Anesth Pain Med 2016; 11: 255-259
http://dx.doi.org/10.17085/apm.2016.11.3.255

■ Clinical Research ■
pISSN 1975-5171 • eISSN 2383-7977

A loading dose of 1 μg/kg and maintenance dose of 0.5 μg/kg/h of dexmedetomidine for sedation under spinal anesthesia may induce excessive sedation and airway obstruction

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Background: For many drugs, dosing scalars such as ideal body weight (IBW) and lean body mass are recommended over the use of total body weight (TBW) during weight-based dose calculations. Doses based on TBW are frequently used, and this may cause under- or over-dosing. Because dexmedetomidine (DEX) overdosing could increase the incidence of side effects, and spinal anesthesia may increase sensitivity to a sedative agent, determining an appropriate dose is critical.
Methods: Eighty patients were randomly divided into 2 groups, the IBW and TBW groups. Patients received a loading dose of DEX 1 μg/kg IBW or TBW for 10 min, followed by a continuous infusion at 0.5 μg/kg/h IBW or TBW after the induction of spinal anesthesia. The patients' vital signs, bispectral index (BIS), peripheral capillary oxygen saturation, time to reach a BIS of 80, airway obstruction score, and coughing were monitored and recorded at 0, 10, 30, and 50 min after the start of the loading dose injection.
Results: The changes in BIS, airway obstruction score, the incidence of side effects, and time to reach a BIS of 80 did not show statistically significant differences between the two groups. However, airway obstruction and/or coughing occurred in both groups, and the average BIS in both groups was lower than the target BIS of 60–80 at 30 and 50 min.
Conclusions: A loading dose of DEX 1 μg/kg for 10 min, and a maintenance dose of DEX 0.5 μg/kg/h of either IBW or TBW, may induce excessive sedation, airway obstruction, and/or coughing under spinal anesthesia. **(Anesth Pain Med 2016; 11: 255-259)**

Key Words: Bispectral index monitor, Dexmedetomidine, Ideal body weight, Spinal anesthesia.

Received: April 8, 2016.
Revised: 1st, June 14, 2016; 2nd, June 26, 2016.
Accepted: June 27, 2016.

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INTRODUCTION

Dexmedetomidine (DEX) is a centrally acting, highly selective α-2 adrenoceptor agonist, which produces sedative and analgesic effects without causing significant respiratory depression [1-4], and is often employed in the perioperative period [5].

Typically, a loading infusion of 1 μg/kg over 10 min is recommended for initiation of procedural sedation in an adult patient; however, for less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 μg/kg administered over 10 min may be suitable. The maintenance infusion is generally initiated at 0.6 μg/kg/h, and titrated to achieve the desired clinical effect with doses ranging from 0.2 to 1 μg/kg/h. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

Some studies reported that DEX based on total body weight (TBW) for sedation during spinal anesthesia was safely administered as a loading infusion of 1 μg/kg over 10 minutes, followed by a continuous infusion of 0.4–0.7 μg/kg/h [6,7]. However, we observed excessive sedation, airway obstruction, and coughing in several cases during spinal anesthesia. Because TBW in many patients is higher than IBW, the IBW-based loading and maintenance doses of DEX are smaller than TBW-based doses. Therefore, we hypothesized that an IBW-based dose of DEX could reduce the incidence of excessive sedation and side effects. DEX overdosing can increase the risk of hypotension, bradycardia, and excessive or prolonged sedation; therefore, determining an appropriate dose is critical.

