Original article

Midazolam as an induction agent in comparison with propofol as a safe and effective alternative

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Abstract:

Introduction: Propofol produce rapid and smooth induction of anesthesia, with rapid metabolism, which would allow it to be used for the maintenance of anesthesia and free from the risk of anaphylactic reactions. Midazolam a new short acting water soluble Benzodiazepine with cardio vascular effects similar to that of diazepam may be an effective alternative for induction of anesthesia.

Methods: In this randomized study, all together 48 patients undergoing various surgical procedures belonging to Orthopedic, General Surgery and Gynecological Surgeries constituted the study group. Group-I (Midazolam Group) received intra-venous Midazolam 0.15mg/Kg for induction of anesthesia and Group-II (Propofol Group) received 2mg/kg intravenous Propofol for Induction of Anesthesia. Induction time, Heart Rate, Non invasive blood Pressure is recorded at 1minute interval for 5 minutes and after that at an interval for 5 minutes for another 30 minutes. Demographic data was analyzed by Student's t-test.

Results: The study showed no statistical significance in hemodynamic responses with either Midazolam or Propofol as an induction agent for General Anesthesia but there was statistically difference with respect to heart rate (P=0.001) .

Conclusion: Midazolam was proven effective compared to Propofol as an induction Agent.

Keywords: Anesthesia, Midazolam, Propofol.

Introduction

An increasing interest in intra-venous anesthetics techniques has resulted from the availability of more efficacious intravenous agents due to the rising cost of traditional volatile agents and because of concern over anesthetics gas pollution in the operation room. An ideal intravenous anesthetic agent should relatively and pleasantly induce anesthesia in one arm brain circulation time. It should cause minimal cardiovascular and respiratory depression but should not cause drug interactions, excitatory phenomena, nausea, vomiting or toxicity. Various intravenous anesthetic agents have been introduced, but thiopentone sodium remains the gold standard while comparing with other agents. The main drawback of thiopentone sodium is its longer elimination half life. Thus, there is requirement of an anesthetic agent with short half life that will allow rapid recovery. For the day care surgery, the rapid recovery anesthetic agent is required. Propofol is the result of such a requirement which was introduced by department of clinical research at the laboratories of ICI pharmaceuticals. It has property of rapid and smooth induction, rapid metabolism and free from the risk of anaphylactic reactions.1 Midazolam a new short

acting water soluble Benzodiazepine with cardio vascular effects similar to that of diazepam may be an effective alternative for induction of anesthesia. Hence Midazolam is being evaluated as an induction agent in comparison with Propofol as a safe and effective alternative to Propofol.

Methods

This is the prospective, randomized and analytical study performed in the department of Anesthesiology in Dhulikhel Hospital, Dhulikhel, Kavre. The study population consisted of 48 patients undergoing various surgical procedures for Orthopedics Surgeries, General Surgeries and Gynecological Surgeries. The inclusion criteria was age group of 18-50 years, both the gender, ASA-I and II, weight of 35-75kgs. The patient with uncontrolled Hypertension, Hypersensitivity to Benzodiazepines or propofol, Chronic Alcoholic or drug abuse, chronic consumption of Benzodiazepines, Pregnant or lactating women, hepatic and renal disease, epilepsy and any emergency surgeries were excluded. Patients were allocated randomly into one of the two groups Midazolam or Propofol Group.

Group-I received injection Midazolam 0.15mg/kg and Group-II received Propofol 2mg/kg for induction. All the patients received 5mg diazepam orally on the night before the surgery and injection Glycopyrrolate 0.2mg intramuscular (IM) one hour before the Surgery.

Group 1 (Midazolam Group) – consists of 24 patients both male and female. All the patients were pre-medicated with Injection Glycopyrrolate 0.2mg intramuscular (IM) one hour prior to induction of anesthesia received intravenous midazolam 0.15mg/kg for induction of anesthesia.

Group 2 (Propofol Group) – Consist of 24 patients both male and female. All the patients were pre-medicated with injection Glycopyrrolate 0.2mg intramuscular (IM) one hour prior to induction of anesthesia received intravenous Propofol 2mg /kg for induction of general anesthesia.

A thorough pre anesthetic evaluation was done a day before the surgery. All elective patients were taken into study, the as per protocol belonging to ASA grade – I and grade- II. The induction procedures were explained to them and informed consent was taken. An ethical approval for the study was taken from IRB-KUSMS/KU.

Results

In both Midazolam group and Propofol group 24 patients including 13 males and 11 females were enrolled for the study, both the groups were comparable with respect to sex.

The mean age in midazolam group was 32±6 years(Mean± SD) with the range of 18 to 40 years, the mean age in propofol group was 31 ± 8 (Mean ±SD) with a range of 22 to 40 years.($P<0.6$).

