Women Health Bull. 2019 January; 6(1):e82741. doi: 10.5812/whb.82741.

Published online 2018 December 4. **Research Article**

Comparison of Maternal Stress Response to Midazolam/Fentanyl and Propofol During Cesarean Delivery Under Spinal Anesthesia: A Double-Blinded Randomized Controlled Trial

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Received 2018 July 30; **Revised** 2018 November 18; **Accepted** 2018 November 20.

Abstract

Background: This research evaluated the effects of propofol and midazolam/fentanyl on maternal blood pressure, heart rate, recall, and full satisfaction with spinal anesthesia. A double-blinded randomized controlled trial was designed.
Methods: The sample size was calculated as 100 patients (a type I error of 5% and statistical power of 80%) who were scheduled for elective cesarean delivery under spinal anesthesia. These patients were randomized into two equal groups by block randomization used for allocation sequence: midazolam/fentanyl and propofol groups. We measured the maternal heart rate (HR), systolic, and diastolic blood pressure (SBP and DBP) before induction, every three minutes in the operating room, and every five minutes until discharge from the recovery room. Data were analyzed by SPSS 18.0 and P value < 0.05 was considered as the significance level.
Results: 100 women (mean age: 29.7 ± 5.1 years and gestational age: 37.2 ± 1.2 weeks) were enrolled. The SBP and HR decreased during the study in both groups, but it was significant only in the midazolam/fentanyl group (SBP: from 120.0 ± 10.3 to 113.9 ± 4.8, P = 0.025; and HR: from 75.0 ± 7.6 to 65.3 ± 5.5, P = 0.046). DBP reduced in both groups, but it was only significant in the propofol group (from 68.5 ± 7.2 to 56.9 ± 2.1, P = 0.039). The maternal recall of the birth time, child weight, and full satisfaction were significantly better in the propofol group than in the midazolam/fentanyl group (P = 0.046, P = 0.009, and P = 0.039, respectively).
Conclusions: Propofol and midazolam/fentanyl could be useful in cesarean sections under spinal anesthesia thought propofol may induce more effective sedation with higher satisfaction. Accordingly, the propofol use during caesarian sections under spinal anesthesia is suggested due to its anti-stress effects, good delivery recall, and good sedation satisfaction.

Keywords: Midazolam, Fentanyl, Propofol, Blood Pressure, Heart Rates, Spinal Anesthesia, Maternal Recall

1. Background

The worldwide number of cesarean sections has increased (1) and the safety of the mother and child is important to select the method of anesthesia and its administration carefully (2). Spinal anesthesia is the preferred type of anesthesia for elective cesarean delivery (2-10) due to its benefits of simplicity, low airway complications, facilitation for postoperative analgesia, decreased blood loss, less neonatal exposure to potentially depressant drugs, and conscious mother at the birth time that creates effective maternal-infant bonding and breastfeeding (2-10).

Although the use of spinal anesthesia reduces mortality and morbidity, it induces a stress response to arise the sympathetic nervous system, which can be associated with postoperative mother morbidity or poor fetal health (11). In addition, pregnant women in this procedure may become anxious because they have unpleasant experiences such as awareness during operation, discomfort due to immobilization on the operating table, nausea, and vomiting (6). Therefore, the prevention from maternal stress is potentially important. Although some research over the last 20 years has led to the improved management of these adverse effects of spinal anesthesia, they remain challenging yet (8).

The pharmacological sedation in spinal anesthesia is not commonly applied. However, some medications may be helpful in this regard: midazolam as a benzodiazepine, propofol with a sedative-hypnotic property that induces unconsciousness for events, and fentanyl as a strong opioid receptor agonist (6, 12-17). Accordingly, we investigated the preventive effects of propofol infusion alone and the

combination of fentanyl and midazolam on the reduction of stress response during cesarean delivery by the spinal anesthesia.