We aimed to investigate whether the use of DEX for sedation under spinal anesthesia at an initial loading dose of

1 μg/kg over 10 min, followed by a maintenance dose of 0.5 μg/kg/h would result in differences in the change of BIS, airway obstruction score, incidence of side effects, and time to reach a BIS of 80, depending on whether IBW or TBW was used for the dose calculation.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee and written informed consent was obtained from the patients prior to inclusion in the study. A total of 80 patients who satisfied the following clinical criteria were recruited: 1) American Society of Anesthesiologists (ASA) physical status classification I or II, 2) age 20–65 years, 3) body mass index (BMI) below 30, and 4) wishers to be slept during operation scheduled for lower extremity operation without premedication. Patients were excluded from this study if they had any of the following: 1) second or third degree atrioventricular block, 2) a psychiatric disorder, 3) known or admitted alcohol or drug abuse, 4) a history of sleep apnea, 5) a BMI ≥ 30, 6) severe cardiovascular disease, or 7) a history of anticoagulant therapy.

None of the patients received premedication, and a multichannel monitor was used for perioperative monitoring of heart rate, noninvasive blood pressure, peripheral oxygen saturation (SpO_2), electrocardiogram, respiratory rate per min, and bispectral index (BIS; A-2000, Aspect Medical Systems, Newton, MA, USA). Each patient was scheduled for surgery after the regional blockade with spinal block. Prior to the spinal block, patients were preloaded with 400–500 ml of electrolyte solutions. Spinal anesthesia was performed in the lateral decubitus position at the level of L3–4 or L4–5 in the midline approach. After reaching an adequate anesthetic level, the peak sensory block level between T8–T10 was confirmed by four consecutive pin-prick tests. All patients maintained spontaneous respiration and received supplemental oxygen by nasal cannula, which was given throughout the duration of the procedure at 3 L/min of fresh gas flow. This study was a randomized, prospective, observational study. Patients were randomly allocated into 2 groups, the IBW and TBW groups, using computer-generated random numbers with Microsoft Excel. Patients were blind to the group to which they were assigned. IBW (kg) by the Devine formula was calculated as: male, 50 + 0.91 [height − 152.4 cm]; female, 45.5 + 0.91 [height − 152.4 cm].

Patients received a loading dose of 1 μg/kg of IBW or TBW over 10 min, followed by a continuous infusion of 0.5 μg/kg/h of IBW or TBW after induction of spinal anesthesia, as per label instructions.

An adequate sedation level for surgery was set at mild-to-moderate, at a BIS of 60–80. The patient's vital signs, BIS, SpO_2, time to reach a BIS of 80, airway obstruction score, and coughing were monitored and recorded at 0, 10, 30 and 50 min after injection of the loading dose. The BIS progressively decreased and maintained a plateau between 30 to 50 min after the start of the loading dose injection [6]. When coughing occurred, the BIS just before coughing was recorded as the BIS of that data collection time point. The airway obstruction score was defined as: 1 = a patent airway; 2 = an airway obstruction relieved by neck extension; 3 = an airway obstruction requiring jaw retraction. Bradycardia was defined as a heart rate less than 50 beats/min, and was treated with an injection of atropine sulfate 0.5 mg. Data were gathered from the patient's medical records, including BIS, airway obstruction score, and the occurrence of bradycardia and coughing. After data collection, the maintenance dose was adjusted for adequate sedation by using continuous BIS monitoring.

Based on a pilot study (BIS of TBW: mean = 53.5, SD = 13.7; BIS of IBW: mean = 59.3, SD = 13.9), we determined the sample size needed to detect a difference of 10 in BIS values with an α of 0.05, power of 80%, and a drop rate of 0.1. A minimum of 33 patients were required in each group. However, we included 40 patients in each group to better validate the results. Data are expressed as mean ± SD. Analysis of sex, physical status, and the incidence of coughing and bradycardia was conducted using the Fisher's exact test. The number of patients with airway obstruction signs was compared using the Pearson Chi-square test. The comparisons of IBW and TBW within each group were statistically analyzed using a paired t-test. The comparisons of other parametric data between groups were statistically analyzed using Student's t-test. Repeated-measures analysis of variance was used to compare the change in BIS over time. Friedman's test was used to compare airway obstruction score over time. P values < 0.05 were considered significant.

