anxious and 0 for those who were not anxious.

Patients with history of allergic reaction to the study drugs, those with significant cardiac , pulmonary, hepatic or renal dysfunction, Obese patients (>130% ideal body weight), those with history of chronic use of sedative drugs, full stomach patients, pregnant patients and epileptic patients were excluded from the study. Sedative premedication was not given to any patient to avoid interference with results. One intravenous cannula was inserted into the patient's dorsum of hand and Ringer's lactate infusion was started. Another wide bore intravenous access was established on the forearm of the other limb, for administration of the study drug infusion.

The patients were subsequently shifted to the operating room and were randomly allocated to receive either Propofol 1mg ml^{-1} or Midazolam 0.1mg ml^{-1} in 5% dextrose in a 50 ml syringe through Injectomat MC Agilia 018190 syringe pump, Fresenius Kabi Laboratories, France. Propofol was initially started at an infusion rate of 6mg kg^{-1} hr^{-1} and Midazolam was started at an initial infusion rate of 0.5mg kg^{-1} hr^{-1} in order to achieve a desired level of sedation of score 4 on the Observer's Assessment of Alertness/ Sedation Scale and the time required in minutes to achieve score 4 was noted in each case by a single observer. The infusion rates were later lowered or raised in order to maintain sedation score 4.

Five minutes after the commencement of the sedative infusion subarachnoid black was instituted in the lateral position via a 22 or 23 gauge spinal needle by injecting sufficient doses of bupivacaine 0.5% in order to achieve an adequate sensory block for the proposed surgery. The optimum level of sensory block was assessed 10 minutes after the injection of the spinal drug and noted.

Heart rate, mean arterial pressure, SPO_2, respiratory rate and anxiety score were recorded initially at 5 minute intervals for 10 minutes and later at 10 minute intervals till the end of procedure. All patients were given supplemental oxygen via venture mask at 4 liters/minute.

Visual Task of Recall of Pictures

Immediately prior to receiving the sedative infusion, each patient was shown a picture of a commonly occurring object (e.g. kite, dog, tree etc.) to assess their baseline recall (picture1)

At 30 minutes after starting the sedative infusion, another picture (picture 2), different from the first picture, was shown to the patient, for assessing intraoperative

Observer's Assessment of Alertness/Sedation Scale

Responsiveness	Speech	Facial Expression	Eyes	Score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethargic Response to name spoken in normal tone	Mild slowing	Mild relaxation	Glazed or mild ptosis (<half the eye)	4
Responds only after name is called out loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis	3
Responds only after mild prodding or shaking	Few recognizable words	Marked relaxation	Glazed and marked ptosis	2
Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation	Glazed and marked ptosis	1

recall.

Similarly, at the end of the sedative infusion a third picture (picture 3) different from the first two pictures was shown to the patient. Each picture was shown to the patient for 30 seconds, during which time the patient was prompted to describe all details he or she saw in the picture.

Verbal Task of Recall of Words

30 minutes after commencing the sedative infusion, in order to assess intraoperative recall, a list of 5 commonly used words were told to the patient, close to him, by a single observer. Each word was repeated twice at 5 second intervals with a pause of 10 seconds between two different words.

4 hours postoperatively, the patient was asked to recall the preoperative, intraoperative pictures and words shown or spoken to him or her. Those correctly recalled were analyzed. If the recall of pictures was unsuccessful, the patients were asked to recognize any of the previously presented pictures among other pictures they had not seen by showing a mixed collection of 5 displayed and undisplayed pictures. Patients were also asked regarding recall of insertion of spinal needle.

During the intraoperative period, evidence of pain on commencement of infusion, bradycardia, hypotension, apnea, involuntary movements, limb twitching, excitatory phenomenon, bradypnea, fall in oxygen saturation, confusion and appearance of rash was noted.