2. Objectives

Our research objectives were to evaluate mothers' blood pressure, heart rate (HR), recall, and their satisfaction with spinal anesthesia during surgery in two intervention groups.

3. Methods

3.1. Study Population

This is a randomized double-blind parallel clinical trial study conducted in Yasuj University of Medical Sciences from October 2016 to July 2017. This study was approved by the Local Ethics Committee of Yasuj University of Medical Sciences. It was registered at Clinical-Trials.gov. under the study number of IRCT201701277745N6. The sample size was calculated as 100 patients based on a type I error of 5%, statistical power of 80%, expected difference of the means of 0.79, and pulled SD of 1.4. The patients were randomized into two groups, each containing 50 members by block randomization used for allocation sequence. We randomly selected our study participants from full-term women who were scheduled for elective cesarean delivery by spinal anesthesia in the surgery rooms of Yasuj Imam-Sajad Hospital. We specified four block sizes with six possible sequences (AABB, ABAB, ABBA, BAAB, BABA, and BBAA) and thus, extracted 25 numbers (excluding 0 and 7 to 9) from the table of random numbers.

All patients were 18 - 42 years old with American Society of Anesthesiologists physical status I. The patients were excluded if they had a history of diabetes, cardiopulmonary disease, hypertension, and opioid use or if they were taking medications for hypertension or HR control, as well as if they had obstetric complications or needed an emergency cesarean.

3.2. Treatment Protocol

A random-number table was generated and an envelope containing the group assignments was prepared for patients, closed, and serially numbered. Before induction of anesthesia, an anesthesiologist that was not involved in patient evaluation and management opened the envelope and prepared midazolam/fentanyl or propofol infusion. None of the other researchers was aware of it. In case of emergency, the anesthesiologist would enter the patient's management process although it did not occur in this study. After arrival in the operating room and intravenous access, 8 mL/kg of ringer solution was infused within 10 minutes before the spinal block initiation. The spinal anesthesia was performed in the sitting position with a 26-gauge needle, using a midline approach at the L4-5 interspace. All patients received 5% lidocaine and 1 mL of fentanyl and marcaine. After intrathecal injection, the patients were turned in the supine position with a sensory block up to T5 dermatome. The surgical technique was the same for all patients. After delivery, the patients were randomly divided into two groups. One group received 0.5 μg/kg/hour fentanyl and 0.05 mg/kg/hour midazolam while another group received 8 mg/kg/hour propofol infusion.

3.3. Data Collection

We prepared a questionnaire for the patients to gather demographic data and information on their underlying diseases, current pregnancy, past history, and drug history. Baseline maternal HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured by an automatic noninvasive monitor and recorded before the induction, every three minutes in the operating room, and every five minutes until discharge from the recovery room. In addition, 24 hours after delivery, the satisfaction with spinal anesthesia and the maternal recall of the delivery were evaluated.

3.4. Ethical Consideration

The study was done in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of Yasuj University of Medical Sciences. At the initiation of the study, the patients were informed completely about the process of the study. Then, we obtained written consent.

3.5. Statistical Analysis

The statistical analysis was performed by the Statistical Package for Social Sciences version 18 (SPSS Inc, Chicago, IL, USA). The data related to continuous variables were presented as means $\pm$ SD and those related to the quantitative or categorical data were shown as percentages and frequencies. The statistical tests used in this study were Chi-square, Independent *t*-test, Repeated Measurement test, and Paired *t*-test. P value < 0.05 was considered significant.

