A COMPARISON OF PROPOFOL, ALFENTANIL AND MIDAZOLAM FOR SEDATION DURING SPINAL ANESTHESIA

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ABSTRACT

Objective: We aimed to compare the efficacy and side effects of propofol, midazolam and alfentanil used for sedation during spinal anesthesia.

Methods: Thirty patients aged. 20-70 years, scheduled for inguinal hernia repair, appendectomy or transurethral resection were randomly assigned to three groups (n=10). The patients were given 1.25 mg/kg propofol i.v. in group I, 1.8 µg/kg alfentanil i.v. in group II and 0.1 mg/kg midazolam i.v. in group III prior performing spinal anesthesia. For maintenance of sedation propofol infusion of 3 mg/kg/h in group I,alfentanil infusion of 40 µg/kg/h in group II and midazolam infusion of 0.1 mg/kg/h in group III were started. The infusion rates were adjusted to maintain an appropriate sedation level. In all patients mean arterial pressure (MAP), heart rate (HR), oxygen saturation (SpO2), end tidal carbondioxide (ETCO2) and respiratory rate (RR) were recorded.

Results: In propofol group; while MAP and HR decreased significantly after bolus dose, the sedation level 2 was achieved within 5 minutes ($p<0.05$). In alfentanil group; while HR, MAP and RR decreased and ETCO2 increased significantly ($p<0.05$), the desired sedation level was not achieved. In midazolam group; the sedation level 2 was achieved at 15th minute and MAP, SpO2, HR and RR decreased significantly ($p<0.05$).

Conclusion: We conclude that propofol is the most appropriate agent for sedation during spinal anesthesia.

Key Words: Anesthetics, intravenous; propofol, Hypnotics, benzodiazepines; midazolam, Analgesics; alfentanil, Anesthetic techniques; sedation, spinal

INTRODUCTION

Regional anesthesia has many advantages over general anesthesia like, lower incidence of deep venous trombosis and pulmonary embolism postoperatively, minimal effects on respiratory functions, no change in cerebral function if hypotension is avoided and provision of excellent postoperative analgesia (1,2). However most patients prefer to have no memory of the surgical procedure and also most surgeons like to be guaranteed of absolute patient immobility. Therefore some form of sedation is necessary during regional anesthesia.

A number of papers suggesting the use of propofol, alfentanil and midazolam as sedative agents during regional anesthesia have been published with conflicted results regarding their efficacy, dose requirements and side effects (2-12).

The aim of this prospective study was to compare the efficacy and side effects of propofol, alfentanil and midazolam used to provide sedation during spinal anesthesia.

MATERIALS AND METHODS

Thirty patients, ASA I-II, aged 20-70 years, scheduled for inguinal hernia repair, appendectomy or transurethral resection under spinal anesthesia were included into the study protocol which was approved by the Institutional Ethical Committee after informed consent was obtained from all subjects. Patients with cardiorespiratory system disorders were excluded.

The main characteristics of patients, duration of surgery and total doses of sedative agents were reported in Table I.

All patients were premedicated with 0.5 mg atropin sulphate and 50 mg pethidin hyrochloride i.m. one hour before surgery. The patients were randomly assigned to three groups (n=10). In lateral decubitus position for performing spinal anesthesia, prior inserting the 22G spinal needle, the patients were given 1.25 mg/kg propofol i.v. in group I, 1.8 μg/kg alfentanil i.v. in group II and 0.1 mg/kg midazolam i.v. in group III. Spinal anesthesia was established by an intrathecal injection of 3 ml hyperbaric 0.5% bupivacain from L4-5 intervertebral space and then the patients were placed supine. After the level of analgesia was assessed by pinprick test, for the maintenance of sedation; propofol infusion at 3 mg/kg/h in group, I, alfentanil infusion at 40 μg/kg/h in group II and midazolam infusion at 0.1 mg/kg/h in group III were started via a syringe pump (1). The infusion rates were adjusted to maintain an appropriate sedation level (level 2: eyes closed but rousable with verbal stimulus) according to a four point sedation scale modified from Wilson et al (9) (Table II). The infusion rates were decreased to half of the beginning dose when the sedation level increased above level 2 or mean arterial pressure decreased below 30% of control and oxygen saturation decreased below 90%.