The sedative infusion was stopped 5 minutes prior to skin closure or end of surgery. Duration of procedure (Dp) was taken as time from commencement of infusion to stoppage of infusion. Total drug used was measured in milligrams.

In the immediate postoperative period, time taken by the patient to achieve sedation score 5, and correctly give full name and address (recorded preoperatively) was noted as Recovery time. Postoperative side effects, if any, such as, nausea, vomiting, apnea, confusion, delirium, etc. were noted and treated.

Statistical Analysis

Block randomised allocation method was used to divide the patients into two equal groups (n==50), with the help of numbered cards.

The results were analyzed using Student's paired & unpaired t test and chi square test. A 'p' value of <0.05 was considered as statistically significant, whereas 'p' value of <0.001 was taken as highly significant.

RESULTS

Demographic data in both the groups was comparable, the mean age being 43.02±13.977 years in the propofol group, 37.42±14.419 years in the midazolam group. Similarly, Mean weight in both the groups was 54.08 ±6.110 kg, & 54.06 ±8.094kg respectively. The groups were also comparable with respect to sex distribution. (Table 1: Patient characteristics)

Mean duration of surgery, which was taken as time from surgical incision to surgical closure, was comparable in both the groups (38.76 ±12.695 min, and 35.6±13.749 min, respectively) and so was the mean duration of sedative infusion.(Table 2:Procedure characteristics). Mean of maximum level of sensory blockade achieved after spinal anaesthesia was comparable as well. Mean infusion rates were 3.190±1.049 mg kg^{-1} hr^{-1} for propofol and 0.077±0.070 mg/kg/hr for midazolam which were required to maintain the same level of sedation. Mean of the total drug requirement was 133.6±13.404mg for propofol and 3.805±0.974mg for midazolam.

Table 1
Patient Characteristics

Group	Propofol	Midazolam
No. of cases (n)	50	50
Mean age (years)	43.02± 13.977	37.42±14.419
Male: female	26:24	27: 23
Mean weight (kg)	54.08±6.110	54.06±8.094

Table 2
Procedure characteristics

Group	Propofol	Midazolam
Mean duration of surgery (min)	38.76±12.695	35.6±13.749
Mean duration of infusion (min)	41.88±12.772	48.82±13.836
Mean Infusion Rates (mg/kg/hr)	3.190±1.049	0.077±0.070
Mean of total drug required (mg)	133.6±13.404	3.805±0.974
Mean of maximum level of sensory blockade	T8.12 ± 1.858	T8.92 ± 1.977

The baseline mean anxiety scores on the 100mm visual analog scale were, 95.4±4.392 for propofol and 94.2±4.328 for midazolam, which were statistically comparable. Mean anxiety scores were seen to rapidly fall at 5 minutes and then at 10 minutes of commencement of sedative infusion. This fall was seen to be statistically highly significant at these two points in both the groups (p<0.001).At the point of 10 minutes, the mean anxiety scores were 3.6±5.252 for propofol and 2.7±4.625 for midazolam.The intergroup difference was however statistically insignificant. (figure 1)

At 20 minutes the score further dropped down to 1±2.857 in the propofol group and 1.6±3.703in the

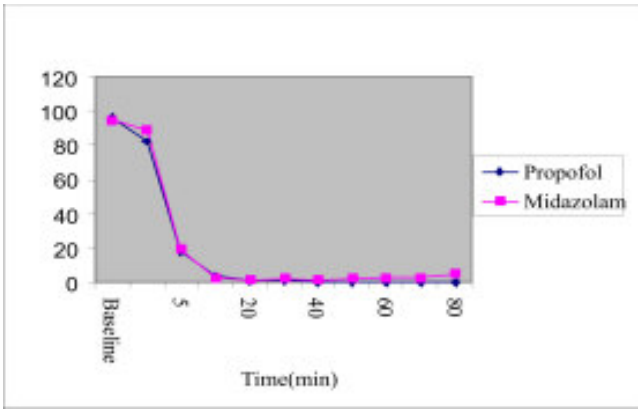

Figure 1
Mean anxiety scores

midazolam group. The anxiety score reached a 0 at around 30 minutes in the propofol group and was maintained at 0 up to the postoperative period. The anxiety score in the midazolam group never reached 0,the lowest value being 1.6, and was maintained in the range of 1.6 to 2.8 up to the end of procedure and postoperatively. The difference in the two groups was statistically insignificant.

