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A comparison of subhypnotic doses of propofol and midazolam during spinal anaesthesia for elective Caesarean section

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Abstract

Background: This study compared two types of sedation in pregnant women receiving subarachnoid anaesthesia for elective Caesarean section.

Methods: This prospective randomised study included 56 women. Patients were sedated with propofol (PROP group, n = 27) or midazolam (MID group, n = 29) via intravenous infusion after extraction of the foetus. The following parameters were assessed at five-minute intervals: degree of sedation, heart rate, arterial pressure, ECG recording and arterial haemoglobin oxygen saturation. Moreover, we recorded drug doses, changes in infusion rates to ensure a desirable degree of sedation and adverse side effects. The maternal recall of delivery and satisfaction with sedation were also evaluated.

Results: The incidence of increased sedative infusion rates was higher in the PROP group (59.3% vs. 37.9%). In contrast, decreased infusion rates were observed in the MID group (41.4% vs. 29.6%). After the initial dose, a desirable level of sedation was easier to obtain in the PROP group (77.7% vs. 55.1%), whereas excessive sedation was noted more frequently in the MID group (34.5% vs. 11.5%). The deepest degree of sedation was found in 2 PROP patients and 1 MID patient. In the PROP group, excessive sedation was rapidly alleviated by reducing the infusion rate. In the MID group, excessive sedation was observed throughout the examination, despite reduced infusion rates. No significant intergroup differences were found for desired sedation levels.

The mean heart rate and arterial pressure were lower in the PROP group. In the MID group, only 5% of patients developed an elevated systolic RR. No ECG alterations were observed in any patient. A haemoglobin oxygen saturation level below 92% was found in 1 patient from each group.

Logorrhoea was characteristic in the PROP group (44.4%). The incidence of nausea and vomiting were higher in the MID group. Other side effects (e.g., headache, backache, erythema and chills) were observed in a subset of patients from both groups.

In the MID group, birth recall was significantly lower (82.8% vs. 96.3%). Full satisfaction with sedation was declared by 89.6% of MID patients and 92.6% of PROP patients.

Conclusions: Midazolam and propofol induce effective and safe sedation in patients receiving subarachnoid anaesthesia for Caesarean section. Propofol appears to be more useful for Caesarean section sedation when compared with midazolam because of its shorter action, antiemetic effects and better maternal recall of foetal delivery.

Key words: obstetric anaesthesia, Caesarean section, sedation, propofol, midazolam

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Spinal anaesthesia is the method of choice for elective Caesarean section. It allows mothers to be involved in the child's delivery but also exposes them to awareness-related stress during the later stages of the procedure. The stress intensity was higher in woman undergoing a Caesarean section when compared with women delivering spontaneously [1–3]. The use of pharmacological sedation after extraction of the foetus by Caesarean section under subarachnoid anaesthesia is not widely applied; however, it is useful in some patients, e.g., those presenting with an extremely high stress

level. Enhanced stress can result from poor foetal health after delivery, discomfort associated with immobilisation on the operating table, chills that accompany anaesthesia, nausea and vomiting. Pregnant women experience particularly enhanced vegetative reactions under stress situations. The present study compared two sedatives, propofol and midazolam, based on their usefulness, efficacy and safety in the study population to improve the patient's comfort and reduce childbirth-related stress.

Table 1. The Ramsey scale according to [4]

1	Conscious, cooperative, oriented
2	Drowsy
3	Responsive to commands
4	Responsive to mild stimuli
5	Responsive to pain stimuli
6	Unresponsive

METHODS

A prospective, randomised study included 56 ASA I pregnant women undergoing elective Caesarean sections under subarachnoid anaesthesia between January 2010 and December 2012. The exclusion criterion was a positive history of drug allergies. The study design was approved by the local bioethics committee (NN-6501-218/04), and all patients provided a written informed consent for participation in the study. The patients were not premedicated. Within the prophylaxis of hypotension, all patients were transfused with a non-balanced electrolyte solution at a volume of 15 mL kg^{-1} before anaesthesia. Spinal anaesthesia was routinely conducted by injecting a hyperbaric solution of 0.5% bupivacaine (0.5% Marcaine Spinal Heavy, Astra Zeneca, Sweden) through a 26 G/90 mm spinal needle (Balton, Poland). After spinal block, patients were placed on the operating table in the horizontal position with the body elevated to the left at an angle of 10–15%. Next, passive oxygen therapy was initiated. Following stabilisation of the sensory block at the TH5 level, a Caesarean section was performed routinely. Newborns were presented to mothers who were also informed as to the time of extraction, child's weight and length and Apgar scores. Subsequently, sedation with propofol or midazolam was administered in a randomised manner.