In all patients; heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO2), end tidal carbondioxide (ETCO2) (via a nasal sampling line), respiratory rate (RR) and sedation score were recorded before bolus dose, with 5 minute intervals during sedative infusion and 15 minute intervals during recovery period. 100% oxygen with a face mask was applied to patients whose SpO2 decreased below 90%. The patients were questioned for recall of intrathecal injection postoperatively. The results were analysed statistically using ANOVA and Tukey Kramer test and a $p<0.05$ was accepted as statistically significant.

RESULTS

There were no significant differences between groups with respect to patients age, weight, sex and duration of surgery ($p>0.05$) (Table I). Total doses of drugs (bolus+infusion) were also reported in Table I.

MAP decreased significantly at 5th minute and remained constant in propofol group while the decrease was significant at 20th minute in alfentanil group and at 10th minute in midazolam group ($p<0.05$) (Table III). HR decreased significantly at 5th minute in propofol group, at 30 th minute in alfentanil and midazolam group ($p<0.05$) (Table III). In alfentanil group heart rate remained decreased during recovery also.

While RR remained unchanged in propofol group ($p>0.05$), it decreased significantly at 5th minute in alfentanil group and at 30th minute in midazolam group ($p<0.05$) (Table IV). Only in alfentanil group, ETCO2 increased significantly at 5th minute ($p<0.05$) (Table IV). SpO2 did not change significantly in propofol group ($p>0.05$) (Table V). We had to administer 100% O2 continuously in alfentanil group and intermittently in midazolam group.

While the patients achieved the sedation level 2 within 5 minutes in propofol group and in 15 minutes in midazolam group ($p<0.05$), the desired sedation level was not achieved in alfentanil group (Table V). None of the patients in propofol group, 2 patients (20%) in midazolam group and 8 patients (80%) in alfentanil group recalled intrathecal injection.

Table I. The characteristics of patients, duration of surgery and total doses of sedative agents

	Propofol	Alfentanil	Midazolam
Age (years)	54.7±13.3	52.7±13.1	50.1±17.9
Weight (kg)	72.7±3.1	70.2±6.1	72.8±3.9
Sex (F/M)	1/9	1/9	1/9
Duration of surgery (min)	68.0±24.5	63.5±22.7	60.0±22.1
Total dose (mg)	203.4±10.4	2.79±1.2	6.98±1.9

Table II. Sedation scale

SCORE	DEGREE OF SEDATION
1	Fully awake
2	Eyes closed but rousable with verbal stimulation
3	Eyes closed but rousable with mild physical stimulation
4	Eyes closed and unrousable with mild physical stimulation

Table III. Mean arterial pressure and heart rate

	Mean arterial pressure (mmHg)			Heart rate (beat/min)		
	Propofol	Alfentanil	Midazolam	Propofol	Alfentanil	Midazolam
0 min	93.2±9.9	96.9±12.5	99.6±11.0	88.5±13.6	88.6±19.9	93.6±12.0
5.min	78.2±9.9*	92.9±14.0	89.8±14.7	82.0±10.7	88.5±19.0	89.9±14.5
10.min	79.3±4.9	94.2±12.0	88.6±11.6*	80.8±14.5*	86.3±18.8	90.7±11.1
15.min	77.5±6.9	87.3±7.3	83.7±9.0	79.8±14.8	83.6±18.1	86.6±11.8
20.min	75.5±6.5	83.8±8.1*	81.2±7.0	75.4±13.5	81.1±18.4*	86.3±12.5
25.min	75.5±9.9	84.3±11.8	77.2±6.7	76.0±12.7	77.1±17.7	84.7±11.3
30.min	73.2±8.8	85.8±9.5	76.3±5.9	73.6±15.0	78.8±15.7	81.0±10.5*
35.min	71.1±7.9	85.4±7.4	74.2±6.3	70.9±12.5	76.7±14.7	79.0±12.4
40.min	70.5±9.5	84.4±7.2	71.8±8.7	70.8±12.5	76.5±13.2	78.1±13.6
45.min	69.3±9.7	84.0±9.3	70.1±7.7	69.1±11.9	77.7±14.7	77.7±9.1