The mean weight in Midazolam group was 53±11 kgs (Mean ±SD) was similar to the weight of patients in Propofol group with Mean ±SD of 52±5kgs ($P<0.63$)

Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Blood Pressure (MBP) and Heart Rate (HR), were compared for both within the group and between the group changes.

In Midazolam group, pre-induction baseline systolic blood pressure (SBP) was 124±12mmHg (Mean±SD), diastolic blood pressure (DBP) 80±8 mmHg , mean blood pressure (MBP) was 95+8mmHg (Mean±SD) and heart rate was 95±15 bpm (Mean±SD).(Table-1)

Table 1: Comparative study between baseline awake values

Pre induction value	Midazolam Group	Range	Propofol Group	Range	p-value
Heart rate (bpm)	80±8	66 to 117	78±7	60 to 90	0.0001
SBP (mmHg)	124±12	100 to 158	124±13	10 to 148	0.81
DBP (mmHg)	80±8	70 to 90	75±9	50 to 98	0.05
MBP (mmHg)	98±8	80 to 107	90±9	76 to 113	0.17

In Propofol group, pre-induction, SBP was 124±13 mmHg. DBP was 75±9 mmHg, MBP was 98±8mmHg and heart rate was 95.29±14.8 bpm (Mean±SD). There was no statistically significant difference between the two groups with respect to SBP ($p=0.81$), DBP ($p=0.053$) and MBP ($p=0.0001$) but there was statitistically difference with respect to heart rate ($p=0.0001$) (Table-1)

Regarding systolic blood pressure, in Midazolam group the decrease in SBP from baseline was statistically significant at all points of time. (P<0.001). Likewise in Propofol group the decrease in SBP from baseline was statistically significant at all points of time. (P < 0.001). SBP decreased in both the groups after induction from baseline awake values.

There was a statistically significant difference in the SBP at 2nd, 3rd, 4th, 5th and 15th minutes after induction of anesthesia. The decrease in SBP was more in propofol group (102±12 mmHg and 113±11 mmHg) than in midazolam group (115±12 mmHg and 113±11 mmHg) at 2nd and 3rd minutes after induction of anesthesia. (Table – 2)

Table 2: SBP

Time	Midaszolam Group		Propofol Group		Between the group p-value
	Mean±SD	Within * the group p- value	Mean±SD	Within ~ the group p- value	
Baseline	124±12	-	124±13	-	0.92
1st minute	116±13	0.001	108±4	0.0001	0.06
2nd minute	115±12	0.001	102±16	0.0001	0.006
3rd minute	113±11	0.001	102±13	0.0001	0.003
4th minute	113±17	0.001	105±13	0.0001	0.042
5th minute	111±16	0.001	102±11	0.0001	0.02
10th minute	114±13	0.001	106±20	0.0001	0.09
15th minute	114±11	0.001	106±13	0.0001	0.03
30th minute	116±11	0.001	110±13	0.0001	0.09

* When compared to baseline within the same group.

~ When compared between groups at a given point of time.

Regarding diastolic blood pressure, in midazolam group decreased following induction of anesthesia from a baseline value 80±8 mmHg to 75±15 mmHg by the end of 30minutes.The decrease in DBP from baseline was statistically significant at all points of time except 15th and 30th minute (P<0.05).

In propofol group the decrease in DBP from baseline was statistically significant at all points of time. (P<0.0005)

DBP decreased in both the groups after induction from baseline awake values. There was a statistically significant difference in the DBP changes at 3rd, 5th, 10th and15th (P<0.05) minutes of time after induction of anesthesia. (Table-3)

Table 3: DBP

Time	Midazolam		Propofol		Between the group p-value
	Mean±SD	Within * the group p- value	Mean±SD	Within ~ the group p- value	
Baseline	80±8	-	75±9	-	0.04
1st minute	72±16	0.0028	69±8	0.0001	0.049
2nd minute	72±14	0.0031	66±6	0.0001	0.06
3rd minute	73±11	0.0001	64±10	0.0001	0.008
4th minute	69±14	0.0001	63±8	0.0001	0.07
5th minute	71±11	0.0001	62±7	0.0001	0.005
10th minute	72±13	0.0001	63±8	0.0001	0.01
15th minute	74±15	0.0101	65±8	0.0001	0.02
30th minute	75±15	0.0569	68±8	0.0005	0.06

* When compared to baseline within the same group.

~ When compared between groups at a given point of time.