Twenty-seven patients (PROP group) received propofol at an induction dose of 0.5 mg kg^{-1}, followed by a continuous infusion from a syringe pump at a speed of 5-8 mg kg^{-1} h^{-1}. To reduce the pain at the infection site, 30 mg of lidocaine was added to the solution.

Twenty-nine patients (MID group) were sedated with midazolam at an induction dose of 0.02 mg kg^{-1} followed by a continuous infusion at a speed of 0.05–0.18 mg kg^{-1} h^{-1}. In both groups, the rates of infusions were changed (the MID group changed by 0.05 mg kg^{-1} h^{-1}; the PROP group changed by 1 mg kg^{-1} h^{-1}) to provide and maintain the second or third level of sedation according to the Ramsey scale (Table 1). The drug infusion was discontinued after placing the final sutures to secure the skin.

Throughout the sedation period, the following parameters were monitored at 5-minute intervals: sedation level (according to the Ramsey scale; 1-6), heart rate (HR), systolic and diastolic arterial pressure (RRs and RRd), heart rate (ECG) and arterial haemoglobin oxygen saturation (SpO_2). The recorded changes in these parameters (n = 199 measurements in the MID group and n = 178 measurements in the PROP group) were considered significant at a HR ≥ 120 min^{-1} or ≤ 60 min^{-1}, RRs ≥ 150 mm Hg or ≤ 90 mmHg, RRd ≥100 mm Hg or ≤ 45 mm Hg, and SpO_2 ≤ 92%. The duration of the procedure and continuous drug infusion, induction, maintenance and total doses of propofol and midazolam, frequency of changes to the infusion speed, and the incidence and nature of clinical side effects were recorded. The day after delivery, the satisfaction with spinal anaesthesia and sedation and the maternal recall of the time of extraction, birth weight and length and Apgar scores were evaluated.

Data were statistically analysed using Statistica 10 (StatSoft, Tulsa, USA). The Mann-Whitney U test was used to compare quantitative variables (after checking for the normality of distribution with the Shapiro-Wilk test) and determine the median and range. The chi-square test was used for qualitative variables with the Yate's correction. A P value < 0.05 was considered to be statistically significant.

RESULTS

No significant intergroup differences were observed for patients' age, weight, surgery duration and sedation duration (Table 2).

In the MID group, the medians for the induction, maintenance and total doses were 1.40 mg (0.75–2.00), 3.5 mg (2.9–5.2), and 5.1 mg (3.7–7.00), respectively. In the PROP group the medians for the induction, maintenance and total doses were 35 mg (24–50), 175 mg (128–215) and 210 mg (140–260), respectively.

The infusion speed was increased due to too shallow sedation in 11 patients (37.9%) in the MID group and 16 patients (59.3%) in the PROP group. The infusion speed was reduced due to excessive sedation in 12 MID patients (41.4%) and 8 PROP patients (29.6%). The mean sedation level at individual time intervals is presented in Fig. 1. The total drug administered, including the induction dose, was 5.9 mg kg^{-1} h^{-1} for propofol and 0.14 mg kg^{-1} h^{-1} for midazolam.