After starting the sedative infusion, 5 minutes prior to giving the subarachnoid block, the mean time required to achieve sedation score of 4 was noted as 6.62±1.091

Table 3
Sedative Properties

Group	Propofol	Midazolam
Mean time taken to achieve sedation score 4 (min)	6.62±1.091**	10.1±1.373**
Mean time taken to recover from sedation (score 5)(min)	4.16±1.404**	10.44±2.149**

minutes in the propofol group, while it was seen to be 10.1±1.373 minutes in the midazolam group. This difference in the mean time was seen to be statistically highly significant (p<0.001). (Table 3: Sedative properties)

Mean time taken to recover from sedation after stoppage of sedation, 5 minutes prior to skin closure was noted as 4.16±1.404 minutes in the propofol group, and 10.44±2.149 minutes in the midazolam group. This difference in the mean recovery times was seen to be statistically highly significant (p<0.001).

Mean heart rate, Mean arterial blood pressure, mean SPO2, mean respiratory rate were compared in both the groups, at regular intervals throughout the procedure.

Mean heart rate in both the groups remained stable throughout the procedure, as compared to their respective mean baseline heart rate values (p>0.05).Similarly, Mean arterial pressure values were not significantly altered from their respective baseline values, in both the groups,

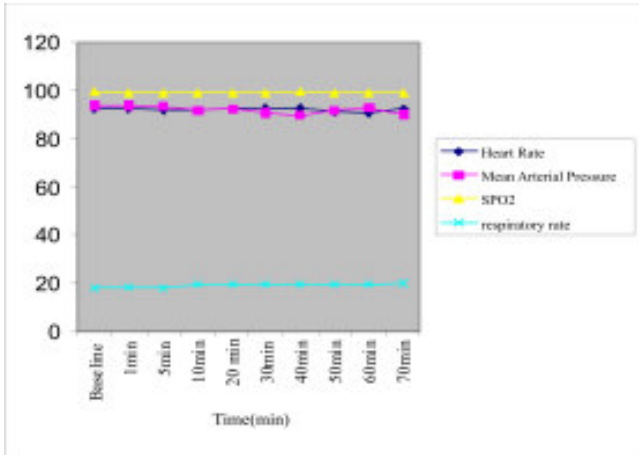

Figure 2
Vital parameters with propofol

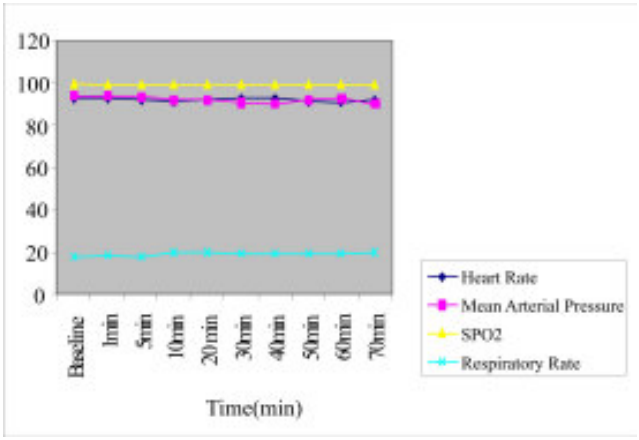

Figure 3
Vital Parameters with midazolam

throughout the procedure, barring a few statistically insignificant changes (p>0.05). (Figure 2 and Figure 3)

Mean values of SPO2 remained stable throughout the procedure in both the groups, with no statistically significant aberrations (p>0.5). Also, mean respiratory rates in both the groups did not change significantly throughout the procedure from their mean baseline values (p>0.5).