Regarding MBP in Midazolam group, the decrease in MBP was statistically significant at all points of time except at 30th minute ($P<0.001$). In Propofol group the decrease in MBP from baseline was statistically significant at all points of time. ($P < 0.001$).There was a statistically significant difference in the MBP at all points of time except 1st minute after induction of anesthesia. (Table-4). The maximum decrease in MBP after induction of anesthesia in Propofol group was 76±6 mmHg in 5th minute. There was statistically significant difference in maximum decrease in MBP after induction from Base line awake value between the two groups. Time at which the maximum decrease in MBP after induction occurred in Midazolam group and propofol group was at 5th minutes, which was statistically significant. (Table-4)

Table 4: MBP

Time	Midazolam Group		Propofol Group		Between the group p-value
	Mean±SD	Within * the group p- value	Mean±SD	Within ~ the group p- value	
Baseline	95±8	-	92±9	-	-
1st minute	86±13	0.001	82±7	0.001	0.055
2nd minute	86±12	0.001	78±8	0.001	0.006
3rd minute	86±9	0.001	77±10	0.001	0.003

Time	Midazolam Group		Propofol Group		Between the group p-value
	Mean±SD	Within * the group p- value	Mean±SD	Within ~ the group p- value	
4th minute	84±14	0.001	77±8	0.001	0.042
5th minute	84±11	0.001	76±6	0.001	0.019
10th minute	86±11	0.001	77±11	0.001	0.095
15th minute	87±12	0.001	79±8	0.001	0.029
30th minute	82±12	0.007	82±8	0.001	0.095

* When compared to baseline within the same group.

~ When compared between groups at a given point of time.

In Midazolam group, pre-induction heart rate was 80 ± 8 bpm. With induction of anesthesia there was no significant change in Heart Rate over the next 30 minutes.

In propofol group, Pre-induction Heart Rate was 78 ± 7 (Mean±SD) bpm. With induction of anesthesia there was no significant decrease in heart rate over the next 30 minutes. There was a highly significant difference in the heart rate changes between the two groups at all the points of time (p=0.0001). (Table-5)

Table 5: Heart Rate

Time	Midazolam Group		Propofol Group		Between the group p-value
	Mean±SD	Within * the group p- value	Mean±SD	Within ~ the group p- value	
Baseline	95±15	-	78±7	-	-
1st minute	97±11	0.32	76±8	0.2	0.0001
2nd minute	97±14	0.44	76±9	0.38	0.0001
3rd minute	95±11	0.83	76±9	0.45	0.0001
4th minute	93±11	0.27	76±10	0.48	0.0001
5th minute	91±12	0.05	75±10	0.17	0.0001
10th minute	91±12	0.16	76±7	0.26	0.0001
15th minute	91±8	0.08	74±6	0.04	0.0001
30th minute	91±8	0.10	75±8	0.19	0.0001

* When compared to baseline within the same group.

~ When compared between groups at a given point of time.

The incidence like cough was 12.5% (n=6) in Propofol group whereas it was 0% (n=0) in midazolam group. The incidence of hiccough was 16.6% (n=8) for midazolam group. Whereas it was 8.3% (n=4) in Propofol group had hiccough.

The mean induction time (sec) for Midazolam group was 31.16±1.73 i.e. Mean± SD which was similar to the mean Induction time for Propofol group i.e. 31.29±1.98 (mean±SD) which are statistically significant for both the groups. Mean Induction doses used were 7.96mg of Midazolam and 100mg of Propofol corresponding to 0.15mg/kg and 2mg /kg respectively. Apnea occurred in both the midazolam and Propofol groups, with no further need of extra dose of 25%(n=12) of induction dose.

Four patients in propofol group complained of mild pain at the site of injection of the drug which is 16.6% (n=8). Whereas only 2 patients complained of pain which is 8.3% (n=4) in midazolam group. The incidence of side effects during induction was comparable between 2 groups and clinically significant.

The incidence of post operative complications were low in midazolam group only 2 patients in midazolam group had nausea which is 8.3% (n=4), five patients in Propofol group had nausea which is 16.6% (n=8)

There was no incidence of vomiting in Midazolam group whereas 2 patients in Propofol group had an incidence of vomiting, the percentage of incidence of vomiting is 8.3% (n=4) in propofol group where as it is Zero in midazolam group.

There was only one incidence of tenderness in Propofol group at injection site which accounts 4.2% (n=2) whereas it is 0% (n= 0) in midazolam group.

The over all patient acceptances for the same anesthesia were also higher with midazolam. For 75% (n=36) in midazolam group it was a good acceptance whereas 8% (n=3) in Propofol group accepted as good.

54.2% (n=26) in Propofol group satisfied with the anesthesia whereas 25% (n=12) in midazolam group accepted as satisfactory.