The desired sedation level (Ramsey score of 2 or 3) was achieved after the induction dose in 21 PROP patients (77.7%) and 16 MID patients (55.1%). The desired sedation level was

Table 2. Medians for the patients' age, body weight, and duration of surgery and sedation

	MID (n = 29)	PROP (n = 27)	*P*-value
Age (years)	32 (21–40)	29 (18–43)	0.06
Body weight (kg)	68 (53.5–109)	66.5 (50–123)	0.37
Duration of surgery (min)	50 (27–95)	54 (40–80)	0.25
Duration of sedation (min)	35 (12–75)	35 (5–60)	0.81

Table 3. Percentage of patients (%) in the study groups with a defined sedation level at individual time intervals

Measurement points (min)	N		1		2		3		4		5		6	
	MID	PROP	MID	PROP	MID	PROP	MID	PROP	MID	PROP	MID	PROP	MID	PROP
0	29	27	41.4%*	14.8%*	34.5%	51.8%	20.6%	25.9%	0%	7.5%	13.5%	0%	0%	0%
5	29	27	13.9%	7.5%	37.9%	48.1%	24.1%	33.3%	24.1%	11.1%	0%	0%	0%	0%
10	29	26	3.5%	3.8%	17.2%	23.2%	44.8%	53.8%	34.5%*	11.5%*	0%	7.7%	0%	0%
15	28	26	3.6%	3.8%	17.9%	19.2%	42.8%	42.4%	32.1%	26.9%	3.6%	7.7%	0%	0%
20	28	26	0%	0%	21.4%	19.2%	39.3%	46.2%	35.7%	34.6%	3.6%	0%	0%	0%
25	24	24	0%	0%	37.5%	37.5%	20.8%	33.3%	37.5%	29.2%	4.2%	0%	0%	0%
30	21	17	0%	0%	28.6%	41.2%	52.4%	35.3%	19%	23.5%	0%	0%	0%	0%
35	11	5	9.1%	0%	36.3%	20%	27.3%	60%	18.2%	20%	9.1%	0%	0%	0%

*$P < 0.05$
1, 2, 3, 4, 5, 6 — sedation level according to the Ramsey scale [4]
N — number of patients at individual time intervals (dependent on surgery duration)
MID and PROP — study groups (midazolam and propofol, respectively)

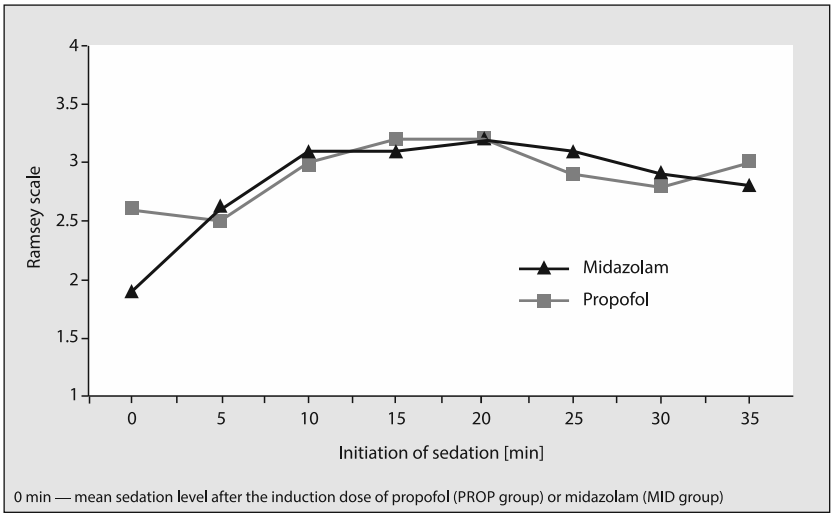

Figure 1. Mean sedation levels in the study groups and individual time intervals according to the Ramsey scale

not provided in a statistically significantly higher number of MID patients. At minute 10 of the infusion, the number of MID women too deeply sedated was statistically significantly higher (4 on the sedation scale) when compared with the PROP group. In the PROP group, the fifth level of sedation was found in 2 patients after 10 minutes of infusion. This was quickly corrected by reducing the speed of propofol infusion. In the MID group, the fifth level of sedation was observed in one patient after 15 minutes of infusion. This sedation level was maintained throughout the observation period despite reductions in infusion speed (Table 3). A comparison of mean sedation levels at individual time points revealed no statistically significant intergroup differences (Fig. 1).