4. Results

A total of 100 women were enrolled. All patients were able to complete the study. Therefore, our study group was

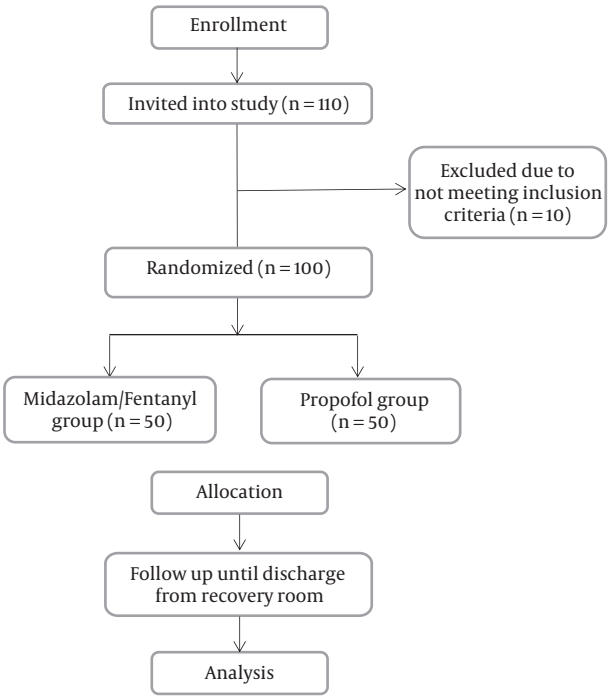

Figure 1. RCT flowchart

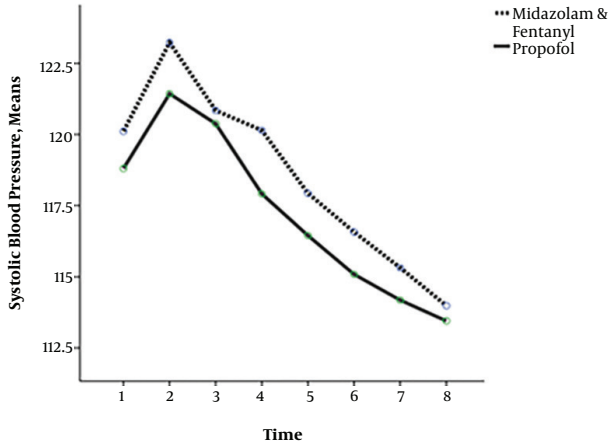

Figure 2. Comparison of systolic blood pressure between the study groups

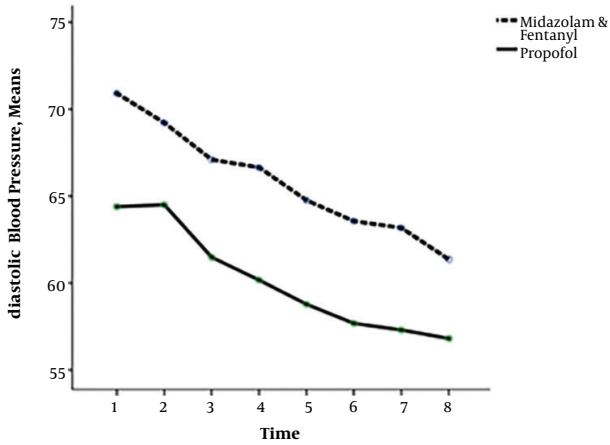

Figure 3. Comparison of diastolic blood pressure between the study groups

divided into two equal groups: propofol group and midazolam/fentanyl group (Figure 1).

There was no significant difference in baseline data between the groups at the beginning of the study (Table 1, P > 0.05). The mean age in the propofol group and midazolam/fentanyl group was 30.3 ± 5.2 and 29.1 ± 4.9, respectively (P = 0.374). The gestational age was 37.4 ± 1.2 in the propofol and 37.2 ± 1.1 in the midazolam/fentanyl group (P = 0.456).

As shown in Table 2 and Figure 2, the SBP decreased during the study in both intervention groups, but the Repeated Measurement test revealed that it was significant only in the midazolam/fentanyl group (from 120.0 ± 10.3 to 113.9 ± 4.8, P = 0.025). The Paired *t*-test showed that nearly all of the SBP levels significantly decreased compared to the before surgery measurement of the SBP in both groups (P < 0.001).