Baseline recall was comparable in both the groups as evidenced by recall of picture 1, as 98% patients in the propofol group and 96% patients in the midazolam group could recall the picture shown to them, when asked four hours postoperatively. Intraoperative amnesia was deep in both the groups as evidenced by 8% of patients in the propofol group being able to recall picture 2 and 4% patients being able to recall the same in the midazolam group. Intraoperative amnesia was seen to be deeper with midazolam as only 6% patients could recall 1 of the 5 words spoken to them intraoperatively, as compared to 36% patients in the propofol group who could do the same. None of the patients in both the groups could recall more

Table 4
Amnestic Properties

Group	Propofol	Midazolam
Recall of picture 1	98%	96%
Recall of picture 2	8%	4%
Recall of picture 3	62%	16%
Recall of all 5 words	0%	0%
Recall of 3 words	0%	0%
Recall of 1 word	36%	6%
Inability to recall any word	64%	94%
Recall of insertion of spinal needle	8%	54%

than 1 word, while 64% in the propofol group and 94% patients in the midazolam group were unable to recall even a single word spoken to them intraoperatively. (Table 4: Amnestic Properties)

A greater percentage of people in the midazolam group (54%) as compared to lesser in the propofol group (8%) could recall the insertion of the spinal needle.

There were negligible postoperative side effects in either of the groups. 4% patients in the midazolam group complained of giddiness, and 2% of the patients in the same group complained of mild nausea, which subsided without any treatment. There was no episode of vomiting, airway obstruction, etc., in any of the patients in both the groups. (Table 5: postoperative side effects)

Table 5
Postoperative Side effects

Group	Propofol	Midazolam
Giddiness/Drowsiness	0%	4%
Nausea/Vomiting	0%	2%
Bradycardia	0%	0%
Hypotension	0%	0%
Airway problems	0%	0%

DISCUSSION

Loud noises, untoward remarks, etc., perceived in the intraoperative period by patients, can have long term undesirable effects on their psyche.[7] The provision of good sedation, thus, becomes increasingly important, if the advantages of spinal anaesthesia are to be exploited to the full.

The most widely used technique for administering sedation in regional anaesthesia is the intermittent intravenous bolus dose technique. This technique has been shown to be associated with peaks and troughs in plasma concentration producing significant side effects and delayed recovery.[8] Continuous infusions have been proved to produce, lesser side effects, faster recovery, easy controllability over the desired depth of sedation and, should the regional block prove to be ineffective, easy conversion to general anaesthesia.[9,10]

We chose the OAA/S scale for assessment of sedation over other scales suggested by different authors,[11] as it was easier to use, comprehensive and inclusive of parameters such as facial expression and eyelid ptosis in addition to speech and responsiveness, which are not there in other sedation scales. Similarly the OAA/S scale has been shown to have an inter-rater agreement that varies between 85% and 96% depending on the level of sedation, which is higher than most of the popular scales used for the same purpose, making it the most suitable choice if precise assessment of sedation is required.[12] The score of 4 was chosen as it most closely met the conditions of conscious sedation.

Sedation: In our study, the desired level of sedation was achieved much faster by propofol infusion as compared to midazolam, (6.62 vs. 10.1minutes) and the difference in the findings was seen to be highly significant ($p<0.001$).Similarly, Recovery with propofol was much faster than that with midazolam (4.16 vs. 10.44minutes) and the difference in the findings was again statistically highly significant ($p<0.001$).