The medians of pulse, arterial systolic and diastolic pressure were lower in the PROP group (Table 4). A statistically significant intergroup difference was observed in the num-

Table 4. Median heart rate and arterial blood pressure

	MID (n = 199)	PROP (n=178)	*P*-value
Heart rate (min^{-1})	97 (57–161)	88 (59–140)	< 0.001
Systolic pressure (mm Hg)	120 (70–180)	115 (70–190)	< 0.01
Diastolic pressure (mm Hg)	65 (30–130)	60 (25–90)	< 0.01

n — number of measurements in patients from individual study groups

Table 5. Percentage of measurements for HR, systolic blood pressure (RRs), diastolic blood pressure (RRd) and saturation that were divergent from the assumed normal value

Haemodynamic parameters and saturation	MID (%) (n = 199)	PROP (%) (n = 178)	*P*-value
HR			
≥ 120 min^{-1}	7,5	3.9	0.136
≤ 60 min^{-1}	3	1.1	0.203
RRs			
≥ 150 mm Hg	2,5	5	0.192
≤ 90 mm Hg	6,5	3.4	0.161
RRd			
≥ 100 mm Hg	5	0	< 0.01
≤ 45 mm Hg	2	3.9	0.268
SpO_2			
≤ 92%	0.5	0.6	0.937

n — number of measurements in patients from individual study groups

ber of patients with diastolic pressure increases (Table 5). None of the patients developed arrhythmias or other ECG abnormalities. The SpO_2 dropped below 92% in one patient from each group.

The most common side effect of propofol was short-term slight venous pain after the induction dose despite the use of 30 mg of lidocaine. This side effect was reported by approximately 25% of patients. Logorrhoea was characteristic of propofol sedation. Nausea and vomiting were observed more frequently in the MID group. The remaining side effects, i.e., headache, backache, erythema, chills, were found a subset of patients from both groups (Table 6).

The maternal recall of the time of birth and the physical parameters of the child was statistically significantly poorer in the MID group when compared with the PROP group. Patients were more likely to not remember the length and Apgar scores. A full satisfaction with sedation was comparable between groups (Table 7).

Table 6. Side effects

	MID (n = 29)	PROP (n = 27)	*P*-value
Logorrhoea	0%	44.4%	< 0.001
Nausea and vomiting	58.6%	29.6%	< 0.05
Vein irritation (pain on drug supply)	0%	25.9%	< 0.005
Headache	10.3%	11.1%	0.926
Erythema	10.3%	11.1%	0.565
Chills	17.2%	11.1%	0.549
Backache	0%	11.1%	0.60

Table 7. Recall of foetal parameters and sedation satisfaction (average data)

	MID (n = 29)	PROP (n = 27)	*P*-value
Time of birth	89.6%	100%	0.086
Foetal weight	82.6%	85.2%	0.805
Foetal length	82.6%	100%	< 0.05
Apgar score	75.7%	100%	< 0.01
	82.8%	96.3%	< 0.005
Satisfaction with sedation	89.6%	92.6%	0.700

DISCUSSION

Pregnant women undergoing elective Caesarean sections under subarachnoid anaesthesia are often anxious about the unpleasant experiences associated with awareness during surgery. After being informed about the possible use of hypnotics after baby extraction, the patients more eagerly accepted this suggested method of anaesthesia. The drug commonly used for intraoperative sedation is midazolam. Due to quick elimination, midazolam can be administered via intravenous infusion at a rate of 0.5-1 mg kg^{-1} min^{-1}. However, its amnestic effects can impair mental functions, including the perception and memory of mothers who want to remember the moment their baby is born and shown to them.

Similarly, propofol administered in subhypnotic doses induces sedation with preserved awareness, defined as a medically controlled state of depressed consciousness. The potential superiority of propofol over midazolam is due to its high clearance ratio and short life time; thus, propofol can be better controlled to achieve and maintain desirable sedation levels [5, 6].

In our study, sedation levels were evaluated according to a 6-point scale. Our aim was to maintain a score of 2 or 3. The quality and ease to obtain the desired level of sedation were acceptable in both study groups, although the PROP group showed superior results. The total drug doses were comparable with those reported in other sedation-focused studies. To achieve the 4^{th} level of sedation, Wilson and co-workers [7] used a lower total dose of propofol and a higher total dose of midazolam.