Although the DBP reduced in both intervention groups during the cesarean section, this was significant in the propofol group (P = 0.039 by the Repeated Measurement test, Table 3 and Figure 3). The Paired *t*-test showed that all of the DBP levels significantly decreased compared to the before surgery measurement (P < 0.001). In addition, all the DBP levels during the operation were significantly lower in the propofol group than in the midazolam/fentanyl group (P < 0.001, except in the two first measurements).

Moreover, Table 4 and Figure 4 show that similarly, the HR levels decreased during the operation in both intervention groups, but it was significant only in the midazolam/fentanyl group (from 75.0 ± 7.6 to 65.3 ± 5.5, P = 0.046 by the Repeated Measurement test). The Paired *t*-test showed that all of the HR levels significantly decreased compared to the before surgery measurement (P < 0.001). Only in the first measurement after the beginning of the operation was the HR level significantly lower in the midazolam/fentanyl group than in the propofol group (P = 0.003).

No significant cardiac, hemodynamic, or respiratory complications were encountered. The most common side

Table 1. Patient Characteristics in the Study Groups

Patient Characteristics	Groups, Mean ± SD		P Value
	Propofol, N = 50	Midazolam/Fentanyl, N = 50	
Age (y)	30.3 ± 5.2	29.1 ± 4.9	0.853
Weight (kg)	75.2 ± 5.4	74.1 ± 4.8	0.231
Gestational age (week)	37.4 ± 1.2	37.2 ± 1.1	0.456
Surgical time (min)	74.1 ± 5.3	75.1 ± 6.1	0.856
Volume of intravenous fluid (mL)	2542.3 ± 152.4	2530 ± 89.2	0.555
Urine output (mL)	236.2 ± 12.1	254.2 ± 26.8	0.635

Table 2. Distribution of Systolic Blood Pressure Among the Study Groups

Systolic Blood Pressure	Groups, Mean ± SD						P Value
	Propofol, N = 50			Midazolam/Fentanyl, N = 50			
Before surgery	118.9 ± 7.9			120.0 ± 10.3			0.530
1	121.5 ± 7.4			123.8 ± 7.1			0.267
2	120.4 ± 6.7			120.8 ± 6.2			0.746
3	117.9 ± 5.9			120.2 ± 9.2			0.142
4	116.5 ± 5.6			117.9 ± 5.6			0.223
5	115.1 ± 5.0			116.5 ± 5.5			0.194
6	114.2 ± 5.2			115.3 ± 5.8			0.317
7	113.5 ± 5.1			113.9 ± 4.8			0.659
P value of repeated measurement test	0.582			0.025			0.273
The P value of Paired *t*-test related to systolic blood pressure during surgery							
Before-surgery systolic blood pressure	1	2	3	4	5	6	7
Propofol group	< 0.001	0.005	0.057	< 0.001	< 0.001	< 0.001	< 0.001
Midazolam/fentanyl group	0.002	0.391	0.931	0.020	0.001	< 0.001	< 0.001

effect of propofol was short-time venues pain after the drug induction (8 cases, 16.0% vs. no cases in the other group, P = 0.003). Nausea and vomiting were observed more frequently in the midazolam/fentanyl group (28 patients, 56.0% in the midazolam/fentanyl group vs. 14 cases, 28.0% in the propofol group, P = 0.048). In our study, none of the babies had 5-min Apgar score < 7.

Although the maternal recall of birth and child parameters was better in the propofol group than in the midazolam/fentanyl group, a statistically significant difference was seen in the recall of the birth time and fetal weight (P = 0.046 and P = 0.009, respectively, Table 5). In addition, a full satisfaction with sedation was seen in the two groups but it was significantly higher in the propofol group than in the midazolam/fentanyl group (P = 0.039).

5. Discussion

Spinal anesthesia is the preferred method for elective cesarean section due to being simple and rapid anesthesia onset with complete muscle relaxation. Pregnant women undergoing this procedure are commonly anxious due to consciousness during the operation. This study evaluated the effects of propofol and midazolam/fentanyl on their stress response (by checking the mother's blood pressure and HR). We also compared sedation satisfaction and the maternal recall of birth and child parameters in the two groups.