*p<0.05

Table IV. The respiratory rate and end tidal carbon dioxide tension

	Respiratory rate			ETCO2 (mmHg)		
	Propofol	Alfentanil	Midazolam	Propofol	Alfentanil	Midazolam
0 min	18.3±3.3	16.6±3.9	20.4±3.2	37.5±4.3	40.9±6.8	36.1±2.6
5.min	17.5±2.6	13.8±2.7*	20.4±2.9	37.7±3.1	45.1±7.9*	36.2±4.2
10.min	16.7±4.5	15.2±4.1	17.6±6.6	36.3±4.0	40.6±7.4	36.3±3.5
15.min	16.6±3.5	15.1±3.9	19.3±3.4	37.8±3.7	41.6±8.8	36.1±4.4
20.min	17.1±3.3	14.7±3.9	19.1±3.9	36.3±3.7	43.2±9.4	36.5±4.7
25.min	16.2±3.3	13.4±2.9	17.5±3.5	36.7±4.6	44.0±10.0	37.7±3.4
30.min	15.7±4.0	13.3±3.1	15.7±2.5*	36.4±4.0	43.9±10.2	36.4±4.6
35.min	15.7±3.0	12.4±3.1	16.3±2.7	36.5±4.5	45.4±8.9	35.6±4.1
40.min	15.8±3.1	13.3±5.3	16.8±2.8	36.9±3.6	45.1±9.4	36.0±3.1
45.min	15.1±3.0	13.3±2.6	17.5±2.9	36.0±3.7	45.1±11.7	37.0±1.2

*p<0.05

Table V. Oxygen saturation and sedation scores

	Oxygen saturation			Sedation score		
	Propofol	Alfentanil	Midazolam	Propofol	Alfentanil	Midazolam
0 min	97.1±1.8	97.5±1.5	97.0±1.7	1.0±0.0	1.0±0.0	1.0±0.0
5.min	96.4±2.6	97.0±1.8	95.3±2.2.	2.4±0.5*	1.2±0.4	1.6±0.5
10.min	96.3±1.8	97.8±1.8	96.1±2.6	1.9±0.7	1.2±0.4	1.3±0.4
15.min	95.7±2.2	98.1±1.4	95.2±2.6*	1.8±0.7	1.3±0.4	2.1±0.5*
20.min	95.9±2.4	98.0±2.0	95.9±2.7	2.1±0.5	1.5±0.5	2.2±0.4
25.min	96.2±2.7	97.6±1.7	95.4±2.8	2.0±0.6	1.3±0.3	2.4±0.6
30.min	96.2±2.5	97.3±2.1	96.0±2.6	2.2.±0.6	1.3±0.4	2.4±0.6
35.min	96.5±2.6	97.7±1.8	95.3±2.4	2.1±0.5	1.3±0.4	2.5±0.7
40.min	96.3±2.8	97.1±1.6	95.4±2.7	2.2±0.6	1.4±0.4	2.5±0.5
45.min	96.0±2.0	97.3±1.8	96.1±2.6	2.3±0.6	1.4±0.4	2.3±0.6

*p<0.05

** Patients received 100% oxygen in alfentanil and midazolam group

DISCUSSION

The goal of sedation during regional anesthesia is to provide comfort during local anesthetic injection, prevent patient movement which may make regional block technically difficult, allow patient to remain calm and comfortable during operation and provide a degree of perioperative amnesia. However insufficient sedation may cause sudden patient movement during injection whereas too much sedation may result in disorientation, hypoventilation, cardiovascular depression and loss of conscious cooperation. Therefore, ideal sedative drug for regional anesthesia must have sedative-hypnotic, amnestic and anxiolytic properties with minimal effects on circulation and respiration, must provide ease of titration to the desired level of sedation and rapid recovery with no residual drowsiness and amnesia (1,8).