RESULTS

All 80 patients completed the study, with 40 patients per group and no drop-outs. The parameters of sex, age, ASA physical status, height, IBW, TBW, and time required to reach a BIS of 80 were not significantly different between the two groups. However, IBW in both groups was less than the corresponding TBW, and IBW in the IBW group was less than the TBW in the TBW group ($P < 0.001$ for both). The loading dose of the IBW group was less than that of the TBW group ($P < 0.001$), and the total dose of the IBW group was less than that of the TBW group ($P < 0.001$) (Table 1).

The changes in BIS did not show statistically significant differences between the groups, but the average BIS values in both groups at 30 and 50 min were lower than the target BIS of 60–80 (Table 2). The airway obstruction score (Table 3) and the incidence of side effects, including bradycardia, airway obstruction, and coughing, did not show statistically significant differences between the groups. However, the proportion of patients who experienced airway obstruction was 25% in the IBW group and 30% in the TBW group. Coughing occurred more frequently in the TBW group than in the IBW group (Table 4).

Table 1. Patient Demographic Data

	IBW group (n = 40)	TBW group (n = 40)	P value
Sex (M/F)	23/17	25/15	0.653
Age (yr)	43.6 ± 14.2	48.5 ± 12.5	0.156
ASA (I/II)	22/18	25/15	0.284
Height (cm)	165.8 ± 8.9	165.9 ± 10.8	0.092
Body weight (kg)			
IBW	60.9 ± 9.8*	60.1 ± 11.6	0.761
TBW	68.1 ± 9.8	71.3 ± 12.5	0.200
Loading dose of DEX (μg)	60.9 ± 9.8	71.3 ± 12.5	< 0.001
Total dose of DEX (μg)	81.0 ± 13.0	96.7 ± 17.2	< 0.001
Time required to reach BIS 80 (min)	7.8 ± 5.4	7.9 ± 4.0	0.938

Values are mean ± SD or number of patients. IBW: ideal body weight, TBW: total body weight, DEX: dexmedetomidine, BIS: bispectral index. *$P < 0.001$ compared to TBW in TBW group.

DISCUSSION

In the present study of spinal anesthesia for lower extremity surgery, DEX at a loading dose of 1 μg/kg for 10 min, followed by a maintenance dose of 0.5 μg/kg/h, induced excessive sedation, airway obstruction, and/or coughing, irrespective of whether IBW or TBW was used for weight-based dose calculations.

Regional anesthesia (RA) is the preferred anesthetic technique in terms of merits and demerits, and other advantages of RA over general anesthesia (GA) have already been demonstrated in a number of other studies [8-10]. Patients electively scheduled for surgery experience various levels of anxiety, due to factors such as cultural background, age, personality types, surgery type, previous anesthetic experience, education status, and preoperative information [11-14].

Anxiety while awake during the operation is reported in many studies as one of the common reasons for preferring GA

Table 2. Bispectral Index Score

	IBW group (n = 40)		TBW group (n = 40)	
	Mean ± SD	95% CI	Mean ± SD	95% CI
T0	91.8 ± 4.7	89.9–93.3	92.0 ± 3.5	90.9–92.8
T10	69.6 ± 13.9	63.8–75.4	69.5 ± 15.3	62.5–74.3
T30	52.5 ± 15.1	48.7–56.8	54.2 ± 16.0	49.3–60.1
T50	55.3 ± 14.6	49.8–61.0	53.5 ± 16.4	48.9–59.2

Values are mean ± SD. No statistically significant differences were noted between the groups ($P = 0.924$). IBW: ideal body weight, TBW: total body weight, CI: confidence interval, T0: prior to loading dose, T10: 10 min post-loading dose, T30: 30 min post-loading dose, T50: 50 min post-loading dose.