SBP and DBP reduction is a common pharmacodynamic feature of propofol by inhibiting the sympathetic nervous system and baroreflex regulatory mechanisms and involving the endogenous vasoactive species. The cardiovascular mechanism after applying midazolam and fentanyl has been shown to decrease SBP and DBP by de-

Table 3. Distribution of the Diastolic Blood Pressure Among the Study Groups

Diastolic Blood Pressure	Groups, Mean ± SD		P Value
	Propofol, N = 50	Midazolam/Fentanyl, N = 50	
Before surgery	68.5 ± 7.2	69.8 ± 8.3	0.089
1	66.6 ± 5.9	69.2 ± 6.4	0.090
2	61.5 ± 5.1	67.1 ± 6.4	0.001
3	60.2 ± 4.7	66.6 ± 6.7	0.001
4	58.8 ± 3.9	64.8 ± 8.8	0.001
5	57.7 ± 3.0	63.5 ± 7.1	0.001
6	57.4 ± 2.7	63.1 ± 7.3	0.001
7	56.9 ± 2.1	61.3 ± 6.1	0.001
P value of repeated measurement test	0.039	0.889	0.001

The P value of Paired *t*-test related to diastolic blood pressure during surgery							
Before-surgery diastolic blood pressure	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Propofol group	0.975	< 0.001	< 0. 001	< 0.001	< 0.001	< 0.001	< 0.001
Midazolam/fentanyl group	0.193	0.004	0.001	< 0.001	< 0.001	< 0.001	< 0.001

Table 4. Distribution of Heart Rate Among the Study Groups

Heart Rate	Groups, Mean ± SD		P Value
	Propofol, N = 50	Midazolam/Fentanyl, N = 50	
Before surgery	75.7 ± 7.7	75.0 ± 7.6	0.632
1	75.7 ± 7.8	73.3 ± 6.9	0.003
2	71.4 ± 6.7	70.3 ± 6.6	0.119
3	68.8 ± 6.6	68.7 ± 7.3	0.904
4	66.5 ± 5.9	66.8 ± 6.4	0.584
5	65.2 ± 5.5	65.4 ± 5.9	0.614
6	64.6 ± 5.1	65.3 ± 5.5	0.142
P value of repeated measurement test	0.869	0.046	0.551

The P value of Paired *t*-test related to heart rate during surgery					
Before-surgery heart rates	**1**	**2**	**3**	**4**	**5**
Propofol group	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Midazolam/fentanyl group	0.012	< 0.001	< 0.001	< 0.001	< 0.001

creasing systemic vascular resistance and myocardial contractility (18-20).

Both propofol and midazolam/fentanyl could reduce blood pressure and HR during caesarian section; however, the results revealed that it was significant in the midazolam/fentanyl group for SBP and HRs and in the propofol group for DBP. Thus, almost all of these measurements during the operation were significantly lower than the first corresponding measurements. We conducted that stress response during operation, which can increase blood pressure and HR, may be controlled by both of our trial drugs.

Midazolam is commonly used for intraoperative sedation, and has a rapid elimination; thus, it can be administered for this purpose (19-21). Nevertheless, its amnestic effects cannot be avoided, as the current results showed that nausea and vomiting were the most side effects in this group. Fentanyl is an opioid pain medication with a rapid onset and short duration of action that provides a suitable sedation, analgesic, and stable hemodynamic effects (22). An intravenous combination of midazolam and fentanyl