Traditionally benzodiazepines have been the most widely used drugs for sedation. Sedation, amnesia and anxiolysis are well recognized pharmacologic features of benzodiazepins like midazolam with relatively short elimination half-life values (2-4 hours) however the persistence of sedation and amnesia into the postoperative period and the resultant psychomotor impairment can delay recovery and is undesirable (3,9). As with all benzodiazepins, there is great interpatient variability in midazolam dose requirements making hardly titration of drug to effect essentially (1,2,10). In our study as we compare fixed doses of agents with different onset times, 2 patients in midazolam group recalled intrathecal injection with 0.1 mg/kg bolus dose although midazolam is known to have strong amnestic properties. Because of the difficulty in dose titration of midazolam during infusion, we could achieve the desired sedation level at 15th minute and observed oversedation with an infusion dose of 0.1 mg/kg/h, had to stop infusion and apply oxygen intermittently during early perioperative period. Forster et al (14) administered midazolam 0.15 mg/kg in healty volunteers and reported that it reduced the ventilatory response to carbondioxide, systolic and diastolic blood pressure slightly and increased heart rate. We observed a significant decrease in respiratory rate and heart rate at 30 th minute, in mean arterial pressure at 10th minute and in oxygen saturation at 15th minute. However we concluded like Fanard et al that it was impossible to differentiate the cardiovascular effects of midazolam from that of spinal anesthesia.

There has long been interest in using propofol with a rapid onset and recovery for sedation during local and regional anesthesia as well as gastrointestinal endoscopies (4-7). The use of low dose propofol infusion for sedation during spinal anesthesia was initially described by Mackenzie and Grant (4) in 1987 and the authors concluded that 63 µg/kg/min propofol infusion resulted in a sleep like state from which patients were arousable with verbal commands and maintenance of desired sedation level was easily achieved by varying infusion rate. Janssen et al (5) used propofol infusion for patients undergoing herniography under spinal anesthesia, Nolte et al (6) used 1.5-2 mg/kg/h propofol infusion during epidural anesthesia and Duboi et al (7) used propofol infusion for gastrointestinal endoscopies and these authors concluded that propofol produced excellent and easily controllable sedation and amnesia. In our study with propofol 1 mg/kg bolus and 3 mg/kg/h infusion, we achieved the desired sedation level within 5 minutes and could easily titrate this level by changing the infusion rate. Also like Rosa et al (15) we did not observe any adverse effects on respiratory rate, end tidal carbon dioxide tension or oxygen saturation. Amnesia was reported by all patients.

Comparative studies of propofol with midazolam have shown the superiority of propofol in respect to predictability of effect, control of sedation and rapidity and quality of recovery. Ferrari et al (8) during retro-bulbar block, Fanard et al (2) during epidural anesthesia, Wilson et al 59) during spinal anesthesia, Patterson et al (10) during gastrointestinal endoscopy compared propofol and midazolam and they all agreed about less predictability and slower recovery of midazolam. Although Wilson et al (9) reported that midazolam produced more effective amnesia, Patterson et al (10) concluded that the short duration of hypnosis after a bolus dose of propofol resulted in more recall however the use of more supplemental doses or infusion of propofol would have reduced recall.

Opioid analgesics are often administered in combination with sedative-hypnotic drugs to reduce pain resulting from the injection of local anesthetic solutions, however when used alone, they generally do not produce adequate sedation and may be associated with undesirable effects. But Coe et al (11) used 40 µg/kg/h alfentanil infusion to supplement regional anesthesia since alfentanil has rapid onset and no cumulative effect after repeated doses and Yee et al (12) used 20 µg/kg alfentanil i.v. during retrobulbar block and concluded that it may be used for sedation. However we could not achieve desired sedation level with 1.8 µg/kg bolus and 40 µg/kg/h alfentanil infusion and could not increase the infusion rate as we observed significant increase in end tidal carbondioxide tension, decrease in respiratory rate, oxygen saturation and heart rate.

In this comparative study of propofol, midazolam and alfentanil; we conclude that propofol is superior to midazolam and alfentanil in providing adequate and easily controllable sedation with rapid-smooth onset and recovery during spinal anesthesia.

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