Discussion

Propofol is the second most frequently used drug for induction of intravenous general anesthesia after thiopentone. There are however certain absolute contra-indications for its use like Propofol sensitivity and shock. Due to its cardio-respiratory depressive effects, propofol is not the drug of choice in Shock patient or patients with cardio respiratory diseases, .Midazolam a new short acting water soluble Benzodiazepine with cardio vascular effects similar to that diazepam may be an effective alternative for induction of anesthesia.

This Study was done to evaluate the efficiency of Midazolam. In its ability to depress the central nervous system to ascertain whether it can be a safe and effective alteration of propofol.

In our study the demographic data were comparable for age, weight and sex in both the groups. As per our study, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Blood Pressure (MBP) and Heart Rate (HR), were compared for both within the group and between the group changes.

Regarding systolic blood pressure, in Midazolam group the decrease in SBP from baseline was statistically significant at all points of time. ($P<0.001$).Likewise in Propofol group the decrease in SBP from baseline was statistically significant at all points of time. ($P < 0.001$).

The finding of the present study resembles with the study carried out by Celebioglu B et al who concluded that there was no significant changes in SBP between two groups undergoing elective Coronary artery by-pass graft (CABG) [2].Likewise similar study conducted by Reinhart DJ et al revealed no statistically significant differences between the regimens.[3] The study carried by Kataria et al found that there was significantly lesser fall in SBP in propofol group compared to midazolam group.[4]

Regarding diastolic blood pressure, in midazolam group decreased following induction of anesthesia from a baseline value 80±8mmHg to 75±15mmHg by the end of 30minutes.The decrease in DBP from baseline was statistically significant at all points of time except 15th and 30th minute ($P<0.05$).In propofol group the decrease in DBP from baseline was statistically significant at all points of time. ($P<0.0005$)

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Regarding MBP in Midazolam group, the decrease in MBP was statistically significant at all points of time except at 30th minute ($P<0.001$). In Propofol group the decrease in MBP from baseline was statistically significant at all points

of time. ($P < 0.001$).There was a statistically significant difference in the MBP at all points of time except 1st minute after induction of anesthesia

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In Midazolam group, pre-induction heart rate was 80 ± 8 bpm. With induction of anesthesia there was no significant changes in Heart Rate over the next 30 minutes.

In propofol group, Pre-induction Heart Rate was 78 ± 7 (Mean±SD) bpm. With induction of anesthesia there was no significant decrease in heart rate over the next 30 minutes. Brossy and coworker found that HR increased significantly above baseline after induction and intubation in both groups (propofol and thiopentone) but unlike our study in which significant differences between two groups existed, they observed no difference between the two groups. [5]

Pain during Injection

In the present study the incidence of pain during injection was slightly higher with propofol though it was not statistically significant. This correlates with reports by Conner et al 1978, Reeves SG et al 1997. 6,8 In midazolam 8.3% of patients had pain compared to 16.6% in the propofol group complained of pain on injection. No patients in midazolam group had cough at the same time 12.5% of patients in propofol group had cough the incidence of hiccough was 16.6% in midazolam group whereas only 8.3% of patients in propofol group had hiccough.

Post Operative Features

Midazolam was remarkably free of side effects. Only 8.3% of patients in midazolam had mild side effects like nausea whereas the incidence of nausea was 16.6% in propofol group.

There was no incidence of nausea and vomiting in patients belong to midazolam group. This incidence was 8.5% in propofol group. However Shah et al reported that nausea and vomiting was absent in propofol group compared to 6.67 in midazolom group.[7]

Only 1 out of 24 patients in propofol group had thrombophlebitis whereas there was no incidence of thrombophlebitis in midazolam group. Our finding resembles with Shah et al who reported that 3.3% of the propofol group had thrombophelbitis compard with 0% in madazolam group.[7]

Venous irritation at the site of injection was minimal in both groups. The incidence of thrombophlebitis was similar to that reported by Reves et al 1979, Reitan et al 1987, Abraham and Kaur 1997.[8, 9, 10]

Gamble et al 2001, found thrombosis and thrombophlebitis in 2 patients each after midazolam and propofol between 7-10 days after surgery, even though there was no sign of venous irritation in the first week.[11]

Patient acceptance of anesthesia was good in 75% patients in midazolam group whereas the patient's acceptance in propofol group was 45.8%

Patient's acceptance of anesthesia was satisfactory in 54.2 in propofol whereas it was 25% in midazolam group. Overall although midazolam does not supersede propofol it certainly a useful hypnotic with a few advantages over propofol for induction and maintenance of balance anesthesia.

Conclusion:

In conclusion, midazolam caused no adverse hemodynamic changes at the time of induction and maintenance of anesthesia in ASA physical status I and II as compared to propofol. Hence midazolam was proven to be effective compared to propofol .

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