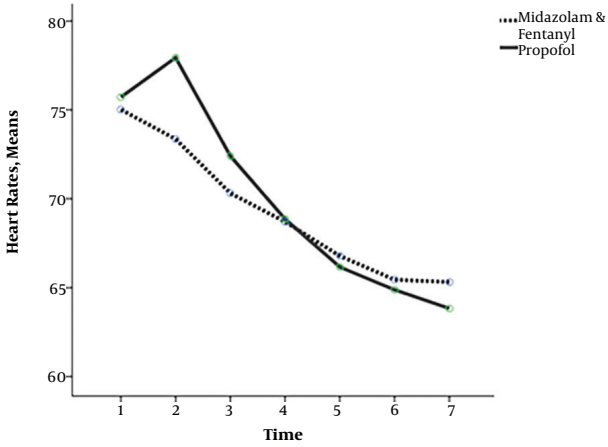

Figure 4. Comparison of heart rate between the study groups

Table 5. Maternal Recall of the Fetal Parameters and Total Sedation Satisfaction in the Study Groups

Characteristics	Groups, No. (%)		P Value
	Propofol, N = 50	Midazolam/Fentanyl, N = 50	
Time of birth	50 (100.0)	40 (80.0)	0.046
Fetal weight	50 (100.0)	43 (86.0)	0.009
Fetal length	43 (86.0)	39 (78.0)	0.057
Apgar score	44 (62.0)	25 (50.0)	0.060
Satisfaction with sedation	48 (97.0)	44 (88.0)	0.039

can achieve the desired effects of adequate sedation and analgesia (23).

In addition, propofol administered in sub-hypnotic doses induces sedation with preserved awareness, defined as a medically controlled state of depressed consciousness (19, 20, 24). The advantage of propofol over midazolam/fentanyl is its high clearance ratio and short lifetime; moreover, it can be better controlled to obtain and keep the desired sedation level (8). Propofol provided adequate sedation for a similar proportion of time to midazolam, but the recovery was faster with propofol, and midazolam was seen to be associated with deeper intraoperative amnesia (14, 20).

A study in the United States among patients undergoing plastic surgical procedures showed that midazolam/fentanyl and propofol are effective sedatives, but the onset and offset were quicker with propofol, while midazolam was more cardio stable (13).

Another study conducted in Poland on pregnant women undergoing elective cesarean sections under subarachnoid anesthesia concluded that midazolam and propofol induce effective and safe sedation. Propofol appears to be more useful for sedation compared to midazolam because of its shorter duration of action and antiemetic effects (8).

Although the maternal recall of birth and child parameters was good in two groups, it was better in the propofol group than in the midazolam/fentanyl group, in line with other studies (8, 20). Nevertheless, another study showed that it had no difference between the two groups (25).

Like another study (13), we found a high full satisfaction with sedation in the two groups that was higher in the propofol group than in the midazolam/fentanyl group. Another study in Poland revealed that sedation with both of them provided a high and comparable satisfaction with the procedure (8). In addition, a study concluded that the patients' recall of intraoperative events was low but somewhat higher in the midazolam/fentanyl group than in the propofol group (13).

Propofol and midazolam/fentanyl used in our study did not have significant effects on the cardiovascular and respiratory systems, which was in agreement with previous research (8, 24, 25). Nevertheless, some studies have reported that sedatives can depress them (26-28).

Since the maternal satisfaction with sedation, as well as the maternal recall of birth procedure and baby parameters, significantly was better in the propofol group than in the midazolam/fentanyl group, it can be said that propofol may induce sedation with more effectiveness and suitability compared to midazolam/fentanyl in cesarean sections under spinal anesthesia.

5.1. Conclusions

The results of the current study showed that both of the studied drugs could be useful in cesarean sections by spinal anesthesia. However, it seems that propofol induces more effective sedation with higher satisfaction than midazolam/fentanyl does. Therefore, sedation with propofol during caesarian section by spinal anesthesia is recommended due to its anti-stress effects, better recall of birth and fetal parameters, and full sedation satisfaction.

Footnote

Funding/Support: The Vice-Chancellery of Research and Technology of Yasuj University of Medical Sciences financially supported this study.

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