Table 3. Airway Obstruction Score and Incidence (1/ 2/ 3)

	IBW group (n = 40)	TBW group (n = 40)
Prior to DEX infusion	40 (100%)/0 (0%)/0 (0%)	40 (100%)/0 (0%)/0 (0%)
10–20 min post-infusion	33 (82.5%)/6 (15%)/1 (2.5%)	31 (77.5%)/9 (22.5%)/0 (0%)
20–30 min post-infusion	31 (77.5%)/8 (20%)/1 (2.5%)	29 (72.5%)/11 (27.5%)/0 (0%)
30–50 min post-infusion	31 (77.5%)/8 (20%)/1 (2.5%)	30 (75%)/10 (25%)/0 (0%)

Values are number of patients (%). No statistically significant differences were noted between the groups ($P = 0.362$). IBW: ideal body weight, TBW: total body weight, DEX: dexmedetomidine. Airway obstruction score is as follows: 1 = patent airway, 2 = airway obstruction relieved by neck extension, 3 = airway obstruction requiring jaw retraction.

Table 4. Incidence of Side Effects

	IBW group (n = 40)	TBW group (n = 40)	P value
Bradycardia	1	0	1.0
Airway Obstruction	10	12	0.549
Coughing	0	5	0.055

Values are number of patients. No statistically significant differences were noted between the groups. IBW: ideal body weight, TBW: total body weight.

[11,15]. Thus, many patients accepted RA under the condition of being asleep during the operation. However, oversedation is associated with an increased incidence of side effects and length of stay in the postanesthetic care unit, and under-sedation can be associated with patient agitation. Therefore, achieving a balance is vital to optimize patient sedation.

Although a discrepancy among the Ramsay sedation score, the observer's assessment of alertness and sedation (OAA/S) score, and BIS scoring when DEX was used as the sedative agent was reported [16], BIS values are still correlated with anesthetic depth of inhalational and intravenous anesthesia and propofol- and midazolam-induced sedation [17,18]. It has been reported that OAA/S scores and BIS are correlated with the alert, sedation, and deep sedation state [19], and BIS is a consistent marker for the depth of sedation [20]. BIS monitoring has the advantages of maintaining sedation without external stimulation and disturbing the level of sedation, and it allows for objective, real-time assessment. Therefore, we used BIS for estimating the degree of sedation.

Spinal anesthesia may increase sensitivity to a sedative agent, and high spinal block was associated with increased sedation [21,22]. Bupivacaine-induced spinal block decreases midazolam, thiopental, and propofol hypnotic requirements [23,24]. Spinal anesthesia itself is reported to have sedative effects; therefore, a low loading dose of DEX alone is believed to bring adequate sedation [21].

DEX is one of the preferred agents for adequate sedation without significant respiratory depression, and the incidence of side effects on the hemodynamic response depends on the dose and speed of infusion [25,26]. Although DEX decreases salivary secretion through sympatholytic and vagomimetic effects [27], deep sedation may depress the swallowing of saliva, and this can induce coughing. Coughing may decrease the quality of sedation, thus interfering with the operation. One advantage of DEX for sedation is that it can cause sedation without severe respiratory depression. Although we could not find any reports that DEX causes airway obstruction and coughing, we noted during our study that DEX induced airway obstruction and coughing in several cases, and this interfered with surgery in those cases.

For many drugs, dosing scalars such as IBW are recommended over TBW during weight-based dose calculation to avoid overdosing. Despite statistically significant differences in loading and total doses and body weights between the two groups in this study, there were no statistically significant differences in BIS score, airway obstruction score, the incidence of side effects, and the time required to reach a BIS of 80. It is thought that the body weight difference between the groups was not large enough to make a difference in BIS, because the study only included patients with a BMI below 30. However, airway obstruction and/or coughing occurred in both groups, and the average BIS in both groups was lower than the target BIS of 60–80 at 30 and 50 min.

In conclusion, DEX at a loading dose of 1 μg/kg for 10 min, and a maintenance dose of 0.5 μg/kg/h of either IBW or TBW, may induce excessive sedation, airway obstruction, and/or coughing under spinal anesthesia for lower extremity surgery. Therefore, further studies to determine a lower loading and/or maintenance dose are needed to improve the quality of sedation and reduce side effects.

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