In a similar study, 13 the authors compared midazolam and propofol infusions for BIS guided sedation in spinal anaesthesia. The time to reach the required sedation level in their study was 11 min in the Midazolam group while it was 6 min in Propofol group ($p=0.0$). Recovery in their study, with midazolam was slower than with propofol (18.6 ± 6.5 vs. 10.10±3.65 min) ($p=0.00$). Their findings were thus, similar to our findings. Some other authors have studied the effects of propofol and midazolam infusions as sedative supplementations to regional anaesthesia and their findings were comparable to ours.[14, 15]

Anxiolysis: We saw a rapid fall in anxiety scores from their respective baseline values in both the groups at 5 minutes and at 10 minutes from the commencement of the infusions, thus showing the rapid onset anxiolytic effect of both the drugs. However, propofol outweighed midazolam in its advantage of maintaining a mean score of 0 for a pretty longer time, while with midazolam the mean anxiety score never reached 0 and ranged between 1.6 and 2.8.The inter group difference in the mean anxiety scores was statistically insignificant ($p>0.5$).In a similar study[16] the anxiolytic property of midazolam and propofol was compared for outpatient bronchoscopic procedures. According to the authors, midazolam and propofol were comparable in terms of anxiolysis, a finding which was similar to ours. The VAS scale used by us was similarly used by other authors to assess anxiolysis with propofol infusion in regional

anaesthesia, and their findings were comparable with ours.[17]

Vital parameters: Propofol and midazolam both are known to inhibit sympathetic activity and decrease systemic vascular resistance resulting in some amount of Bradycardia and hypotension.[18,19] We observed that, both propofol and midazolam in sedative infusions did not significantly alter mean heart rate or mean arterial blood pressure throughout the procedure. Our findings were comparable to those of some other authors who found that subanaesthetic sedative doses of midazolam and propofol do not alter baseline cardiovascular variables.[20]

Similarly, both these drugs are also known to depress respiratory function when given in inducing doses.[21-23] In our study, neither propofol nor midazolam infusion, caused any significant alteration in mean respiratory rate or mean SPO_2 throughout the procedure. The cardio-respiratory function stability seen with both the drugs in our study can be possibly attributed to the fact that they were administered in subanaesthetic infusions.

Amnesia: Both propofol and midazolam possess the property of causing transient anterograde amnesia with impairment of, chiefly, the explicit memory.[24,25] While intraoperative amnesia is desirable for the psychological wellbeing of the patient, postoperative amnesia is undesirable, as the ambulatory patient is expected to remember postsurgical discharge instructions in day-case surgical procedures.

We used the visual task of recall of pictures to assess, intraoperative and postoperative recall. A verbal task of recall of words was also used to assess intraoperative amnesia.[26,27] These tasks had to be modified to some extent, from the form in which they were originally suggested by the authors, in order to suit the requirements of our social setup, keeping in mind, the modest literacy of majority of our patients.

It appeared to us that midazolam produced deeper intraoperative amnesia in comparison to propofol. The amnesia with Midazolam extended into the postoperative period as well, thus producing more postoperative amnesia than propofol.Our results were comparable to those seen by other authors who used similar tasks for assessment of amnesia.

A greater proportion of patients in the midazolam group could recall the insertion of the spinal needle than propofol.This difference could possibly attributed to the slower onset of sedation with the former, as the spinal needle prick was given just 5 minutes after starting the sedative infusions.

Postoperative side effects: The postoperative recovery period was relatively uneventful except for a few minor complaints. 2 patients in the midazolam group in our study complained of giddiness, in lying down position, on opening their eyes. This complaint lasted for about 15 minutes postoperatively and subsided without any treatment. 1 patient in the midazolam group complained of moderate nausea, which was not followed by vomiting. This symptom lasted for a period of 10 minutes and subsided without any treatment. Patients in the propofol group did not show any postoperative complications. None of the patients showed evidence of airway problems, involuntary movements etc.

When given as a sedative adjunct to spinal anaesthesia, both propofol and midazolam in equisedative infusions offer good anxiolysis and good cardio respiratory stability. Propofol has the advantage of providing faster onset of sedation, a rapid clear headed recovery from the same and lesser postoperative impairment of recall while midazolam offers better intraoperative amnesia.

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