The induction dose of midazolam did not cause sedation in 41.4% of patients. In the PROP group, adequate sedation was not achieved in 14.8% of patients. This difference can be

attributed to the quicker onset of action of propofol [5, 7] (Table 3). After 10 minutes of infusion, the number of MID patients with excessive sedation was statistically higher. This result was due to drug accumulation and poorer dose control.

However, subarachnoid anaesthesia for Caesarean section itself can be associated with maternal sedative effects, which is likely to result from the deafferentation related to this type of anaesthesia or psychophysiological effects that release C-section tension, including pain and anxiety related to the baby [2].

Both of the drugs used in our study did not have significant effects on the cardiovascular system and respiratory efficiency. However, numerous studies have shown that sedatives can depress both systems [8–10].

The available literature on the effect of midazolam on the cardiovascular system is minimal. Midazolam can slightly reduce the mean arterial pressure (MAP) and systemic vascular resistance while accelerating the heart rate. Hypotension can be induced by the direct depressive effects on cardiac contractility.

Hypotension is also caused by propofol, which dilates venous and arterial vessels, inhibits the sympathetic system and reflexes from baroreceptors and exerts depressive effects on the myocardium [11, 12]. The median systolic and diastolic arterial pressures were lower in the PROP group when compared with the MID group. There were no intergroup differences in arterial blood saturation.

Pain at the infection site of propofol is commonly reported with an incidence ranging from 30 to 90%. The addition of lidocaine to the anaesthetic can reduce this incidence by 70–80% [13, 14]. In our study, 26% of PROP patients reported pain at the injection site, despite administration of 30 mg of lidocaine (i.e., a dose higher than 0.2 mg kg^{-1}).

The incidence of nausea and vomiting during subarachnoid anaesthesia for Caesarean sections is estimated to occur in 60% of cases. Subhypnotic doses of propofol infusion reduced the incidence of postoperative nausea and vomiting from 65-70% to 25% when compared with the placebo group [15]. These results are consistent with our findings. Notably, excessive sedation can be associated with the risk of aspiration of gastric contents into the airway. In our study, the mean sedation level did not exceed 4 on the Ramsey scale. Previous studies demonstrated that a propofol infusion of 1 mg kg^{-1} h^{-1} reduced the number of nausea and vomiting incidents from 63% (placebo group) to 23% (propofol group) [16]. According to Heidari and colleagues [17], the administration of 75 μg kg^{-1} of midazolam induced antiemetic effects when compared with the placebo (3.7 ± ± 1.6 in a visual analogue scale vs. 4.9 ± 2.2 in the placebo group) [17]. In our study, nausea and vomiting were more common in the MID group, and this difference was statistically significant. This results confirms the superior antiemetic effects of propofol when compared with midazolam.

The incidence of other side effects were comparable between groups. According to previous studies comparing the degree of intra- and post-operative amnesia after infusions of midazolam or propofol, the amnestic action of midazolam was more potent [7]. Our data confirm this finding. Mood and behaviour changes, such as euphoria or logorrhoea, are characteristic in patients anaesthetised with propofol [18, 19]. Likewise, the PROP group showed a significant increase in the occurrence of euphoria and logorrhoea.

Full satisfaction with anaesthetic management was comparable between groups. Manninen reported similar findings in a study of sedation for radiological procedures [20].

In conclusion, midazolam and propofol induce effective and safe sedation in patients undergoing subarachnoid anaesthesia for Caesarean sections. Due to its shorter action, propofol appears to be more useful than midazolam for pregnant women during Caesarean sections. In women with high preoperative stress levels, sedation with propofol during subarachnoid anaesthesia for Caesarean section is recommended.

CONCLUSIONS

1. Propofol exerts stronger adverse effects on the cardiovascular system of pregnant women during Caesarean section when compared with midazolam.
2. Propofol has a quicker onset of action and enables better control of the sedation level when compared with midazolam.
3. Sedation with propofol results in fewer side effects, such as nausea and vomiting, in patients undergoing subarachnoid anaesthesia.
4. Patients receiving propofol during subarachnoid anaesthesia demonstrate a better recall of neonatal birth parameters.
5. Sedation with either of the studied drugs provides a high and comparable satisfaction with the procedure.

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